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THE GENETIC STUDY OF DIABETIC RETINOPATHY (O66)

S. Abhary ,[1] K. P. Burdon,[1] N. Petrovsky[2] and J. E. Craig[1]
[1] *Department of Ophthalmology, Flinders Medical Centre, Bedford Park, Australia*
[2] *Department of Endocrinology, Flinders Medical Centre, Bedford Park, Australia*

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM), whereby hyperglycaemia causes damage to retinal blood vessels. Clinical experience has shown that ocular manifestations often do not correlate with glycaemic control or disease duration. DR is also known to have a heritable component. Identifying genetic markers for high risk of developing DR would allow for refined screening algorithms, earlier intervention and ultimately better understanding to facilitate strategies to reduce the morbidity associated with DR. We have investigated 2 candidate genes, vascular endothelial growth factor (VEGF) and carbonic anhydrase (CA) for a role in DR. VEGF is a multifunctional cytokine that plays a role in angiogenesis and microvascular permeability. CA is an enzyme shown in animal studies to increase retinal leakage and intraretinal oedema. A total of 556 subjects with DM were recruited — 191 patients with type 1 DM and 365 with type 2 DM. This study group included 225 subjects with no DR, 141 nonproliferative DR (NPDR), 123 proliferative DR (PDR) and 79 with macular oedema. DNA and DR grading were obtained from all subjects. Subjects were genotyped for 15 VEGF and 10 CA single nucleotide polymorphisms (SNPs). All SNPs were in Hardy Weinberg Equilibrium. No association was observed between CA polymorphisms and DR. Multiple SNPS in VEGF were associated with various diabetic eye gradings. Most significantly the AA genotype of the VEGF rs14304 polymorphism was found to play a protective role against the development of both combined severe DR and proliferative DR ($p = .0064$) and macular oedema ($p = .003$).

MULTIPLE MTDNA DELETION IN A PATIENT WITH TYPICAL CLINICAL FEATURES OF MELAS (P34)

K. K. Abu-Amero, A. Hellani, M. Al-Mahed and I. Al-Sheikh
Genetics, King Faisal Specialist Hospital, Riyadh, Saudi Arabia

We describe a 34-year-old Saudi woman who had clinical symptoms suggestive of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). We sequenced her entire mitochondrial DNA coding region in DNA samples extracted from her blood and skeletal muscles and we also looked for deletion(s). We did not detect any pathological mutation; however, we detected multiple deletions in DNA sample extracted from muscles. Muscle biopsy and MRI findings were indicative of MELAS. We also sequenced the mtDNA polymerase (POLG1) nuclear gene, without finding any mutation(s). To our knowledge, this is the first report of multiple deletions in skeletal muscle in a MELAS patient lacking mutations in the POLG1 gene.

SPECTRUM OF FACTOR VIII MUTATIONS IN ARAB PATIENTS WITH SEVERE HAEMOPHILIA A (P35)

K. K. Abu-Amero, A. Hellani, M. Al-Mahed and I. Al-Sheikh
Genetics, King Faisal Specialist Hospital, Riyadh, Saudi Arabia

Haemophilia A is an X-linked recessive bleeding disorder caused by mutations in the factor VIII gene. The mutation spectrum is known in various populations, but not in Arabs. We selected 20 unrelated Arab patients with severe hemophilia A. Those patients underwent detailed clinical examination and their plasma FVIII:C activity was also measured. We extracted DNA from their blood samples and we looked for intron 22 inversion, deletions, insertions and base substitutions in the factor VIII gene. Intron 22 inversion was common (detected in 11 patients, 55%), 8 base substitutions (6 of which are novel) were detected in 9 patients (45%) and none had an insertion or deletion. Out of 8 base substitutions detected, 7 were potentially pathologic and this correlated well with the severe clinical phenotype observed. A larger study with more Arab patients from various Arab countries is needed in order to establish a solid conclusion about the prevalence of various mutations in this unique ethnic group. For the families included in this study, the results obtained can be helpful for carrier testing, prenatal diagnosis or preimplantation techniques for detection of unaffected embryos.

IMPACT OF EXPANDED NEWBORN SCREENING FOR DIETITIANS (O22)

R. Akroyd, C. De Luen, D. Knoll, D. Webster and C. Wilson
Lab Plus, Starship Children's Hospital and Auckland City Hospital, Auckland, New Zealand

Newborn metabolic screening has been a national program in New Zealand since 1969. Until 2006 babies were screened for phenylketonuria (PKU), maple syrup urine disease, galactosaemia, congenital hypothyroidism, cystic fibrosis, congenital adrenal hyperplasia and biotinidase deficiency. With the advent of tandem mass-spectrometry technology, expanded metabolic screening commenced December 2006 screening for a total of 28 disorders, including those of amino acid metabolism (aminoacidopathies, urea cycle disorders and organic acidaemias) and of fatty acid oxidation (full list available on web site http://www.moh.govt.nz). The first 12 months approximately 60,000 babies were tested and 1 case of PKU (and 2 hyperphenylalaninaemia), 5 cases of medium chain acyl-CoA dehydrogenase deficiency (MCAD) — 3 singletons and 1 set of twins, 2 infants with glutaric aciduria type 1, one case of translocase deficiency and one of multiple acyl-CoA dehydrogenase deficiency. The rate of symptomatic testing for inborn errors of metabolism is low relative to other similar countries hence the rate of diagnosis without screening is similarly low, that is, only 2 cases of MCAD were clinically diagnosed in 2004–2006 (expected number based on Australian statistics 10). Expanded screening has significantly increased dietitian workload specifically — introduction of special diet, maintaining metabolic stability during times of rapid growth and implementation of emergency regimes. It is envisaged that the workload will continue to increase as more cases are diagnosed, treated and remain well.

TWO NEW PATIENTS WITH OSTEOGENESIS IMPERFECTA RESULTING FROM INBORN ERRORS IN PROLYL-3 HYDROXYLATION (P16)

M. Alcausin, R. Morello, J. Bateman, S. Lamande and D. Sillence
Department of Clinical Genetics, Children's Hospital at Westmead, Department of Molecular and Human Genetics, Baylor College of Medicine, Murdoch Children's Research Institute, Australia

In the fibrillar collagens, proline is generally hydroxylated at the 4 position. A proline in the α1(I) procollagen chain is hydroxylated specifically at pro 986 by a complex of proteins including P3H1 leprecan coded for by P3H1/LEPRE1, Cartilage Associated Protein (CRTAP) and Cyclophilin B. Mutations in P3H1/LEPRE1 are known to result in the OI phenotypes, types IIC and VII and CRTAP mutations in types III D and VIII. Two patients from our Australian experience illustrate the phenotypic features. The first patient a male was born to Lebanese parents. At 3 months of age, he had bowing of all limbs, recurrent fractures and a broad bone appearance of the femurs. His sclerae and teeth were normal. His course was one of severe progressively deforming OI although he was noted to have fewer fractures than expected. He died of cardiorespiratory failure at 12 years of age. Biochemical studies of type I procollagens showed normal amount of type I overall but slowly migrating over-modified type I chains. Molecular DNA studies revealed a homozygous 8bp deletion in exon 1 of CRTAP: c.24_31del8. Clinical and molecular features were consistent with a diagnosis of OI type IIC/VII. The second patient was born to first cousin parents from the Middle East. She had deformities of all long bones with recurrent fractures and normal sclerae. Collagen electrophoretic studies showed slowly migrating over-modified type I procollagens. Molecular DNA studies revealed a homozygous nonsense mutation in exon 14 of LEPRE1: c.2041C>T (p.R681X). Clinical and molecular features were consistent with the diagnosis of OI type VIII.

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'I THINK IT'S AN IMPORTANT THING': RELATIVES' ATTITUDES TO POPULATION CARRIER SCREENING FOR FRAGILE X SYNDROME (O2)

A. D. Archibald,[2] S. Wake[4] A. M. Jaques,[1] J. Cohen[3] and S. A. Metcalfe[1,2]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Department of Paediatrics, The University of Melbourne, Australia*

[3] *Fragile X Alliance, Australia*

[4] *Genetic Health Services Victoria, Australia*

Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability. Population carrier screening for FXS can identify carriers and provide them with information about their health and their risk of having a child with FXS. There is limited information on community attitudes to offering population carrier screening for FXS, including attitudes of people with a family history of FXS. This study aims to explore the views and attitudes of relatives of people with FXS to offering carrier screening in the general population. In-depth interviews are being conducted with relatives of people with FXS in Victoria, Australia. Relatives include parents, grandparents, aunts, uncles and siblings. Participants are asked about their experiences of FXS and their attitudes to population carrier screening. To date, 15 relatives have participated in the study and interviews will continue until data reaches saturation. Participants have given rich insights into their experiences of having a child or relative with FXS and discussed their experiences of carrier testing. All participants were supportive of population carrier screening for FXS. Participants discussed their views on when to offer population carrier screening for FXS and how knowledge of FXS carrier status impacts on the individual and the family. These initial results provide a valuable insight into families' views on population carrier screening. Findings from this study will help inform future development of carrier screening programs.

OFFERING POPULATION CARRIER SCREENING FOR FRAGILE X SYNDROME: A QUALITATIVE ATTITUDINAL STUDY (O121)

A. D. Archibald,[1,2] Y. M. Bylstra,[1] S. Wake,[4] A. M. Jaques,[1] J. Cohen[3] and S. A. Metcalfe[1,2]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Department of Paediatrics, The University of Melbourne, Australia*

[3] *Fragile X Alliance, Australia*

[4] *Genetic Health Services Victoria, Australia*

Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability. Currently, most carriers are identified following the diagnosis of an affected relative however, not all carriers are detected in this way. Population carrier screening for FXS has the potential to identify more carriers and provide them with information about their health and their risk of having a child with FXS. The overall aim of this study is to explore community attitudes to population carrier screening for FXS. Interviews and focus groups were conducted with 127 participants: healthcare providers (55), relatives of people with FXS (15), nonpregnant women (31), pregnant women (8), teachers (7) and high school students (11). Participants discussed a range of themes relating to their attitudes to population carrier screening for FXS including: the acceptability of screening; making informed reproductive decisions; impact of carrier status on life choices; implications for society; the variability of features of FXS and the importance of raising awareness about FXS. Overall, participants were supportive of population carrier screening for FXS, provided it was optional and follow-up genetic counselling was available. While participants felt the ideal time to offer screening was prior to pregnancy and that screening should be offered through general practitioners clinics, some believed prenatal screening is more practical. This is the first attitudinal study to explore community views. These results provide support for screening and are a valuable insight into the wide range of issues involved. Findings from this study will help inform future development of carrier screening programs.

HETEROGENEITY OF FOCAL EPILEPSIES IN A GENETICALLY ISOLATED FOUNDER POPULATION (O96)

D. Azmanov,[1] D. Angelicheva,[1] I. Tournev,[2] V. Guergueltcheva,[2] M. Velizarova,[2] D. Zlatareva,[3] A. Jablensky,[4] J. Sander[5] and L. Kalaydjieva[1]

[1] *Western Australian Institute for Medical Research, The University of Western Australia, Australia*

[2] *Department of Neurology, Medical University, Hungary*

[3] *Tokuda Hospital, Sofia, Bulgaria*

[4] *Centre for Clinical Research in Neuropsychiatry, The University of Western Australia, Australia*

[5] *University College, London, United Kingdom*

Epilepsy is one of the common serious neurological disorders, affecting millions of people worldwide, with about 1/3 resistant to currently available treatment. Epilepsy shows extensive clinical and genetic heterogeneity and is one of the examples of disorders where large-scale association studies, relying on the 'common disease-common variant' paradigm, may not be productive. Existing knowledge of the genetic and pathophysiological basis of human epilepsies comes mostly from studies of large, well-characterized families with mendelian forms of epilepsy. Despite their major contribution to human genetics, isolated founder populations have very rarely been explored in epilepsy research. Our project deals with focal epilepsies in the Roma/Gypsies, where previous data on limited genetic diversity and strong founder effect lead us to expect greater homogeneity in the genetic basis of epilepsy and sharing of founder mutations between affected individuals and families. Our investigations so far have led to the identification of a new 5q locus and a possible second locus (modifying gene) on 10p in a single large pedigree, characterized by variable electrophysiology and seizure semiology and secondarily generalized tonic-clonic convulsions. Neither locus contributes to the genetic basis of epilepsy in the remaining large families. The analysis of another extended kindred, with similar clinical findings and apparent incompletely penetrant dominant inheritance, shows a pattern typical of complex disorders, with several loci of small individual contribution. The data point to the heterogeneity of epilepsy even in genetically restricted subisolates within a young founder population.

VERIFICATION OF CONSUMERS' EXPERIENCES AND PERCEPTIONS OF GENETIC DISCRIMINATION AND ITS IMPACT ON UTILISATION OF GENETIC TESTING (P40)

K. Barlow-Stewart,[1] S. Taylor,[2] S. Treloar,[3] M. Stranger [4,5] and M. Otlowski [4,5]

[1] *Centre for Genetics Education, Royal North Shore Hospital, Sydney, Australia*

[2] *Department of Social Work and Human Services, Central Queensland University, Rockhampton, Australia*

[3] *Centre for Military and Veterans' Health, The University of Queensland, Brisbane, Australia*

[4] *School of Law, University of Tasmania, Hobart, Australia*

[5] *Centre for Law and Genetics, University of Tasmania, Hobart, Australia*

A major component of the Australian Genetic Discrimination Project 2002–2005 was to undertake a systematic process of verification of consumer accounts of alleged genetic discrimination, defined as the differential treatment of an asymptomatic person on the basis of their real or assumed genotype or genetic characteristics. Asymptomatic individuals reporting incidents in a survey conducted through Australian clinical genetics services 1998–2003 were recruited for the subsequent verification process. Others were recruited through genetics support groups and referrals from clinical genetics professionals. Verification of alleged incidents of genetic discrimination was determined, with consent, through interview, document analysis and, where appropriate, direct contact with the third party involved. Reported incidents of negative treatment in life insurance, employment, and health service domains met criteria for verification in 27/99 instances. Verification was possible in 14 cases (7 breast and ovarian cancer; 3 HNPCC; 3 Huntington disease and one each of hereditary haemochromatosis and polycystic kidney disease). All involved life insurance products. Issues included fear of genetic discrimination that impacted upon uptake and access to genetic testing for relatives; overly broad exclusion clauses; inability to increase policy amount; denial of insurance; coercion to access genetic test results and lack of recognition of prophylactic and screening strategies in underwriting decisions. In the course of verification, the decision-making process underpinning the life insurance underwriting was elucidated and reversal of adverse decisions following challenges to the company or provision of expert clinical genetics advice was confirmed. Verification is a potentially fruitful but a complex and challenging process.

PERFORMANCE OF THE SOUTH AUSTRALIAN (SA) EXPANDED NEONATAL SCREENING PROGRAMME USING TANDEM MASS SPECTROMETRY (MSMS) (P24)

B. A. Bartlett, E. Ranieri, R. L. Gerace, J. R. Harrison and J. M. Fletcher

South Australian Neonatal Screening Centre, Department of Genetic Medicine, Women's and Children's Hospital, Child, Youth & Women's Health Service, Adelaide, Australia

The South Australian expanded neonatal screening program using MSMS commenced in February 1999. Over 200,000 dried blood-spot specimens collected at 48 hours of age from infants were analysed on an MDS-SCIEX API365 and API 4000 MSMS against 14 stable isotopes of the AC and 10 of the AA. Of the total dried blood-spots screened re-sampling was requested on 946 infants (0.47%) with a provisional high risk result for an AA and AC profile, 340 (0.17%) and 606 (0.30%) respectively. Of the 340 infants with an abnormal AA profile, 33 (9.7%) were directly recalled for urine and plasma amino acids. We identified PKU (14), hyperphenylalaninaemia (8), tyrosinaemia type III (1), MSUD (1) and OTC (1) pyruvate carboxylase deficiency (1), neonatal haemochromatosis (2), ASL deficiency (1) and citrullinaemia I (1). Repeat AA profiles on the remainder were normal. Of the 606 infants with an abnormal AC profile, 55 (9.1%) were recalled for urine organic acids and plasma acylcarnitine or methyl-

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malonic acid testing. We identified MCAD (15) IVA (2), systemic carnitine deficiency (2), carnitine transporter defect (1), GA1 (1), GAII (3), vLCAD (4), SBCAD (1), probable MMA vitamin B12 responsive (1) confirmation pending, vitamin B12 deficiency (7) and the remainder had normal metabolic screening results. Cases of malonyl-CoA decarboxylase deficiency and cobalamin metabolism defect were confirmed retrospectively. To date 59 infants with a metabolic disorder have been identified, with a PPP value of 60 %, giving an incidence rate in our screened population of 1 in 3300 (CI: 2,709–3,980).

AMRF: A PROGRESSIVE MYOCLONOUS EPILEPSY WITH ASSOCIATED RENAL FAILURE IS CAUSED BY *SCARB2* MUTATIONS (P49)

M. A. Bayly,[1] M. Bahlo,[3] L. M. Dibbens,[1,2] A. Oshlack,[3] J.D. Silver,[3,4] M. Katerelos,[5] D. F. Vears,[6,7] R. Lüllmann-Rauch,[8] J.,Blanz[9] K. W. Zhang,[6] J. Stankovich,[3,10] R. M. Kalnins,[11] J. P. Dowling,[12] E. Andermann,[13] F. Andermann,[13] E. Faldini,[14] R. D'Hooge,[14] L. Vadlamudi,[6,7] R. A. Macdonell,[11] B. L. Hodgson,[1] J. Savige,[6] J. C. Mulley,[1,2,15] G. K. Smyth,[3] D. A. Power,[11] P. Saftig[16] and S. F. Berkovic[6,7,11]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *School of Paediatrics and Reproductive Health, University of Adelaide, Australia*

[3] *The Walter and Eliza Hall Institute of Medical Research, Australia*

[4] *Department of Mathematics and Statistics, The University of Melbourne, Australia*

[5] *Burnett Institute at Austin, Austin Health, Australia*

[6] *Department of Medicine (Austin Health and Northern Health), Melbourne, Australia*

[7] *Epilepsy Research Centre, The University of Melbourne, Australia*

[8] *Anatomisches Institut, Universität Kiel, Germany*

[9] *Zentrum Biochemie und Molekulare Zellbiologie, Abt. Biochemie II, Universität Göttingen, Germany*

[10] *Menzies Research Institute, University of Tasmania, Australia*

[11] *Departments of Neurology, Nephrology and Anatomical Pathology, Austin Health, Australia*

[12] *Department of Anatomical Pathology, Alfred Hospital, Australia*

[13] *Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital McGill University, Canada*

[14] *Laboratory of Neurochemistry and Behaviour, Born-Bunge Foundation, University Antwerpe, Belgium*

[15] *School of Molecular and Biomedical Science, University of Adelaide, Australia*

[16] *Department of Biochemistry, University Kiel, D-24098 Kiel, Germany*

AMRF is a lethal inherited form of progressive myoclonus epilepsy associated with renal failure. The autosomal recessive gene defect underlying AMRF was unknown and the lack of large pedigrees and lethality of the disorder precluded a conventional mapping strategy. A novel homozygous mapping strategy using three unrelated affected subjects was employed to map the disorder to a region of chromosome 4. Microarray RNA expression analysis was then used to prioritize candidate genes within this region. Sequence analysis of the prime candidate gene *SCARB2* (also known as *Limp2*) detected mutations in three Australian families. These consist of a splice-site mutation and two different frameshift mutations. All the mutations are predicted to lead to premature protein truncation and RT-PCR studies have confirmed this for the splice site mutation. Additionally a nonsense mutation was found in one of the originally reported AMRF families from Quebec and a frameshift identical to one of the Australian families was found in another previously reported Canadian case. In human, AMRF is associated with inclusions in the brain and severe focal glomerulosclerosis. *Limp2*$^{-/-}$ mice also have a predominant cerebro-renal phenotype with intracellular inclusions in cerebral and cerebellar cortex. The pleiotropy observed with deficiency of *SCARB2/Limp2* both within and between species, suggests a variety of roles for this ancestral lysosomal membrane protein. We are currently investigating whether *SCARB2* mutations contribute to the pathogenesis of other progressive myoclonic epilepsies (PMEs). We are also exploring the possibility of a founder mutation being present in the French–Canadian population.

AUTOMATED EXTRACTION OF DNA FROM NEWBORN SCREENING CARDS (O44)

B. Bennetts and K. Slater

Department of Molecular Genetics, The Children's Hospital at Westmead, Australia

The extraction of amplifiable DNA from newborn screening cards is central to the development of molecular genetic testing within newborn screening programs. To date molecular genetic assays have been restricted to a small subset of cards. In the future it is likely that a variety of molecular genetic assays will be performed on all cards. For these reasons it is important to establish methods of extraction which take advantage of automation and which deliver sufficient DNA to be used in a variety of assays. *Method:* A pilot study for Fragile XA testing from cards was undertaken. A liquid handler (Eppendorf EpMotion 5075) with Sigma/Corbett reagents and Whatman glass filter plates was used to extract DNA into a final volume of ~120 l. Control cards were used to determine the number of 3 mm punches necessary to provide sufficient DNA. DNA was amplified with Fragile XA primers using 1 l of DNA and visualised on polyacrylamide gels. *Results:* DNA from a single 3mm punch could be detected but the use of four punches was chosen as a balance between ensuring adequate amplifiable DNA and sufficient material left on the card for possible follow-up testing. All 200 cards were able to be amplified and the DNA has remained stable over a number of months. *Discussion:* The consistent quality and volume of DNA indicates it is sufficient to perform a large number of molecular assays. The automation of the extraction indicates that it could easily be incorporated into a newborn screening program.

EFFECTS OF THE COMMON ALPHA-ACTININ-3 POLYMORPHISM ON GLUCOSE TOLERANCE, OBESITY AND RISK OF TYPE 2 DIABETES (O94)

Y. Berman, N. Yang, K. Quinlan, J. Seto, J. Raftery, S. Garnett, C. Cowell and K. North

NRU, Children's Hospital at Westmead, Australia

A common polymorphism in the ACTN3 gene results in complete deficiency for alpha-actinin-3 protein in 18% of the population worldwide. Alpha-actinin-3 deficiency is underrepresented in sprint athletes, overrepresented in endurance athletes, and is associated with reduced muscle strength and sprint performance nonathlete cohorts. Our mouse model of alpha-actinin-3 deficiency shows improved skeletal muscle oxidative metabolism, increased muscle glycogen, improved fatty acid utilisation, and altered glucose tolerance. We have performed microarray analysis of muscle from our Actn3 KO mouse compared to wild type. Deficiency of alpha-actinin-3 is associated with altered expression of genes known to affect glucose metabolism and development of obesity, including BMP1, Glut3, Wnt4, IGFBP5, and Dkk3. We have examined the effect of ACTN3 genotype in a number of human cohorts, and will present results of association studies between alpha-actinin-3 deficiency and obesity and type 2 diabetes. We are now conducting studies of the response to high fat feeding in control and knockout mice, to explore the mechanisms by which Actn3 genotype may influence the development of obesity and type 2 diabetes.

3-HYDROXYISOBUTYRIC ACIDURIA IN A CHILD WITH A SEIZURE DISORDER (P21)

B. Bettany,[1] D. Knoll,[1] C. Sharpe,[2] C. de Luen,[1] S. Rattray[1] and C. Wilson[1]

[1] *National Testing Centre, LabPlus, Auckland Hospital, New Zealand*

[2] *Starship Hospital, Auckland, New Zealand*

3-hydroxyisobutyric aciduria is a very rare disorder of valine metabolism. Less than 15 cases have been described with the phenotype being quite variable. Children with developmental delay, recurrent vomiting and seizures have all been reported. A clear association with an enzyme deficiency or a molecular defect has not yet been established although some patients do appear to have exacerbation of their symptoms with catabolic events or a valine load. We present a 1-year-old Chinese girl who presented with a 6-month history of mild developmental delay and a two month history of abnormal movements. On examination she was alert and looked well but had unusual shuddering like movements and myoclonic jerks. An EEG was severely abnormal and consistent with an epileptic encephalopathy although not typical of hypsarrhythmia with a slightly more organised background. Urine organic acids revealed a moderate increase in 3-hydroxyisobutyric acid which was present, albeit to a somewhat lesser extent, on repeat testing. A 100mg/kg oral valine load resulted in marked elevation of her urinary 3-hydroxyisobutyric acid at 2–4 hours with a gradual to a moderately elevated level at 8 hours. Her symptoms did not worsen during the loading test. This confirms the finding of abnormal 3-hydroxyisobutyric acid metabolism but at this stage is not enough to establish a causative relationship.

NONINVASIVE PRENATAL DIAGNOSIS OF TRISOMY 21 USING FETAL PLAC4 RNA IN MATERNAL PLASMA (P43)

T. Bose,[1] C. Nicholls,[1] A. Gardner,[1] J. Thomas,[2] P. Muller,[2] J. Robinson[2] and S. Yu[1]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, South Australia*

[2] *Department of Obstetrics and Gynaecology, Women's and Children's Hospital, Adelaide, South Australia*

Current routine prenatal diagnosis is invasive and carries a 1–2 % risk of miscarriage. Several strategies have been investigated for noninvasive prenatal diagnosis (NIPD), including study of fetal cells and cell free fetal DNA in maternal circulation, and isolation of fetal cells from cervical lavage. This study aims to develop a methodology for NIPD using fetal RNA from maternal plasma. Data mining was used to select several genes on chromosome 21 with high placental and low leucocyte gene expression. Differential expression of the PLAC4 gene between placental tissue and maternal leucocytes was confirmed in our laboratory. SNP analysis of the PLAC4 gene using mother-baby pairs with differing genotypes confirmed that we can identify a fetal genotype in maternal plasma (RNA) without maternal contamination. No expression of the PLAC4 gene was

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found in maternal plasma post delivery, confirming clearance of fetal PLAC4 RNA after delivery. We have identified a polymorphic marker on the PLAC4 gene (c.5740_5741ins39, GenBank NM_182832) and tested its usefulness for NIPD in 15 mother-baby pairs. Four (two euploid and two trisomy 21) of 15 fetuses were heterozygous for c.5740_5741ins39. Allelic ratios were calculated using area under the curve (small allele/large allele) following capillary electrophoresis (CE). Allelic ratios of the two euploid fetuses were between 2-2.6, whereas allelic ratios of the two trisomy 21 fetuses fell outside this range (0.6 and 6.9). Our study has demonstrated in principle that the polymorphic PLAC4 marker c.5740_5741ins39 may be used for NIPD of trisomy 21 using standard PCR and CE methodology.

CLINICAL PRESENTATIONS WITH ABNORMAL O-GLYCANS (O19)

F. Bowling, T. Wallis and T. Munce
Mater Children's Hospital, South Brisbane, Australia

Genetic diseases that affect the biosynthesis of protein O-glycans are a rapidly growing group of disorders. The biological roles of oligosaccharides appear to span the spectrum from trivial to those that are crucial for the development, growth, function, or survival of an organism. Some O-glycosylation disorders affect only a particular O-glycan type, certain disorders affect more O-glycan types, and others also affect the biosynthesis of other glycoconjugates. The clinical variations within a disorder and among the different inborn errors of O-glycan metabolism are enormous. Disorders of O-glycosylation are known to cause a range of principally neuromuscular conditions but include familial calcinosis, multiple exostoses, skeletal dysplasia, Ehlers Danlos variants, corneal dystrophy, cerebellar syndromes, muscular dystrophy, and severe thrombocytopenia. O-glycosylation biosynthesis is a very complex process with an enormous number of genes involved. 24 different genetic disorders in O-glycosylation and 10 different genetic disorders that affect both N- and O-glycosylation have been described. We report key clinical, metabolic, and protein features of a cohort of 6 patients showing abnormal Apo-C III isoforms and normal Transferrin isoforms with a range of further symptoms including diabetes, optic atrophy, sialuria, myopathic weakness, and spinal muscular atrophy. The Apo-CIII isoforms showed increased asialo and mono-sialo patterns, excepting sialuria which had increased disialo. Further characterisation with mass spectrometry showed both specific and more general abnormal O-glycan structures.

MONITORING OF PROPIONIC ACIDEMIA (P13)

F. Bowling
Mater Children's Hospital, South Brisbane, Australia

The chronic treatment of propionic acidemia (PA) is challenging. Dietary protein must be judiciously prescribed to prevent overwhelming the residual capacity of the deficient enzyme, but at the same time providing adequate amino acids to prevent catabolism and support growth, for which the requirements vary from individual to individual and from time to time, particularly as a child grows. Intercurrent illness is a special risk. Recommendations for monitoring of PA include plasma ammonium, amino acids, or acylcarnitines, urine organic acids and ketones. The aim of this study was to compare the predictive value of laboratory analytes that can be used to monitor and assess patients with PA. *Study Design:* Nonrandomized masked evaluation 5 cases over a 6-month period. *Setting:* Two tertiary care children's hospitals. *Data:* Each child had regular testing (~q2/52) & also when unwell. Plasma ammonium, acylcarnitines (incl C3:C16 ratio), glycine, and urine methylcitrate, 3-HO-propionate, tiglyglycine were quantitated. *Outcomes:* All children presented to the hospital when unwell and were evaluated by experienced Pediatric Emergency Physicians who assessed the child as clinically 'Unwell'/'At risk' before laboratory investigations were known. *Analysis:* A Receiver Operating Curve Test comparison was undertaken to ascertain predictive values for 'Unwell/At risk'. Urinary methylcitrate was found to be the best predictor. Plasma ammonium was also a good predictor. Propionylcarnitine was not a good predictor. Urine methylcitrate is recommended as the most informative (and convenient) test for home monitoring.

MEASURING THE IMPACT OF GENETIC DISEASE IN THE WESTERN AUSTRALIAN POPULATION (O92)

K. Brameld,[1] S. Maxwell,[1] P. O'Leary[1] and J. Goldblatt[2]
[1] *Office of Population Health Genomics, Department of Health, Western Australia, Australia*
[2] *Genetic Services of Western Australia, Australia*

Aim: To measure the burden of genetic disease resulting from single gene or chromosome disorders in Western Australia as defined by cases receiving inpatient hospital care. *Method:* ICD codes for single gene and chromosomal disorders were identified in consultation with relevant experts. All hospital inpatient records with these codes in any diagnosis field were extracted from the WA Data Linkage System together with any other linked hospital records for the period 1980–2006. The resulting dataset was analysed to determine trends in the incidence, prevalence and hospital admissions for single gene and chromosome disorders in the WA population. *Outcomes:* The study will provide information on the burden of genetic disease in terms of single gene and chromosome disorders in Western Australia and the associated use of hospital services. This information will be used to inform service and policy development including the requirement for genetic testing, screening and counseling services according to demographic factors. The study will also provide data for the evaluation of genetic health services.

THE USE OF AFFYMETRIX 50K SNP ARRAY IN PATIENTS WITH INTELLECTUAL DISABILITY: THE SOUTH AUSTRALIAN EXPERIENCE (O34)

D. Bratkovic,[1,2] J. Nicholl,[2] E. Haan,[2] J. Liebelt,[2] E. Thompson[2] and S. Yu[2]
[1] *Department of Paediatrics and Child Health, Flinders University, Australia*
[2] *Department of Genetic Medicine, Children, Youth & Women's Health Service, Adelaide, Australia*

Array technology is revolutionising cytogenetics, particularly in the detection of micro duplications and deletions. 17 patients with intellectual disability and/or malformations were studied using a commercially developed SNP array platform (Affymetrix 50k SNP array) to assess the feasibility of using this platform for the investigation of such patients. *Methods and Subjects:* 17 patients selected into 3 clinical groups. *Group 1:* Apparently balanced chromosomal translocation and abnormal phenotype *Group 2:* Normal chromosomes and abnormal phenotype *Group 3:* Known chromosomal abnormality All patients were examined clinically and their phenotype documented and scored. DNA was tested using the Affymetrix 50k SNP array and confirmed by FISH; human genomic variation databases were checked to exclude known polymorphisms. *Results:* 18 copy number imbalances (CNI) were detected. *Group 1* (6 subjects, 9 CNI): One confirmed and presumably pathogenic abnormality — de novo 11q13.4 deletion at the insertion breakpoint of a visible 16p insertion into chromosome 11. *Group 2* (6 subjects, 8 CNI): One confirmed and presumably pathogenic abnormality — de novo 1q44 deletion. *Group 3* (5 subjects, 1 additional CNI): All known abnormalities detected. 7q22.1 deletion was detected in one subject. *Conclusion:* The Affymetrix 50k SNP array is a platform with high sensitivity for the detection of chromosomal copy number abnormalities. The high sensitivity is coupled with a high false positive rate making it ultimately unsuitable for use as a first line investigation. The detection rates seen in this study are similar to the reported literature; however, direct comparison is difficult due to small sample size.

GENOMEWIDE ASSOCIATION STUDIES: HOW WILL THEY IMPACT ON US? (O79)

M.A. Brown
Diamantina Institute of Cancer, Immunology and Metabolic Medicine, University of Queensland, Australia

The history of studies of the genetics of common diseases has until recently been one of much toil and little reward. All that changed in 2007, with the advent of the genomewide association study approach, pioneered by the Wellcome Trust Case Control Consortium (WTCCC). The WTCCC in one study identified 25 genes definitely associated with 7 common diseases, more than doubling the number of genes that had been identified for ANY common human disease previously. This has stimulated major efforts in most common human diseases using this approach, with numerous successes, but also leaving plenty of remaining challenges. Not all diseases have proven tractable to this approach, and for most diseases, only a small proportion of the overall genetic risk has been explained. Reasons for this include genetic heterogeneity, involvement of multiple variants in associated genes, epistasis, and in some cases, inadequate sample sizes. Most disease-associated polymorphisms identified have been associated with odds ratios of 1.1–1.3. This should not be surprising, as we knew from previous linkage studies that the genes involved in common diseases were likely to be common variants with small effect. A common misconception is that these genes are unimportant to find. The effect size of the genetic association in a population does not however directly correlate with the importance of the gene to a disease, as the genetic association depends on the extent and functional significance of the genetic polymorphisms present. The small effect sizes do impact on the utility of the genetic studies as diagnostic or prognostic tests. However even in these early days of such research, examples do exist where genetic findings are clearly of value in diagnosis. The era of the genomewide association study may not crack all genes or all diseases, but its impact will affect us all.

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GENETIC TESTING AND COUNSELLING FOR THALASSAEMIA IN PREGNANT COUPLES (P56)

S. Brown, L. Bristowe, L. Worgan and A. Colley

Department of Clinical Genetics, Liverpool Health Service, Liverpool NSW Australia

A retrospective study was conducted looking at the referrals for thalassaemia counselling in pregnant couples between 2003 and 2007 at the Liverpool Health Service. The Sydney South West population of 800 000 is a highly diverse multicultural society including people from various Middle Eastern and South East Asian countries. The majority of referrals regarding thalassaemia are received after a couple is pregnant and at least one partner has been identified as a suspected carrier due to low MCV and MCH levels on FBC. Many referrals are from general practitioners, although a significant proportion of pregnant women are not referred until they attend the Antenatal Clinic in their second trimester. Late referrals coupled with complex globin gene mutations often lead to limitations in our ability to offer prenatal diagnosis. Counselling and education of these couples is different to those who attend the genetics clinic early in pregnancy, and prenatal diagnosis is often only directed at future pregnancies. In couples where prenatal diagnosis is available, uptake is relatively high, with view to termination of an affected pregnancy. It is therefore important to see at-risk couples in the genetics clinic prior to, or as early as possible, in a pregnancy so that education about management and prognosis of children with thalassaemia major, and the option of prenatal diagnosis, is available.

MOLECULAR CHARACTERISATION OF TWO INTERSTITIAL CHROMOSOME DELETIONS USING ARRAY CGH AND FISH (P10)

S. Brown,[1] W. Waters,[1] J. Nicholl,[1] E. Haan,[2] R. Hutchinson[1] and T. Hocking[1]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *South Australia Clinical Genetic Service, Women's and Children's Hospital, Adelaide, Australia*

Case 1: An 8-year-old boy presented with mild delays/learning difficulties, behavioural issues and difficulty with social interaction. He has short stature (3rd percentile), bilateral esotropia (surgically corrected 2003), astigmatism and continuing strabismus. He has a past history of apparent hypoxia immediately after birth and earlier significant global developmental delay. Cytogenetic studies questioned the banding pattern of the long arm of one chromosome 10. A small deletion was suspected so further studies were initiated. Array CGH and FISH studies confirmed an interstitial deletion of 10q 26.2. Array CGH sized the deletion to be approximately 2Mb. FISH studies on parental blood chromosomes showed no abnormalities of this region. *Case 2:* Chromosome analysis on blood from a 4-year-old boy with global developmental delay (especially speech) showed an interstitial deletion in the short arm of one chromosome 5 from p15.1 to 15.31. FISH studies using the Vysis Cri-du-Chat probe (D5S23) and a 5p subtelomeric probe confirmed the interstitial deletion. Subsequent FISH studies using probes specific for the cry, dysmorphism and speech regions showed all to be deleted and allowed the size of the deletion to be estimated at 6Mb. Array CGH(with FISH confirmation) also sized the deletion at approximately 6Mb and allowed for further definition of the deletion breakpoints. In addition, comparison with published data on the cry, dysmorphic features and speech regions in Cri-du-Chat syndrome was possible.

A MODULAR VIEW OF GENETIC DISEASES (O50)

H. G. Brunner

Department of Human Genetics, Nijmegen University medical Center, Nijmegen, the Netherlands

When Victor McKusick started compiling all known conditions in man that have Mendelian inheritance, he created an alphabetic list of disease entities sorted by inheritance pattern. OMIM represents an up-to-date description of the human phenome, at least as far as monogenic diseases are concerned. An instant hit 40 years ago, the Online Mendelian Inheritance In Man knowledgebase now has over 5000 diseases, and is a fantastically useful resource for those practicing medical genetics, as well as for anyone trying to understand the genetic basis of human diseases. But there is obviously more to the human phenome than a list of diseases. For instance, what appears to be clinically one disease may turn out to have a number of different pathogenetic mechanisms when viewed at the gene expression or protein level. Similarly, even for a single pathogenetic mechanism the actual genes may vary, reflecting genetic heterogeneity. Most importantly, viewing the human phenome as a simple list of diseases ignores the fact that separate genetic diseases may share some or all of their pathogenesis. When this shared pathogenesis is reflected in phenotypic overlap, we have to decide whether we should regard these diseases as distinct entities, or as variants of one (meta-) disease. This is commonly called a splitter and lumper debate, terms for which the use again dates back to early work by Victor McKusick. Such splitter and lumper debates are now commonly resolved by molecular studies, and the message is that phenotypic overlap is a very good predictor of functional relatedness of the underlying genes. A striking example of shared pathogenesis that is reflected by overlapping phenotypes is the occurrence of cystic kidneys, retinal degeneration, polydactyly and brain malformations in an expanding list of genetic conditions due to mutations in genes encoding components of the cilium. Because of this overlap in phenotype, researchers can make a pretty good guess even by clinical phenotype alone of what conditions are potential ciliopathies. From this and other examples, it has been hypothesized that phenotypic overlap may be a general indicator of shared pathogenesis. This concept has been validated in a number of recent studies. Some of this pathogenic overlap involves homologous genes that perform similar functions, while other overlap involves the proteins that are involved in the same pathways, for example, through protein-protein interactions. As an example of the latter, we can see how a number of proteins involved in retinal, renal, and brain diseases all interact molecularly. Interestingly, the phenotypes associated with mutations in these genes also form a group of overlapping syndromes or a syndrome family. Our results and those of others link together into one network, the genes underlying various forms of retinitis pigmentosa, including Leber congenital amaurosis with nephronophthisis, senior Loken syndrome, and the more complex Meckel, and Joubert syndromes.

'GENOTYPE TO PHENOTYPE' DIAGNOSIS USING MICROARRAY ANALYSIS (O129)

D. Bruno,[1] J. Schoumans,[1] D. Ganesamoorthy,[1] C. Ngo,[1] L.Hills,[1] W. Francis,[1] B. Kenney,[1] D.Amor[2] and H. Slater[1]

[1] *Cytogenetics Laboratory, VCGS Pathology, Australia*

[2] *Genetic Health Services Victoria, Murdoch Children's Research Institute, Royal Children's Hospital, Australia*

Commercial microarrays and software are now available to cytogeneticists for detection of submicroscopic chromosome analysis at levels of resolution which were unimaginable only a few years ago. However, several problems still need to be solved inculding quality control, standardization of methodology and reporting, validation of results and most importantly distinction of pathogenic from benign copy number variation (CNV). Notwithstanding these challenges, several reports have been published within the last 12 months describing numerous new syndromes associated with specific CNVs in children with an idiopathic mental retardation (MR)/ congenital abnormality (CA) disorder but a normal karyotype. Having identified the first case, others have been identified by either screening a large number of samples from MR/CA patients with a locus specific test or through searching for similar genome screen results in laboratory consortia and/or databases. These early findings promise considerable improvements in diagnosis with approximately 15–20% of idiopathic cases showing association with a convincing pathogenic CNV. We have completed a pilot study of 120 similar cases where, with the agreement of referring clinical geneticists, requested microdeletion tests have been replaced with genome screens using 250k Affymetrix microarrays. 16% of these cases were found to have a pathogenic CNV, either a well-established syndrome or a recently described one. This so-called 'genotype to phenotype' approach promises very significant advantages of diagnostic speed, lower laboratory testing costs, and genomic descriptions of the underlying mutation but it also prompts urgent need for policies on the types of referral that are appropriate for microarray analysis.

OUR EXPERIENCE OF USING AFFYMETRIX 250K MICROARRAYS FOR CYTOGENETIC DIAGNOSIS (O33)

D. Bruno,[1] J. Schoumans,[1] D. Ganesamoorthy,[1] C. Ngo,[1] L. Hills,[1] W.Francis,[1] B. Kenney,[1] D. Amor[2] and H. Slater[1]

[1] *Cytogenetics Laboratory, VCGS Pathology, Australia*

[2] *Genetic Health Services Victoria, Murdoch Children's Research Institute, Royal Children's Hospital, Australia*

Commercial microarrays are now available for detection of submicroscopic chromosome analysis at levels of resolution that were unimaginable only a few years ago. The promise of this technique has been shown within the last 12 months with description of several new microdeletion and microduplication syndromes. Our own data from a pilot study of 120 children with idiopathic mental retardation with or without other congenital abnormalities includes many of these new syndromes suggesting they are relatively common. There is some suggestion than many others will be private mutations but it is too early to know if this will be the case. Despite the obvious promise of microarray analysis, there are several issues that still need addressed at the individual laboratory level before this can be seen as a robust and established analytical method. These include choice of platform and analytical software, the challenge of processing and storing vast amounts of data, quality control, setting resolution limits, determination of inheritance, distinction of pathogenic from polymorphic copy number variation, nomenclature, reporting and training. At a general level, there are issues of standardization of reporting, contribution to databases to facilitate interpretation, ethics of genome screening

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of phenotypically normal parents, accreditation of scientists and laboratories and last but not least funding. The presentation will describe our approach to data analysis, threshold setting, confirmation, interpretation and reporting. Our findings have significant impact on setting guidelines for our clinicians to refer suitable cases that are likely to be much broader than originally expected.

VALIDATION OF A-CGH IN POLAR BODY ANALYSIS (O134)

T. Buchholz,[1] M. Klehr-Martinelli,[1] B. Seifert[2] and M. Bals-Pratsch[2]

[1] *Centre for Polar Body Diagnosis, Gyn-Gen-Lehel, Munich, Germany*

[2] *Center for Reproductive Medicine, Regensburg, Germany*

Chromosomal aneuploidies are the major cause of pregnancy loss or implantation failure. Therefore many efforts were made for the detection of aneuploidies in preimplantation diagnostic. In the past years we were able to gain much experience with polar body (PB) analysis by fluorescence in situ hybridisation (FISH). Both aneuploidy testing and translocation analysis are well established in our lab. The main disadvantage of this technique is that only a maximum of 10 chromosomes can be analysed during the restricted time frame due to the german embryo protection law. In order to be able to analyse all 23 chromosomes, an accurate and stable procedure to amplify a single cell to get a sufficient amount of DNA has to be carried out. Different approaches for single cell amplification were evaluated for example DOP-PCR, linker adapter PCR or whole genome amplification with different kits. Benefits and downsides will be discussed. Amplified PB DNA as well as amplified oocyte DNA was used for validation for new approaches in PB analysis, particularly for different CGH-arrays. Computer assistant analysis cut the time from start to result to a maximum of 20h by using a bac CGH-array. Alterations in various features, ie. amount of PB and oocytes DNA, hybridisation time, kind of reference DNA, with or without dye swab, were studied and will be discussed. Particular interest was given to the phenomenon of Y-chromosome hybridisation, despite Y DNA in PBs and oocytes and strict contamination precautions. This peculiarity will be discussed in consideration of the literature.

FETAL LIVER CELL TRANSPLANTATION FOR METHYLMALONIC ACIDURIA USING MICE WITH AN INTERMEDIATE PHENOTYPE (O58)

N. E. Buck,[1] S. D. Pennell,[1] L. Wood,[1] J. Pitt,[2] K. J. Allen[3] and H. L. Peters[1]

[1] *Cell & Gene Therapy Group, Murdoch Childrens Research Institute and Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia*

[2] *VCGS Pathology, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia*

[3] *Gut and Liver Research Group, Murdoch Childrens Research Institute and Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia*

We aim to investigate the use of fetal liver cells for the treatment of methylmalonic aciduria (MMA) using a mouse model with an intermediate phenotype of MMA. Fetal liver cells (embryonic day 16–18) from congenic enhanced green fluorescent-tagged mice were transplanted into a MMA mouse model and then culled 4 weeks later. Donor cell engraftment was determined using quantitative real time PCR and flow cytometric analysis. Disease correction in these mice was assessed based on urine and plasma MMA concentration and mouse weight change. Initial studies indicated that optimal conditions for fetal liver cell transplantation included pre-transplantation sublethal irradiation followed by transplantation with 5 million cells. Fetal liver cells delivered via the tail vein were able to engraft and repopulate liver, spleen and BM of wildtype and MMA mice at 4 weeks posttransplantation. We anticipated an equivalent level of donor cell engraftment between wildtype and MMA mice in the absence of selective advantages based on underlying pathological damage. Surprisingly, the MMA mouse model demonstrated reduced bone marrow and liver engraftment. Disease correction was not effected within the study time frame. Higher levels of engraftment than those seen in this study or allowing longer experiment times may be required for correction of disease. The potentially inhibitory effect of elevated organic acids on bone marrow and liver engraftment warrants further investigation. In conclusion, liver engraftment of a mouse with mild metabolic liver disease transplanted with donor fetal liver cells is possible; however, the methods need to be modified to affect the disease condition.

A GENOME WIDE SCAN FOR GENETIC MODIFIERS OF PSEUDOEXFOLIATION SYNDROME (O95)

K. P. Burdon,[1] A. W. Hewitt,[1] M. Brown,[2] P. Mitchell,[3] S. Sharma[1] and J. E. Craig[1]

[1] *Department of Ophthalmology, Flinders University, Australia*

[2] *Musculoskeletal Genetics Group, UQ Diamantina Institute, The University of Queensland, Australia*

[3] *Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Australia*

Pseudoexfoliation (PEX) syndrome is an age-related disorder characterized by accumulation of fibrillar extracellular deposits in the anterior ocular structures. It is the single largest known cause of glaucoma, a common, blinding disease. Recently, common coding variants in the LOXL1 gene were associated with PEX, however, many unaffected individuals carry the risk allele, suggesting that additional factors contribute to the risk of PEX. We have undertaken a pilot genome-wide scan to identify these genetic factors. We have obtained genome-wide SNP data for 109 PEX cases and 50 elderly controls with no PEX but homozygous for the LOXL1 risk allele. This strategy is expected to provide improved power to identify factors that modify the LOXL1 associated risk in carriers. Preliminary analyses reveal several regions of association besides LOXL1. Of particular interest is a cluster of SNPs on chromosome 16, adjacent to the MAF gene that has been previously implicated in ocular disease. Four SNPs in this region show p values for association of 0.00007 or less (OR 0.33, 95%CI: 0.19–0.55). The inclusion of 1500 historic controls used by the Wellcome Trust Case Control Consortium, increased the level of significance to $p = 2.1 \times 10\text{-}8$, lifting this region to genome wide significance. SNPs with associations at the $p = 1 \times 10\text{-}5$ level are also found on chromosomes X, 4, 6, 7, 10, 11 and 14. These SNPs are intragenic in plausible candidates including TRAF3, components of the complement pathways and multiple genes in the MAP kinase stress response pathway. These findings are undergoing follow-up in additional PEX cases and controls.

CONSECUTIVE DIFFERENT TRISOMIES IN AN ADVANCED MATERNAL AGED WOMAN. INHERITED PREDISPOSITION OR CHANCE? (P1)

M.J. Burgess

Nepean Hospital, Sydney West AHS, Australia

HS, a 41-year-old woman, pregnant for the third time, was referred to the Department of Clinical Genetics for advanced maternal age prenatal genetic counselling. Her first pregnancy was discovered to have trisomy 18 after a high risk nuchal translucency ultrasound scan followed by an amniocentesis. Her second pregnancy was found to have trisomy 21 diagnosed from a rapid FISH taken from a chorionic villus sample (CVS). With this current pregnancy, after counselling HS decided to undergo both a nuchal translucency ultrasound scan (screening test) and CVS (diagnostic test). The tests revealed a normal male karyotype; 46, XY. During the initial session, the genetic counsellor gave HS her age related risk as her risk of having another pregnancy with a trisomy. The concept of a woman's age related risk and the fact that this history could be due to chance were discussed. Interesting genetic counselling issues such as a client who is determined to have both a screening and definitive test is explored. A review of the current literature on recurrent trisomies is also included.

VITAMIN K EPOXIDE REDUCTASE COMPLEX SUBUNIT 1 GENE POLYMORPHISM IN THE MANAGEMENT OF WARFARIN DOSING (P38)

K.A. Byron, K. Riordan and A. E. Dear

Molecular Diagnostics, Gribbles Pathology, Australia.

Warfarin is the most frequently prescribed oral anticoagulant in Australia. Its use is problematic due to the narrow therapeutic range and significant inter-individual variability in response to standard doses. Recent identification of a single nucleotide polymorphism (SNP) at position –1639 in the vitamin K epoxide reductase complex subunit 1 gene (VKORC1) has been identified as contributing significantly to the anticoagulant effect of warfarin. We aimed to determine, in an Australian population, the genotype frequency of the VKORC1 (–1639) SNP and its effect on the warfarin maintenance dose in patients attending an anticoagulation clinic. 150 de-identified DNA samples from a random population were selected to determine the genotype frequency of the VKORC1 (–1639). 46 patients attending a routine anticoagulation clinic were selected for VKORC1 (–1639) genotyping and correlation with maintenance warfarin dose. VKORC1 (–1639) genotype frequencies in a random Australian population were found to be: wild type GG (41%), variant GA (45%) and variant AA (14%). Maintenance dose of warfarin was highest within the GG genotype (mean = 4.1 mg), and lowest in the AA (mean = 1.7 mg) genotypes. These results confirm that the VKORC1 (–1639) SNP is present in an Australian population with frequencies that approximate those previously described and that functional sequelae in relation to warfarin dose is observed depending on the VKORC1(–1639) genotype in the setting of the anticoagulation clinic.

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THE REVISED NUTRIENT REFERENCE VALUES: RELEVANCE AND ROLE IN MANAGING CHILDREN WITH INBORN ERRORS OF METABOLISM (O14)

S. Capra

Faculty of Health Sciences, University of Queensland, Australia

The recommendations for nutrient intakes were unchanged in Australia for many years. From 2002-2005, the National Health and Medical Research Council undertook a rigorous, formalised review process to establish values for use with Australia and New Zealand. Starting with a review of the US values released throughout the 1990's, expert reviewers were engaged to undertake updated reviews of each nutrient with reference to the Australian and New Zealand context. These reviews were then closely evaluated by a working party comprised of individual experts and representatives from the nutrition community (DAA) and the food industry (Australian Food and Grocery Council). Forty-two nutrients were viewed with final recommendations for reference values for thirty-three. Estimated average requirements, adequate intakes, upper limits and recommended dietary intakes have been developed. In addition, acceptable macronutrient distribution ranges and dietary targets for optimising diets for lowering chronic disease risk have been included. Together these recommendations make up the nutrient reference values (NRVs). The completed document was published in 2006. For nutrition professionals, there are challenges in terms of long held views on adequate diets, food groups and optimal macronutrient ranges. The NRV changes are the most significant change that nutritionists will face this decade. The challenge for professionals is in the interpretation, especially when they may form part of the clinical decision making for groups for who they were not intended. In children especially, the evidence base is often weaker, with extrapolations from breast fed infants and adults forming the basis of some of the recommendations. Children with specific needs pose particular challenges as our duty of care must be weighed against real evidence. This presentation will explore these issues in detail and pose the question — how are the NRVs to be used in practice with children with special nutritional and metabolic needs?

INTRODUCTION OF A CYSTIC FIBROSIS SCREENING KIT FOR INFERTILE COUPLES: 1 YEAR'S EXPERIENCE (O4)

L. Carey, A. Trninic, M. Hipwell, J. Campisi and D. Leigh

Sydney Genetics, Australia

With a carrier frequency of 1/25, cystic fibrosis (CF), is one of the most common autosomal recessive disorders in the Caucasian Australian population, While it is usually only considered for its affects on the lungs, digestive system and sweat glands, CF mutations are also associated with male infertility and can result in forms of obstructive azoospermia such as congenital bilateral absence of the vas deferens (CBAVD) and congenital unilateral absence of the vas deferens (CUAVD). Common variants in the poly-T tract of intron 8 can play an important role in the presence of this phenotype. Couples seeking assistance for infertility may therefore be at a higher risk of carrying a CF mutation than the general population. Over a year ago, we introduced a simple CF screening kit to help our team of health professionals with the resources to be able to offer all couples simplified access to CF screening for either the Delta F508 mutation or a comprehensive test for 33 CF mutations. The screening kit includes pre-counselling information and a collection kit with support offered via a free CF information line as well as post-test counselling being available. Since the introduction of the screening kit over 2500 tests have been performed and a positive test result has been found in 108 cases.

TOXICOLOGY AND BIOCHEMICAL GENETICS — CLOSER THAN YOU THINK (O18)

K. Carpenter

NSW Biochemical Genetics Service, The Children's Hospital at Westmead, Australia

The techniques and investigative approaches used in Biochemical Genetics mirror those in clinical and forensic toxicology. Searching for an unknown toxin, whether exogenous or endogenous in nature, may lead us on an unexpected journey of discovery. A urine sample for metabolic screen was received from a 22-month-old boy presenting with short history of reduced level of consciousness and ataxia. Organic acids revealed increased 4-hydroxybutyrate but no 4,5 dihydroxyhexanoate lactone. Repeat sample 4 days later showed no abnormalities, consistent with ingestion of the recreational drug GHB. The family denied access to GHB but indicated the child had swallowed a large number of toy beads (Bindeez), some being vomited, others later appearing in the stool. We placed a small number of beads in water and performed organic acids to test for possible GHB. No GHB was found but a substantial unknown peak was seen which prompted further investigation. A literature search for precursors of GHB was matched with molecular weight and retention time data of the unknown peak and showed a likely release of 1,4 butanediol from the beads, later confirmed. NSW Office of Fair Trading were notified of our findings. A second case of poisoning following ingestion of Bindeez presented to our hospital 4 weeks after the first case. The following day, authorities moved to remove the products from sale and a worldwide recall followed within 24 hours. Previous cases were reported from NZ, USA and UK but none had undergone testing for metabolic disease.

TUMOUR TISSUE IS THE SAMPLE OF CHOICE FOR TESTING IN NF2 PATIENTS WITHOUT A FAMILY HISTORY (O85)

J. Carroll,[1] B.Mercorella,[1] Z. Rudzki,[1] G. Suthers[2] and L.Rawlings[1]

[1] *Institute of Medical and Veterinary Science, Adelaide, Australia*

[2] *South Australian Familial Cancer Unit, Children, Youth and Women's Health Service, Australia*

The neurofibromatosis 2 gene encodes a protein termed merlin (or schwannomin) that links the cytoskeleton to the cell membrane. Constitutional heterozygous inactivating mutations in this tumour suppressor gene cause the autosomal dominant disease Neurofibromatosis Type 2 (NF2). Clinically, NF2 is characterised by nervous system tumours and ocular abnormalities. Vestibular schwannomas, usually bilateral, occur in more than 90% of adult patients and intracranial meningiomas occur in about 50% of patients. Around half of individuals with NF2 have an affected parent and the remaining have NF2 as the result of a de novo gene mutation. Traditionally, molecular genetic testing has been confined to the analysis of blood in all patients presenting with NF2. However, a reported 25–30% of patients with no family history of the disease have somatic mosaicism. Analysis of a blood sample in these mosaic individuals will therefore fail to detect a mutation.* 76 probands have been tested for mutations in the NF2 gene by DNA sequencing and MLPA since 2002. The rates of mutations detected in this cohort are compared across various tissue types for individuals with and without a family history of the disease. Our experience will demonstrate that in NF2 patients with no family history, tumour tissue should be tested in the first instance.

* Kluwe, L., et al. (2005) Screening for large mutations of the NF2 gene. *Genes Chromosomes Cancer, 42*, 384–391.

CLARIFYING THE HEREDITABILITY OF DISEASE THOUGHT THE USE OF TUMOUR TISSUE ANALYSIS (O45)

J. Carroll,[1] Z. Rudzki[1] and G. Suthers[2]

[1] *Division of Molecular Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia*

[2] *Familial Cancer Unit, Department of Genetic Medicine, Children's Youth and Women's Health Service, Adelaide, Australia*

Molecular genetic testing routinely involves the analysis of blood leukocytes in affected individuals to identify the mutation that may have predisposed them to their disorder. In our experience however, the use of tumour analysis in some patients has proven useful in clarifying the hereditability of their disease. Retinoblastoma is a rare paediatric eye cancer that can present as either bilateral or unilateral disease. Bilateral disease is usually heritable and patients remain at increased risk of sarcoma and melanoma in early adult life. Their close relatives are also at high risk of developing retinoblastoma or related malignancies. Unilateral disease is generally somatic and the above concerns do not apply. In bilateral disease mutations in the RB1 gene are present in both peripheral blood and in the tumour while in unilateral disease they only occur in the tumour. This allows the distinction of heritable from nonheritable disease. Many families seek clarification of their disease hereditability when considering reproductive options. Consequently, tumours need to be tested. These samples only exist as formalin-fixed, paraffin-embedded tissue (FFPE) and are frequently some 20 to 30 years old. Mutation detection in such samples can be technically challenging. The major problems are with the quantity and quality of the DNA remembering that sufficient DNA is required to amplify and sequence the 27 exons of the RB1 gene, to perform loss of heterozygosity analysis and determine the methylation status of the promoter. Details of our analysis strategy will be described.

CRYPTIC REARRANGEMENTS WITH PATHOGENIC SIGNIFICANCE AND POSSIBLE PROGNOSTIC INDICATIONS IN HAEMATOLOGICAL DISORDERS (O36)

N. Chia,[1] C. Parmigiani[1] and M. Pidcock[2]

[1] *Cytogenetics Department, ACT Pathology, Canberra Hospital Woden, Australia*

[2] *Haematology Department, ACT Pathology, Canberra Hospital Woden, Australia*

Nonrandom rearrangements have long been associated with the process of leukemogenesis. The use of molecular cytogenetic techniques has changed the characterisation of these abnormalities with the detection of cryptic rearrangements. The prediction of the prognostic significance of variant forms of nonrandom rearrangements remains unclear. This report describes the interpretation of atypical FISH signal patterns observed on what appeared to be cytogenetically common non-random rearrangements

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or a normal karyotype. *BCR-ABL1* plays a pivotal role in the pathogenesis of CML, and other leukemias. Deletions of BCR/ABL1, or BCR or ABL1 have been reported in approximately 15% of t(9;22). We report on two cases of the cryptic deletion detected by FISH investigation. *PML/RARA* is the critical fusion detected in APML. We present two cases, detected by FISH, of a cryptic insertion of the PML into chromosome 17 within the RARA locus, subsequent to a normal karyotype. Inv(16)(p13q22) is a non random rearrangement associated with AML M4Eo. We present two cases with a cryptic rearrangement involving the deletion of the 3' CBFB in one case and a complex rearrangement involving translocation and inversion in a second case. All of these cases are cryptic rearrangements that require correlation between the routine karyotype and FISH investigation. These findings have both treatment and prognostic significance. We present the cytogenetic, haematology and clinical finding over a 12-month period, together with a review of the literature.

NONIMMUNE HYDROPS FETALIS AND FETAL ASCITES ASSOCIATED WITH LYSOSOMAL STORAGE DISORDERS (P22)

S. Chin, B. Fong, C .Nicholls, T. Pyragius, K. Barnard, K. Whenan, A. Leo, K. Nelson, V. Muller, P. Clements and M. Fietz

National Referral Laboratory, Department of Genetic Medicine, Women's and Children's Hospital, CYWHS, Adelaide, Australia

Background: Hydrops fetalis is a description used for generalized edema of the fetus where there is fluid accumulation in the body cavities, the cause being immune or nonimmune. Numerous individual lysosomal storage disorders (LSD) have been shown to cause nonimmune hydrops. Therefore, the National Referral Laboratory (NRL) has for over 15 years been performing a biochemical hydrops screen for up to 17 LSD. *Aim:* To perform a retrospective review of the nonimmune hydrops fetalis cases, including cases of isolated fetal ascites, referred to the NRL from 1992 to 2007. This is to include an analysis of the specific clinical presentation associated with each affected case. *Results:* A total of 105 cases have been referred to the NRL. Of these, we have identified an inherited metabolic cause in about 13% of cases, with the diagnoses including mucopolysaccharidosis type VII (MPS VII), multiple sulfatase deficiency (MSD), congenital disorder of glycosylation type Ia (CDG-Ia), Gaucher disease, galactosialidosis, mucolipidosis type I (sialidosis), sialic acid storage disorder, and Niemann-Pick disease type C. *Conclusion:* Our study confirms the importance of testing for LSD, and other inborn errors of metabolism, in nonimmune hydrops fetalis and cases of isolated fetal ascites. With a precise diagnosis, accurate genetic counselling and prenatal studies for future pregnancies can then be offered.

GENOME-WIDE LINKAGE ANALYSIS OF A FAMILY WITH FAMILIAL HYPERTROPHIC CARDIOMYOPATHY (O73)

C. Chiu,[1,2] J. M. Lind,[3] J. Ingles,[1,2] J.A. Donald [4] and C. Semsarian [1,2,5]

[1] *Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney, Australia*

[2] *Faculty of Medicine, University of Sydney, Australia*

[3] *School of Medicine, University of Western Sydney, Australia*

[4] *Department of Biological Science, Macquarie University, Australia*

[5] *Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia*

Familial hypertrophic cardiomyopathy (FHC) is a disorder characterised by genetic heterogeneity. The genetic cause in up to 50% of FHC cases remains unknown, after routine genetic screening of 8 common FHC genes. This study describes a genome-wide linkage analysis of a 3-generation FHC family with 7 affected individuals where the genetic cause of disease is unknown, after FHC gene screening. The affected individuals have a severe disease phenotype, with 4 requiring an implantable cardiac defibrillator and another dying suddenly from disease. Markers from the 10cM AB PRISM human linkage mapping set (400 microsatellite markers) were genotyped. Two-point linkage analysis was performed using MLINK (version 5.1). LOD scores were calculated for each marker assuming an autosomal dominant mode of inheritance for disease, a penetrance of 95%, a disease allele frequency of 0.001, and equal allele frequencies for the genotyped markers. Suggestive linkage to chromosome 1 at 1q42.2-q43 (LOD = 1.57, $\vartheta = 0.05$), chromosome 4 at 4q31.21 (LOD = 1.65, $\vartheta = 0.05$) and chromosome 17 at 17p13.1 and 17p12 (LOD = 1.65, ϑ=0.05) was identified. Fine mapping of an additional 26 microsatellite markers at these loci supported linkage at 1q42.2–q43 with a maximum LOD score of 2.82 at $\vartheta = 0$ for marker D1S2850. Construction of haplotypes using 10 markers flanking D1S2850, indicated the linkage region is located between markers D1S2800 and D1S2670. This region represents a 5.7Mb interval containing approximately 38 genes. Candidate genes in this region are currently being selected and screened for mutations based on their expression and function in the heart.

FRAGILE X SYNDROME: DILEMMAS ASSOCIATED WITH PILOT STUDY OF NEWBORN SCREENING (O3)

L. Christie, C. Rogers, J. Boyle, S. O'Donnell, A. Hackett and M. Field

GOLD Service, Hunter Genetics, Newcastle, Australia

There is increasing demand to expand current newborn screening protocols to include other genetic conditions which currently do not meet World Health Organisation criteria. The driving force for this is technological advances, increased availability of genetic testing, public acceptance and consumer demands. Newborn screening for fragile X syndrome is an excellent prototype in assessing a new model for these conditions. We report some of the benefits and dilemmas arising from our pilot study examining the feasibility and acceptability of newborn screening for fragile X syndrome. The study was approved by two ethics committees. 200 male and female newborns were tested. The uptake of participation was 94%. All wanted to know if their newborn had a premutation or a full mutation. One premutation male was identified. An early diagnosis enables appropriate interventions, avoids an arduous medical odyssey and enables reproductive choices for parents and families. We would like to discuss the psycho-social impacts of an early diagnosis, advantages and disadvantages of carrier testing of children and predictive testing for premature ovarian failure and fragile X-associated tremor-ataxia syndrome. Other issues for consideration include timing of testing and best practice for obtaining informed consent. The introduction of newborn screening for fragile X syndrome is controversial and discussion within the genetic counselling profession will be valuable to identify potential outcomes, minimize harms and promote benefits.

TPM2 IS ONE GENETIC CAUSE OF CAP DISEASE (O102)

N. F. Clarke,[1] A. Domazetovska,[1] L. B. Waddell,[1] B. Ilkovski,[1] A. Kornberg,[2] C. McLean[2] and K. N. North[1]

[1] *Institute for Neuromuscular Research, Children's Hospital at Westmead, Discipline of Paediatrics and Child Health, University of Sydney, Australia*

[2] *Department of Neurology, Royal Children's Hospital, Melbourne, Australia*

Cap disease is a rare congenital myopathy characterised histologically by pale peripheral crescents (cap-like structures) in type I muscle fibres. In 2007, a heterozygous *TPM2* mutation was found to cause cap disease in two patients.[1,2] We report the third case of *TPM2* cap disease and explore the basis of muscle weakness. The patient is a 10 year old girl with congenital hypotonia and moderate generalised weakness. On muscle biopsy she had congenital fibre type disproportion (CFTD) with rare subsarcolemmal protein inclusions consistent with cap disease. EM showed normal sarcomeric structure and rare cap structures composed mainly of disorganised thin filaments. We screened the patient's *TPM2* coding region and identified the same heterozygous de novo c.415_417delGAG mutation as reported in the original patient[1]. Our patient followed a similar clinical course, developing scoliosis and significant respiratory muscle weakness in adolescence, while fully ambulant. Echocardiography showed reduced systolic cardiac function, a novel association of cap disease. We have subsequently excluded *TPM2* mutations in another patient with typical cap disease, suggesting genetic heterogeneity. Molecular modelling predicts the c.415_417delGAG mutation to remove a glutamic acid residue (E138) from the centre of beta-tropomyosin, disrupting the regular septad repeating amino acid sequence fundamental for tropomyosin dimerisation. Unexpectedly, 2D-gel electrophoresis demonstrated equal quantities of mutant and wild-type beta-tropomyosin in the sarcomeric protein fraction of patient muscle. Since sarcomeric structure is normal by EM, we hypothesise that muscle weakness arises due to a dominant negative effect of the mutant protein on sarcomeric function, most likely from abnormal actin-tropomyosin interactions.

1. Lehtokari, V. L. (2007). *Neuromuscular Disord, 17*(6), 433–442.

2. Tajsharghi, H. (2007). *Arch Neurol, 64*(9), 1334–1338.

IMPROVED DIAGNOSIS OF POMPE DISEASE BY IMMUNE CAPTURED ENZYME ASSAY OF LEUCOCYTE EXTRACTS (P32)

P. R. Clements, N. Hatzirodos and M. J. Fietz

National Referral Laboratory, Department of Genetic Medicine, Women's and Children's Hospital, CYWHS, Adelaide, Australia

Pompe disease is a lysosomal storage disorder caused by a deficiency of acid α-glucosidase. Traditionally, Pompe disease has been diagnosed by analysis of either cultured fibroblasts or a muscle biopsy. Analysis of leucocytes has been compromised by the presence of maltase glucoamylase, which is also able to digest the artificial substrate for acid α-glucosidase at acid pH. Over 7 years ago, the National Referral Laboratory (NRL) commenced using an immuno-capture method for isolating acid α-glucosidase, enabling diagnosis of Pompe disease from dried blood spots[1]. This has led to the diagnosis of over 30 cases of Pompe disease. However, analysis has been complicated by variability in factors such as leucocyte counts, protein

elution and suitable standards. This has led to a number of equivocal results. We have recently commenced using immuno-capture to isolate acid α-glucosidase from leucocyte extracts. Given the increased concentration of enzyme, this has allowed a reduction in incubation time from 24h (as used for dried blood spots) to 2h. In addition, activity can now be calculated against protein concentration, allowing standardization for leucocyte count. To ensure consistency between assays, recombinant acid-glucosidase is used as a quality control standard. To date, results generated from leucocyte analysis are consistent with those from dried blood spots and have allowed the confirmation of one affected case. Further studies are being performed to generate a normal range and assess the improvement in the sensitivity of the assay.

COMPARISON OF URINE SCREENING FOR MPS WITH TANDEM MASS SPECTROMETRY VERSUS CELLULOSE ACETATE ELECTROPHORESIS (O30)

P. R. Clements, G. Owens, M. Fietz, J. R. Harrison, M.Fuller and J. Hopwood

National Referral Laboratory, Department of Genetic Medicine, Women's and Children's Hospital, CYWHS, Adelaide, Australia

Traditionally screening of urine for mucopolysaccharidosis (mps) disorders has involved analysis using a cellulose acetate electrophoretic (CAE) method[1] followed by confirmatory analysis using three or four enzyme assays. Electrospray tandem mass spectrometric (ESI-MSMS) methods have been developed for the quantitative determination of accumulated oligosaccharides in the urine of patients referred to the National Referral Laboratory with a suspected mps disorder.[2] The new method enables not only identification of an MPS but also the subtype thus reducing the confirmation to one enzyme assay. The method involves the derivatisation of oligosaccharides in referred urine samples and the relative levels of 11 sulphated oligosaccharide are measured in multiple reaction monitoring mode by reference to an internal standard. A trial comparison of the two methods over 2 years was conducted over the period January 2006–January 2008. Urine samples (372) referred for mps screening were analysed by both methods. 58 mps cases were detected by both MSMS and by CAE. The MSMS method has been shown to be as reliable as the HVE method and reduces confirmatory assays, time and costs.

1 Hopwood, J. J., & Harrison, J. R. (1982). *Anal Biochem, 119*(1), 120–127.

2 Fuller, M, et al. (2004). *Paediatric Res, 56,* 733–738.

ADAM 12 A PROMISING NEW MATERNAL SERUM MARKER IN SCREENING FOR DOWN SYNDROME IN BOTH FIRST AND SECOND TRIMESTERS OF PREGNANCY (P36)

R. Cocciolone, R. Bird, E. Martin, D. Penhall and L. Raniolo

Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia

Aim: To assess the ability of a new marker (ADAM 12) to better detect Down syndrome affected pregnancies. Introduction: ADAM 12 a placental glycoprotein has been shown as a potential new marker in two separate studies, one in first trimester and the other in second trimester. We further assess this potential across both trimesters. *Methods:* Levels of ADAM 12 were determined retrospectively from stored frozen maternal serum in 47 first trimester and 28-second trimester Down syndrome affected pregnancies and 306 unaffected matched controls. 60 false positive matched first and second trimester same pregnancy samples were also used to assess reductions in false positive rates if ADAM 12 was included in the risk odds calculation. Medians for ADAM 12 were determined from the unaffected controls using polynomial regression. Likelihood ratios derived from log transformed MoM multivariate overlapping Gaussian distributions were used to calculate risks odds of an affected from maternal age risks at delivery. *Results:* ADAM 12 levels were significantly reduced ($p <$ .001, Median MoM = 0.82) in first trimester affected pregnancies but significantly elevated ($p <$ .001, Median MoM = 1.5) in second trimester affected pregnancies. New performances with the inclusion of ADAM 12 into current first and second trimester protocols were; first trimester 3% false positives and 91.5% detection, second trimester 5% false positives and 70.4% detection. *Conclusions:* ADAM 12 is a promising new maternal serum marker for the detection of Down syndrome affected pregnancies in both first an second trimesters, reducing false positives and improving detection. However prospective studies are required to confirm these findings.

THE CHALLENGES SURROUNDING PRENATAL DETECTION OF MOSAIC TRISOMY 16 (P3)

V. Cochrane and G. Morris

Sydney Ultrasound for Women, Australia

Prenatal testing for Down syndrome and other chromosomal anomalies has become a routine aspect of obstetric care. At Sydney Ultrasound for Women we provide nuchal translucency screening between 11 and 13+6 weeks. Patients are counselled on their adjusted risk in order to make an informed choice regarding further diagnostic testing through CVS or amniocentesis. While the decision to undergo diagnostic testing is a complex one, the subsequent decisions associated with an unexpected chromosomal anomaly can further complicate matters. This issue is explored through a case involving a patient who attended our practice for prenatal testing. SS presented for nuchal translucency screening which resulted in a high risk for both Trisomy 21 and Trisomy 13/18. After counselling SS elected CVS that identified a normal disomic pattern for the standard 5-probe FISH, and full trisomy 16 on the long-term karyotype. The results of follow-up amniocentesis showed 26 of 300 uncultured cells (8.9%) with trisomy 16 on FISH, with the long-term culture confirming low-level mosaicism (2 of 58 colonies or 3%). The significance of low-level mosaic trisomy 16 is difficult to predict due to variable clinical outcomes reported in the literature. Throughout the prenatal testing process, SS experienced emotional conflict regarding the decision to continue or terminate her pregnancy. In this poster we focus on the complex psychosocial issues surrounding an abnormal chromosome finding with an uncertain pregnancy outcome. This case highlights a number of counselling issues including maternal anxiety, complex interpretation of results, couple conflict and decisional conflict.

MICROCEPHALY, SHORT STATURE, HYPERACTIVITY AND HYPOGONADOTROPIC HYPOGONADISM; A NOVEL X-LINKED MENTAL RETARDATION SYNDROME ASSOCIATED WITH A NOVEL MUTATION IN THE RNF113A GENE (O125)

M.A. Corbett,[1] T. Dudding,[2] L. Christie,[2] P. S. Tarpey,[3] L. Hobson,[1] J. Boyle,[2] A. Mansour,[4] L.Vandeleur,[1] F. L. Raymond,[5] K. Friend,[1] A. Futreal,[3] M. Partington,[2] M. Stratton,[3] J. Gecz[1,6] G. and Turner[2]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *The GOLD service Hunter Genetics, University of Newcastle, Australia*

[3] *The Wellcome Trust Sanger Institute, Hinxton, United Kingdom*

[4] *The Children's Hospital at Westmead, Australia*

[5] *Cambridge Institute of Medical Research, Cambridge, United Kingdom*

[6] *School of Paediatrics and Reproductive Health and School of Molecular and Biomedical Science, University of Adelaide, Australia*

Mental retardation (MR) is a disorder of intelligence that results in reduced cognitive, language, motor and social capacities. A 30% excess of males compared to females present with MR, suggesting that a disproportionate number of genes associated with cognition are located on the X chromosome. We examined a family with 2 male cousins affected by a novel and likely X-linked MR syndrome. The proband and his affected cousin both had microcephaly with head circumference in the 3rd and 25th centiles respectively, short stature, facial dysmorphism, cutis marmorata, seizures, hypothyroidism, central hypgonadotropic hypogonadism, small penis and absent testes. CAT and MRI scans revealed cerebellar hypoplasia and also a partial absence of the corpus callosum in both boys. All three obligate carrier females in the family had short stature and 100% skewed X chromosome inactivation, one of the three had learning difficulties. Linkage studies suggested that the disease allele was localised to a 7.75 Mb interval from Xq23–q25. We identified a nonsense mutation within the linkage interval in the highly conserved RNF113A gene (c.901 C > T, p.Q301X). The mutation segregated with affected individuals and obligate carrier females in the family and was not observed in 750 control X chromosomes. The mutation was associated with a marked reduction in RNF113A protein expression in extracts from lymphoblastoid cell lines derived from the proband. Proteins similar to RNF113A are usually associated with the ubiquitin dependent protein degradation pathway. We suggest that this mutation disrupts protein degradation pathways that are important for normal neuronal development.

NOVEL INSIGHTS INTO THE MOLECULAR PATHOPHYSIOLOGY OF BORJESON FORSSMAN LEHMANN SYNDROME (O67)

M.A. Corbett,[1] L.Vandeleur,[1] J. Crawford,[1] C.Wilkinson,[2] C. Shoubridge,[1] E. Parkinson-Lawrence,[3] D. Brooks,[3] L. S. Nguyen,[1] W. Just[4] and J. Gecz[1 5 6]

[1] *Neurogenetics Research Unit, Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Microarray Analysis Group, School of Mathematical Sciences, The University of Adelaide, Australia*

[3] *Division of Health Sciences, School of Pharmacy and Medical Sciences, City East Campus, The University of South Australia, Australia*

[4] *Department of Human Genetics, University Clinic Ulm, Ulm, Germany*

[5] *Department of Paediatrics, University of Adelaide, Australia*

[6] *Women's and Children's Health Research Institute, Adelaide, Australia*

Mutations in *PHF6* cause Borjeson-Forssman-Lehmann Syndrome (BFLS), a syndromic form of X-linked mental retardation. The main clinical features of BFLS are intellectual disability, truncal obesity with gynecomastia, hypogonadism and large ears. To date there are 12 different *PHF6* mutations known in 19 unrelated BFLS families and isolated cases.

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PHF6 is a ubiquitously expressed nucleolar protein, which has four nuclear localisation sequences and two PHD-like zinc finger motifs. To elucidate the role of PHF6 in the cell we compared the mRNA gene expression profiles of lymphoblastic cell lines (LCL) from six BFLS patients. We observed significant changes in RNA processing, DNA replication and cell cycle genes, consistent with the known cellular processes of the nucleolus. We also noted that two unrelated patients with a recurrent c.1024 C>T, p.R342X mutation had significantly reduced levels of PHF6, due to nonsense mediated decay of the predominant *PHF6a* mRNA but not of the alternate *PHF6b* mRNA. An examination of PHF6 expression in different tissues detected increased amounts of PHF6b in the brain compared to PHF6a levels. We showed by luciferase reporter assay that the 330bp 3'UTR sequence in PHF6b increases expression. Thus PHF6 expression can be regulated posttrancriptionally. We detected variable levels of PHF6 protein in LCL of patients with BFLS, including low levels of the truncated p.R342X mutant. Based on the heterogeneity of *PHF6* mutations compared with the relative clinical homogeneity of BFLS cases we predict that PHF6 harbours a single functional domain that is disrupted by any mutation in the protein.

THE HUMAN VARIOME PROJECT: PLANS, PROGRESS AND PILOTS (O51)

R. G. H. Cotton[1,2] and Human Variome Project collaborators

[1] *Genomic Disorders Research Centre, Howard Florey Institute, Melbourne, Australia*

[2] *Department of Medicine, The University of Melbourne, Australia*

The Human Variome Project (HVP; www.humanvariomeproject.org) was created to coordinate and curate the collection of all genetic variation, its phenotype and associated disease(s). This is because lack of up-to-date, complete and correctly curated information can lead to excessive web searching, misdiagnosis and wastes valuable healthcare funds. Work to obviate this problem began more than a decade ago with the Human Genome Variation Society (HGVS; www.hgvs.org) promoting collection and display of variants, producing recommendations and software. At the launch of the HVP, 96 recommendations (www.nature.com/ng/journal/v39/n4/pdf/ng2024.pdf) were drawn up by over 50 world experts from over 20 countries to be implemented in the future. The task is large so countless people will need to be involved in a coordinated manner with specially developed tools and protocols. What is needed is an automated, seamless system transferring clinical data (phenotype), genotype and pathological data to hospital records, as well as to databases curated by experts, in a de-identified and ethically acceptable way, initially to LSDBs and finally to central databases/browsers. The International Society for Gastrointestinal Hereditary Tumours (InSiGHT; www.insight-group.org) has volunteered to be a pilot for (a) collection of all mutations and phenotype for their four genes of interest and (b) from all countries. Other pilot studies will be detailed. Many components for this flow have already been developed, often multiple times around the world in an uncoordinated disconnected way. A planning meeting was held in May 25–29 2008 to review these and rationalise future planning (www.humanvariome project.org/HVP2008/).

TRANSFERRIN PROTEIN POLYMORPHISM MIMICKING A CONGENITAL DISORDER OF GLYCOSYLATION (P12)

S. Coupe, K. Green and K. Carpenter

NSW Biochemical Genetics Service, The Children's Hospital at Westmead, Australia

The congenital disorders of glycosylation represent an expanding group of inborn errors of metabolism with a broad spectrum of clinical presentation. The N-glycosylation defects are most commonly identified by analysis of transferrin isoforms using isoelectric focussing, capillary electrophoresis or HPLC. The most abundant transferrin species has 4 sialic acid residues with smaller amounts of tri, penta and hexasialio species present. Di, mono and asialo species are normally not present in significant amounts. Polymorphisms in the transferrin protein are relatively common and a heterozygous genotype will give rise to 2 isoform patterns effectively overlaid on each other. These patterns are normally relatively easy to identify with the electrophoretic shift due to the protein change corresponding to roughly one sialic acid residue, giving rise to 2 almost equally prominent species next to each other. We report a case where the protein change induced a more marked shift equivalent to 3 sialic acid residues and the pattern obtained was initially interpreted as consistent with a CDG defect of indeterminate type. Transferrin isoforms on both parents revealed the mother had the same pattern prompting reevaluation of the interpretation and the protein polymorphism was confirmed by neuraminidase digest that left 2 clear transferrin peaks. We conclude that abnormal patterns on transferrin isoform analysis should, where possible, be followed by analysis of samples from both parents to exclude protein polymorphisms.

CEREBRAL PALSY (CP) AND MITOCHONDRIAL RESPIRATORY CHAIN (MRC) DISORDERS: WHO, WHEN AND HOW SHOULD WE INVESTIGATE? (O56)

A. Cozens and A. Boneh

Metabolic Service, Genetic Health Services Victoria, Melbourne, Australia

Introduction: CP describes a group of motor disorders caused by fixed lesions or structural abnormalities of the developing brain. CP is characterised by a changing pattern of physical signs and symptoms, but the lesions are not progressive. MRC disorders are primary genetic conditions that may present in child or adulthood with a variety of clinical symptoms. These are progressive, neurodegenerative conditions, but there may be long periods of stability, and CP may be diagnosed. Differentiating these conditions provides important prognostic and genetic information for families, and may affect treatment decisions. *Aims:* (1) To describe the clinical, biochemical and imaging features of patients with MRC disorders who were previously thought to have CP; (2) To identify clues to MRC disorders, to identify those who may benefit from investigation. *Methods:* We reviewed records of patients treated at RCH and identified representative cases, presented in detail. *Results:* (1) All 3 types of CP movement disorders were represented: spastic, dyskinetic and ataxic. Dystonia was a prominent feature, including focal dystonias; (2) Absence of evidence supporting a CP diagnosis: normal ante-, peri- and neonatal histories, normal cranial MRI scans; (3) Unusual patterns of motor disability, sudden onset of new signs, and waxing and waning of symptoms, especially weakness; (4) New onset squint; (5) *t* worsens over time, becoming refractory to treatment.

GENOME-WIDE ASSOCIATION STUDY OF ADVANCED GLAUCOMA USING EQUIMOLAR DNA POOLING (O100)

J. E. Craig,[1] A.W. Hewitt,[2] R. A. D. Mills,[1] K. P. Burdon,[1] D.A. Mackey,[2] G.W. Montgomery[3] and S. Macgregor[3]

[1] *Department of Ophthalmology, Flinders Medical Centre, Adelaide, Australia*

[2] *Department of Ophthalmology, Melbourne University, Australia*

[3] *Queensland Institute of Medical Research, Brisbane, Australia*

Glaucoma is the second leading cause of blindness worldwide, and whilst affected individuals are asymptomatic in the early phases, 10% progress to legal blindness. There is a strong genetic component with an increased relative risk of 9.6 for those with an affected first degree relative. We have analysed a subset of the most severely affected individuals with glaucoma from South Australia (n = 205), and the Glaucoma Inheritance Study in Tasmania (n = 183). These cases were selected for high severity study from over 3000 cases. Those with mutations in the glaucoma gene myocilin were excluded. Cases were compared against controls sets of elderly individuals without a family history of glaucoma, and who were specifically examined to exclude glaucoma (SA n = 216, Tasmania n = 153). Equimolar DNA pools were constructed from each group using the Fluoroskan Ascent, with Picogreen dye for accurate DNA quantitation. Case and controls pools were then run in triplicate using Illumina HumHap550 SNP arrays. Using SNPs that passed stringent quality control (QC) algorithms, bead level intensity data was analysed with custom software, applying the χ^2 test for allelic association. Data analysis is ongoing, but joint analysis of the datasets has revealed multiple strongly associated SNPs at chromosomal regions 5q33.2, 6p25.3 and Xq25. One SNP (rs5933350) reached genome-wide significance. Individual follow-up of over 100 SNPs on the Sequenom system confirms that multiple regions of genetic association have been identified, and that several of these are either within or near genes strongly implicated in pathways relevant to glaucoma pathogenesis.

MOSAIC TERMINAL INVERTED DUPLICATIONS ARISING POSTZYGOTICALLY WITH FORMATION OF NEOTELOMERES (O133)

A. Daniel, L. St Heaps, D. Sylvester, S. Diaz and G. Peters

Department of Cytogenetics, Western Sydney Genetics Program, The Children's Hospital at Westmead, Australia

Two inverted duplications were studied to elucidate their structure and mechanism of formation. Both were mosaics with cells of normal karyotype but in each there was a cryptic subtelomeric (ST) deletion. Case 1 had a deletion of one copy of ST 4p in 60% of lymphocytes and a terminal inv dup 4p in the remainder. In case 2, 33% of AF colonies had a deletion of ST 10p with a terminal inv dup 10p in the remainder. Duplicated FISH signals for GATA3 & NEBL loci (Case 2), and for WHSCR (Case 1) confirmed the inv dup structure. At pter on both inv dup there was no ST FISH signal present. However, there was a pantelomeric probe signal for TTAGGG on both the cryptically deleted p-arms and the inv dup suggesting neo-telomeres had formed. In neither case was there evidence from MLPA for telomere capture. We conclude the most likely origin in both cases was by telomeric breakage in the zygote, and delayed repair until after one or more subsequent mitotic divisions. It is proposed the two differently 'repaired'

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daughter cells proliferated in parallel. In the cryptically deleted cell lines there was deletion of the subtelomere and repair through capping by a neotelomere. In the other daughter cell, it is proposed sister chromatid reunion formed a dicentric, which later broke to form an inv dup. One inv dup was repaired without an interstitial specific subtelomere (Case 1) and one with a duplicated interstitial subtelomere (Case 2) and subsequently a neotelomere was formed at the respective pter (both cases).

REPORT ON THE EUROPEAN MOLECULAR QUALITY NETWORK (EMQN) BEST PRACTICE MEETING FOR THE SPINOCEREBELLAR ATAXIAS, PORTO, PORTUGAL OCTOBER 2007 (O42)

M. R. Davis

Neurogenetics Unit, Department of Anatomical Pathology, Royal Perth Hospital, Perth, Australia

The recent but rapid evolution of genetic testing for the spinocerebellar ataxias (SCAs) has seen laboratories across Australasia develop their own testing protocols based on the early literature describing each new gene discovery. The update of these methods and the maintenance of quality control have relied on the efforts of the staff of each laboratory to keep current with the literature rather than any coordinated program. The HGSA has over the last 6 years established a centralised quality assessment program for the SCAs, with recommendations made to each laboratory as part of the process. Continued variations in results between laboratories have indicated the need for an endorsed set of best practice guidelines, a situation also recognised by the EMQN. To this end, an Australasian representative was invited to participate in a meeting to draft the first set of EMQN SCA molecular testing best practice guidelines. Being the first EMQN meeting on this topic, the discussions covered the full range of issues related to SCA testing: requirements for diagnostic testing; which genes to routinely screen; the appropriate use of controls; the most accurate methods for allele size determination; aspects of measurement of uncertainty for allele sizing; limitations of testing methods and ways to overcome them; and appropriate reporting of results. The final version of the guidelines drafted at this meeting will be released mid 2008, at which time the HGSA QA committee will decide whether to endorse them unchanged or make adjustments as relevant to local conditions.

WHAT CAN WE OFFER COUPLES WHEN PREIMPLANTATION GENETIC DIAGNOSIS (PGD) IS NOT AVAILABLE FOR A RARE 6;15 INSERTION? (P2)

T. Davis,[1] C. Beyer,[1] T. Burgess[2] and G. McGillivray[2]

[1] *Monash IVF, Melbourne, Australia*

[2] *Genetic Health Services Victoria, Murdoch Children's Research Institute, Melbourne, Australia*

Preimplantation genetic diagnosis (PGD), involving genetic analysis of a biopsied cell from a preimplantation embryo, is a widely used and accepted technique performed at in vitro fertilisation (IVF) centres worldwide. PGD is a valuable reproductive option for couples at genetic risk of passing on a serious genetic disorder or those at risk of pregnancies with chromosomal imbalance or aneuplodies. A couple was referred to the PGD clinic at Monash IVF after the male partner was found to be a carrier of a rare 6;15 insertion. The couple had experienced three previous pregnancy losses, including one trisomic pregnancy and were interested in PGD. Our practice has been to use commercially available fluorescent in-situ hybridisation (FISH) probes for PGD for chromosomal rearrangements to standardise the tests offered and to ensure quality. A commercial FISH probe was not available to detect unbalanced rearrangements in embryo's generated through IVF for this couple. A research BAC probe was applied to a semen sample from the male partner to identify sperm with balanced and unbalanced chromosome complements in order to estimate the proportion of sperm with an unbalanced chromosome complement. This information will be useful to help the couple make decisions about future pregnancies conceived naturally and through IVF/ PGD.

IRONXS: IS HIGH SCHOOL SCREENING FOR HAEMOCHROMATOSIS ACCEPTABLE AND FEASIBLE? (O70)

M. Delatycki,[1,2,3] M. Wolthuizen,[1] E. Varley,[1] V. Collins,[1] M. A. Aitken,[1] K. Allen,[1,2,4] L. Bond,[1,2] I. Macciocca,[3] G. Wilson,[1] P. Lockhart [1] and S. Metcalfe[1,2]

[1] *Murdoch Children's Research Institute, Australia*

[2] *Department of Paediatrics, The University of Melbourne, Australia*

[3] *Genetic Health Services Victoria, Australia*

[4] *Royal Children's Hospital, Melbourne, Australia*

Background: Hereditary haemochromatosis is an easily preventable iron overload condition that can result in hepatic cirrhosis and reduce lifespan and therefore population screening has been advocated. In the HaemScreen workplace-based study we found > 90% of people attending the information session had screening, but only 6% of those eligible attended. This led us to examine high schools as a setting to offer screening. We report our first year of data from this study. *Methods:* A DVD-based information session was presented to year 10 and 11 students. Testing for the HFE C282Y mutation was by cheekbrush sampling. Questionnaires were completed at the time of testing, 1 month and 12 months postresults, and interviews conducted with homozygotes and a sample of students with other genotypes, parents and teachers. *Results:* 3638 students at 19 schools were eligible to participate. 1533 students had parental consent (42% of eligible students; 45% male; mean age = 15.7 years) of whom 1359 chose testing (37.4% uptake). 7 students were C282Y homozygotes (1 in 194) and 148 were heterozygotes (1 in 9). More than 90% of students answered all knowledge questions correctly. There were no significant differences in general health perception scores or anxiety levels between the 3 genotype groups 1 month postresults, with favourable feedback from interviews. *Conclusions:* One-to-many education by DVD results in very good understanding of the issues necessary for informed decision-making. Preliminary results suggest C282Y homozygotes and heterozygotes understand the meaning of their genotype and are not made significantly anxious by their results.

FAMILY AND COMMUNITY ISSUES IN NEWBORN SCREENING FOR LYSOSOMAL STORAGE DISORDERS (O54)

M. Delatycki

Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Victoria and Genetic Health Services Victoria, Australia

Newborn screening to identify children at risk of preventable disease such as is the case for phenylketonuria is non- controversial. Where newborn screening can identify children with a disease for which no preventative treatment exists, the situation is far less clear. Where newborn screening can identify some children in the first category and others in the second, a complex situation is created. Such is potentially the case with newborn screening for lysosomal storage disorders (LSD). In such a situation, the views of health care professionals, ethicists and families with children with LSDs can be helpful in deciding the best course. A questionnaire including a number of hypothetical clinical scenarios about NBS for MPS was distributed to members of MPS support groups from United States and Australia. 86% of respondents indicated that they would have wanted NBS for their own children. 97% supported the use of NBS in situations where early treatment favourably impacts on outcome and 87% supported NBS when a severe form of MPS was diagnosed, but no treatment is available that improves the outcome. The most common reason cited in support of NBS was that NBS could avoid a delay in diagnosis and the accompanying distress that delayed diagnosis created. The decision to introduce NBS for a group of conditions such as LSD is complex and there are many factors that need to be considered. The families impacted by these conditions provide a unique and important viewpoint.

NUTRITIONAL INTAKE OF AN 11-YEAR-OLD BOY WITH METHYLMALONIC ACIDURIA: COMPARISON WITH NUTRIENT REFERENCE VALUES 2005 (P28)

B. Dennison[1] and B. Wilcken[2,3]

[1] *Nutrition and Dietetics, The Children's Hospital at Westmead, Sydney, Australia*

[2] *The New South Wales Biochemical Genetics and Newborn Screening Services, Children's Hospital at Westmead, Australia*

[3] *University of Sydney, Australia*

Methylmalonic aciduria (MMA) is an autosomal recessive genetic disorder of organic acid metabolism, requiring protein restriction and adequate energy to prevent decompensation when unwell. MG, age 11 years, had a liver transplant at 2 years and a kidney transplant at 8 years. Typical of many children with MMA, MG has restricted himself to a few foods: cornflakes, toast, margarine, hot chips, cheese, some milk, raw apple, sugar and crackers, a dietetic challenge. He takes an energy, mineral and vitamin supplement via gastrostomy tube and uncooked cornflour at night. The standards used to assess nutritional adequacy (Nutrient Reference Values (NRVs) for Australia and New Zealand, NHMRC 2005) are intended for use in populations of healthy individuals, not in individuals with rare metabolic conditions. NRVs are further defined as Recommended Dietary Intakes (RDIs), meeting the needs of 97–98% of matched healthy people, Adequate Intake (AI), Estimated Average Requirements (EARs), meeting the needs of the matched average person, while Upper Limit of intake (UL) relates to avoiding toxicity. A 3-day food record of MG's usual intake (food and GT) shows he meets the RDI and EAR for all nutrients except folate (25% RDI, 40%EAR) and Vitamin C (50% RDI, 70% EAR). His fibre intake is 45% of AI. For MG it is probably wise to aim for at least the RDI to allow for variable bioavailability of synthetic vitamin and minerals.

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X-LINKED *PROTOCADHERIN 19* MUTATIONS CAUSE FEMALE LIMITED EPILEPSY AND COGNITIVE IMPAIRMENT (O75)

L. M. Dibbens,[1,2] P. S. Tarpey,[3] K. Hynes,[1,4] M. A. Bayly,[1] I. E. Scheffer,[5,6] R. Smith,[3] J. Bomar,[7] E. Sutton,[4] D. H. Geschwind,[7] P. Thomas,[4] E. Haan,[1,4] S. Ryan,[8] S. McKee,[9] S. F. Berkovic,[5] A. P. Futreal,[3] M. R. Stratton,[3] J. C. Mulley[1,2,4] and J. Gécz[1,2,4]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *School of Paediatrics and Reproductive Health, University of Adelaide, Australia*

[3] *Wellcome Trust Sanger Institute, Hinxton, United Kingdom*

[4] *School of Molecular and Biomedical Science, University of Adelaide, Australia*

[5] *Epilepsy Research Centre and Department of Medicine, University of Melbourne, Austin Health, Australia.*

[6] *Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia*

[7] *Program in Neurogenetics and Neurobehavioral Genetics, Neurology Department and Semel Institute for Neuroscience and Behavior, David Geffen School of Medicine, University of California at Los Angeles, United States of America*

[8] *AstraZeneca, Wilmington, Delaware, United States of America*

[9] *Northern Ireland Regional Genetics Service, Belfast City Hospital, United Kingdom*

Epilepsy and Mental Retardation limited to Females (EFMR) is a disorder with an X-linked mode of inheritance and unusual expression pattern. Disorders arising from mutations on the X chromosome are typically characterized by affected males and unaffected carrier females. In contrast, EFMR spares transmitting males and affects only carrier females. EFMR is characterized by early onset seizures in previously normal infants, followed by developmental regression of varying severity. Five new EFMR families were ascertained on the basis of their inheritance pattern. Aided by systematic re-sequencing of 737 X chromosome genes we identified different protocadherin 19 (PCDH19) gene mutations in 7 families. Five mutations result in the introduction of a premature termination codon. Study of two of these demonstrated nonsense mediated decay of PCDH19 mRNA. The two missense mutations are predicted to affect adhesiveness of PCDH19 through impaired calcium binding. PCDH19 is expressed in human and mouse developing brain and is the first member of the cadherin superfamily to be directly implicated in epilepsy or mental retardation. We propose the mechanism of cellular interference underlies the female limited expression of the EFMR phenotype. Further, we propose that male carriers of PCDH19 mutations are spared via gene rescue by a related human-specific Y chromosome gene, protocadherin 11Y (PCDH11Y).

IDENTIFICATION OF GENES DETERMINING THE NORMAL POPULATION DISTRIBUTION OF CENTRAL CORNEAL THICKNESS (O106)

D. P. Dimasi,[1] K. P. Burdon,[1] A.W. Hewitt,[2] P. Mitchell,[3] D.A. Mackey[2] and J.E. Craig[1]

[1] *Department of Ophthalmology, Flinders University, Flinders Medical Centre, Adelaide, Australia*

[2] *Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, Australia*

[3] *Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Australia*

The cornea is the clear tissue situated at the front of the eye. Central corneal thickness (CCT) exhibits a normal population distribution (mean ± *SD* of 540±34μm) and is strongly genetically determined. Thin CCT is a risk factor for Open-Angle Glaucoma (OAG), an optic neuropathy that causes irreversible visual loss. OAG has a strong but poorly characterised genetic component. We hypothesised that genes determining CCT variation may be involved in OAG pathogenesis.We have assessed a selection of candidate genes for association with normal CCT variation. Genes were selected on several criteria, including involvement in diseases with extreme CCT values, corneal structure or development. In order to assess the majority of the genetic diversity within these genes, a tag SNP approach was undertaken using the HapMap database. The genes were screened in 957 individuals with CCT measurements from our population-based Blue Mountains Eye Study cohort. Positive results were obtained for individual SNPs in COL1A2, Fibrillin and PAX6 associated with a 5.6 μm (p =.01), 5.2 μm (p =.02) and a 5.1 μm (p = .02) difference in CCT respectively. Specific haplotype associations were also identified. Our results reveal the first reported evidence of genes associated with normal CCT variation. We propose that CCT is determined by a large number of genes with small additive effects and the majority of these remain to be identified. These data have important implications for OAG research, potentially yielding new causative genes or pathways that will enable better understanding of the disease.

MOSAICISM LEADING TO INCONTINENTIA PIGMENTI IN MALES (P60)

E. Douglas,[1] R. Catford,[1] C. Dickson,[2] R. Susman,[3] J. Smith[3] and K. Friend[1]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Department of Neurology, Christchurch Hospital, Christchurch, New Zealand*

[3] *Department of Clinical Genetics, Westmead Children's Hospital, Westmead, Australia*

Incontinentia pigmenti (IP) is an X-linked disorder generally lethal in males. Female carriers of IP present with characteristic skin lesions that are present at birth. Affected individuals may also show other varied and often severe clinical symptoms including seizures, motor and mental retardation, cataracts, optic atrophy and cone/peg-shaped teeth. The *NEMO* gene encoding the regulatory subunit of the IκB kinase complex required for nuclear factor-κB activation, is known to be mutated in IP. A loss of function mutation of *NEMO* (*NEMO*Δ4-10 del) results in the majority of IP cases. Although IP is usually lethal during male embryogenesis, a few males present with IP symptoms. It has been shown that hypomorphic (less severe) mutations of *NEMO* can lead to a disorder similar to IP. Males with a classic IP phenotype, with the four characteristic dermatological stages, have on rare occasion, been reported. Some of these cases have been explained by an abnormal Klinefelter karyotype (47,XXY), leading to skewed X-inactivation. Somatic mosaicism following postzygotic mutation has been demonstrated to explain the presence of IP in a number of karyotypically normal male individuals. The earlier in development the mutation occurs, the greater severity of symptoms is observed. In our laboratory, two males with clinical signs of IP have been investigated. One male revealed low level mosaicism of the *NEMO*Δ4-10 deletion. No mosaicism was detected in the second patient, and the genetic cause is still under investigation. We present this data and summarise the literature in this area.

COMMUNICATION SKILLS TRAINING FOR GENETIC COUNSELLORS: THE IMPACT ON PRACTICE (O7)

K. Dunlop,[1] P. Butow,[2] C.Migeal,[2] P.Heinrich[3] and K. Barlow-Stewart[1]

[1] *The Centre for Genetics Education, NSW Health, Sydney, Australia*

[2] *Medical Psychology Research Unit, University of Sydney, Australia*

[3] *Pam McLean Cancer Communications Centre, University of Sydney, Australia*

Almost all studies to date on communication skills training (CST) have focussed on doctors and nurses in oncology. This study evaluated 3 1-day CST workshops that were conducted in NSW for genetic counsellors and clinical specialists in 2002, 2004 and 2006. The workshops were based on the previously evaluated cancer communications model using actors in role plays with facilitator and group feedback. Anecdotally, participants report great value from these workshops, but providers need real evidence that they make a difference to practice. Participants, many of whom were highly experienced practitioners, completed a short term evaluation (n = 42); 22/42 also completed the follow-up questionnaire 2–5 years later concerning their workshop experience and impact on practice. Aspects highly valued in the workshops included facilitator feedback, actors rather than role-playing with peers, being able to stop and try things differently and group feedback. All participants rated the workshop as an effective training method and that it was more useful than learning the theory of communication. Perceived outcomes on practice include opportunities for participants to reflect on their work; bring focus to the way they say things; and increase the motivation to improve communication skills. An increase in confidence in skills was also reported. The high level of participant experience indicated that the role of the workshop may not necessarily be to teach new skills but rather an opportunity for reflection and focus. This paper also reports on recommendations for CST in genetic counselling generated from the study.

TSC TESTING IN AUSTRALIA (P65)

J. Dzarir,*[1] M. Chopra,*[2] G. Mullan,[1] M. F. Buckley,[1] D. Mowat[2] and P. Taylor[1]

**Joint first authors*

[1] *Molecular and Cytogenetics Unit, Department of Haematology and Genetics, SEALS, Australia*

[2] *Department of Medical Genetics, Sydney Children's Hospital, Australia*

We report the results of a mutation detection validation study for tuberous sclerosis complex (TSC). Samples were collected from 50 individuals who fulfilled criteria for definite TSC. Each sample was analysed for mutations in TSC1 and TSC2, using DNA sequencing and multiplex ligation-dependent probe amplification (MLPA) of all exons. The mutation detection rate was 75%, consistent with previous studies. The distribution of mutations will be presented and compared with previous reports. Following completion of the validation study, a diagnostic service will be available in late 2008. A case highlighting the value of retesting patients who were deletion negative on the earlier MLPA panels will be presented. A cognitively normal adult female with TSC requested gene testing for reproductive reasons in 2006. Testing was undertaken in an overseas laboratory utilising MLPA and gene sequencing and no mutations were

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detected. We retested the DNA sample and an out of frame deletion of exons 13 and 14 in TSC1 was identified, predicted to result in a premature stop codon in exon 15. This case illustrates that earlier MLPA testing may not have included all exons.

EXTREME PHENOTYPIC VARIATION IN LONG QT SYNDROME: UNDERSTANDING THE BEWILDERING BLEND OF SNPS AND MUTATIONS (P59)

C-A. Eddy,[1,3] J. C.Y. Mak,[1,3] J. Crawford,[1] J. R. Skinner[1,2] and A. N. Shelling[1,3]

[1] *Cardiac Inherited Disease Group and Department of Paediatric Cardiology, Auckland City Hospital, New Zealand*

[2] *Starship Children's Hospital, Department of Obstetrics and Gynaecology, Auckland, New Zealand*

[3] *Faculty of Medical and Health Sciences, University of Auckland, New Zealand*

The extreme phenotypic variation seen in patients with long QT syndrome is poorly understood. Even among patients carrying the same pathogenic mutation, the clinical manifestation in affected individuals can range from asymptomatic throughout life to episodes of recurrent seizure and/or syncope and sudden cardiac death at a young age. Single nucleotide polymorphisms (SNPs) in long QT syndrome (LQTS) genes may contribute to this heterogeneity by acting in concert as disease modifiers and be either protective or associated with an increased susceptibility to arrhythmia. To determine whether any are associated with altered risk of developing the LQTS phenotype, we used TaqMan SNP genotyping assays to screen 10 SNPs in the LQTS genes, KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2, in a panel of 84 LQTS patients and 100 healthy New Zealand controls. We identified comparable allele frequencies to those reported in the literature. Although no significant differences were identified in this pilot study, important trends were observed in the SCN5A-intron-1 SNP and the KCNE1-D85N SNP, where minor allele frequencies were notably higher in patients compared to controls. These preliminary findings highlighted some SNPs that were not associated, to any great extent, with an increased or decreased risk as well as others that do show a trend towards being involved with LQTS or modifying the effects of known mutations, and are worth studying further in larger cohorts. This research was approved by the University of Auckland Animal Ethics Committee and supported by the Child Health Research Foundation (Cure Kids) and Greenlane Research and Education Fund.

MULTIPLE MYELOMA AND FISH STUDIES AFTER PLASMA CELL ENRICHMENT (O38)

K. Fagan, N. Bain and B. Green

Hunter Area *Pathology Service, Newcastle, Australia*

Karyotype analyses of bone marrow samples referred for multiple myeloma generally have low abnormality rates detected using traditional cytogenetic methods. FISH on directly harvested marrow samples may increase this detection rate, however large numbers of cells must be scored since the number of plasma cells in the sample may be very low. The European Myeloma Network released guidelines in 2006 specifically relating to how myeloma samples should be anlaysed, that is, 'it is not acceptable to report FISH results in myeloma without either concentrating the plasma cells or employing some means of plasma cell identification so that only these cells are scored'. In light of these recommendations, our laboratory has recently employed a method of processing myeloma samples to enrich for CD138+ plasma cells which are subsequently analysed by targeted FISH. We compare the detection rates using this new technique against our data from the previous 5 years and show improved abnormality detection rates. The additional information obtained helps clinicians make decisions about risk stratification and treatment regimes and, hopefully, will improve outcomes for myeloma patients.

INSERTION AND DELETION MUTATIONS IN THE DINUCLEOTIDE REPEAT REGION OF THE NORRIE DISEASE GENE (O46)

D. J. Fairbairn and V. Hyland

Molecular Genetics Laboratory, Pathology Queensland Central Laboratory, Royal Brisbane Hospital, Herston Hospitals Campus, Brisbane, Australia

Norrie disease pseudoglioma (NDP) is a rare X-linked recessive disorder that is characterised by congenital blindness. In about a third of cases this is accompanied by progressive hearing loss, mental retardation and psychiatric problems but phenotypes can vary within families. The NDP gene has 3 exons and encodes a small secreted protein that is involved in retina development. Our laboratory is involved in NDP gene mutation detection. Many disease causing mutations in NDP have been described, which are mostly point mutations in the coding region. Consequently, the protein coding regions of exons 2 and 3 have received the most attention in the past. However, recent studies have associated polymorphisms in the non-translated CT dinucleotide repeat in exon 1 with disease. This region may play a role in controlling gene expression. In order investigate the significance of deletion and expansion mutations in the CT repeat of exon 1 in Norrie disease and related retinopathies, we have developed a fragment analysis method to accurately size the CT dinucleotide repeat region. In addition, real-time PCR can be used to monitor NDP gene expression. The results from these studies will be presented.

NEWBORN SCREENING FOR FRAGILE X SYNDROME (FRAXA) (O120)

M. Field,[1] B. Bennetts,[2] L. Christie,[1] K. Slater,[2] C. Rogers,[1] J. Boyle,[1] G. Turner[1] and A. Hackett[1]

[1] *GOLD Service, Hunter Genetics, Newcastle, Australia*

[2] *Department of Molecular Genetics, The Children's Hospital at Westmead, Sydney, Australia*

WHO criteria for newborn screening include treatability, acceptability and sensitivity/specificity but not the importance of early diagnosis and reproductive choices. Screening for FRAXA is controversial as no specific treatment is available and premutations are common. With the support of NSW Fragile X association we ran a pilot study to examine the feasibility and acceptability of newborn screening for FRAXA. Mothers were offered participation 1–7 days postnatal. DNA was eluted from standard newborn screening cards. The FRAXA fragment was amplified with a fluorescent labelled primer. PCR products were sized on a polyacrylamide gel. Capillary electrophoresis resolution was used for samples greater than 40 CGG repeats or females with only one apparent PCR fragment. Uptake of participation was 200/212 (94%) and all wanted to know if their newborn had a premutation or a full mutation. Two hundred newborns of both sexes were tested. DNA was successfully extracted from all newborn screening cards. Results were obtained for 100% males and 82% females. One premutation male with 60 CGG repeats was identified. For 18% of females, with either a homozygous repeat size or an expended repeat, further testing is underway. Newborn screening will lead to earlier diagnosis, enable interventions and in the future facilitate early targeted therapies. It will allow reproductive choices for future pregnancies and information for other family members. Newborn screening now faces the possibility of significant expansion, given increasing technological improvements and consumer demand. FRAXA is an excellent prototype for exploring the controversial issues related to expansion of newborn screening.

CGH ARRAY ANALYSIS IN 84 INDIVIDUALS WITH AUTISM SPECTRUM DISORDER (ASD) (P85)

M. Field,[1] R. Ullmann,[2] H. Ropers,[2] L. Christie,[1] L. Banna[3] and G. Turner[1]

[1] *Genetics of Learning Disability (GOLD), Hunter Genetics, Waratah, Australia*

[2] *Max Planck Institute for Molecular Genetics, Berlin, Germany*

[3] *Department of Paediatrics, John Hunter Hospital, Newcastle, Australia*

Although the evidence of a genetic aetiology in ASD is strong, the underlying genetic mechanisms have been elusive. Recent studies suggest that between 7–10% of singleton ASD cases may be due to chromosomal micro-deletions or duplications.[1,2] We report results of a study of 84 individuals diagnosed with ASD based on DSM-IV criteria. 42 were singletons and 42 were from multiplex families. Visible cytogenetic abnormalities and fragile X syndrome were excluded. Participants' DNA was tested using a 32,000 BAC CGH array. *Results:* 43 had no abnormalities detected and in two samples analysis failed. 32 had rearrangements; 29 were determined to be CNV and 3 are awaiting clarification. Seven abnormalities were detected. Two of these, a 22q11.21 deletion not segregating with the phenotype and a paternally inherited 17p12 duplication (both father and son had CMT), were probably not causal for ASD. Five (6%) were clinically significant. Two patients had de novo abnormalities, a 16q16 deletion and a 5q32 deletion. 3 individuals had familial abnormalities; 1 maternal inherited 15q11-12 duplication and 2 familial 16p13.1 duplications.[3] The 16p13.1 duplication (approx 1.5MB) has not been seen in any other experimental cohorts in the laboratory. *Conclusions:* We consider 5 of the identified abnormalities to be causally linked to the ASD phenotype. We believe that the discovery of a rare, but recurrent chromosomal duplication at 16p13.1, inherited from an apparently normal parent indicates that not all inherited genomic imbalances are innocuous. High resolution CGH array demonstrates significant chromosomal imbalance in a small proportion of cases of ASD.

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DIAGNOSIS OF NEURONAL CEROID LIPOFUSCINOSES IN AUSTRALASIA: 1999–2007 (P27)

M. J. Fietz, V. M. Muller, B. Fong, K. Barnard and J. M. Fletcher

Department of Genetic Medicine, Child, Youth and Women's Health Service, Adelaide, Australia

Background: The neuronal ceroid lipofuscinoses (NCL) are a family of neurodegenerative disorders, with most forms presenting with seizures, regression and loss of vision. The age of onset ranges from birth through to adulthood. At least 8 different genes have been isolated, with three encoding lysosomal enzymes and five encoding transembrane proteins. Since 1999, the National Referral Laboratory (NRL) has been performing diagnostic assays for the three most common forms; CLN1 (infantile NCL), CLN2 (classical late-infantile NCL) and CLN3 (juvenile NCL). As of December 2004, the enzyme assays for CLN1 and CLN2 were included in the laboratory's lysosomal enzyme (WCE) panel. *Aim:* To review the biochemical, molecular and clinical data of the NCL cases diagnosed by the NRL. *Results:* 49 new cases of NCL have been diagnosed, consisting of 4 affected by CLN1, 28 by CLN2 and 17 by CLN3. Since December 2004, both new cases of CLN1 and 3/14 cases of CLN2 have been diagnosed as part of the WCE panel. Molecular studies have confirmed the presence of common mutations for each disorder. The majority of patients have a typical clinical history for the relevant disorder. However, a number of exceptions are present, including a later-onset form of CLN2. *Conclusion:* The NCL are a complex family of neurodegenerative disorders with CLN1, CLN2 and CLN3 having a combined Australian incidence of ~1 in 55,000. The inclusion of the enzyme assays for CLN1 and CLN2 in the WCE panel has been important in providing an early diagnosis for these disorders.

INTERNATIONAL STANDARDISATION OF BCR-ABL QUANTITATIVE PCR METHODS FOR PATIENTS WITH CHRONIC MYELOID LEUKAEMIA (CML) TO ALLOW COMPARISONS OF MOLECULAR RESPONSE RATES BETWEEN LABORATORIES AND CLINICAL TRIALS (P50)

L. Fletcher,[1] R. Lawrence,[1] C. Field,[1] J. Prime,[1] B. Sullivan,[1] J. Georgievski,[1] S. Phillis,[1] B. Rudzski,[1] K. Lynch,[2] T. Hughes[1] and S. Branford[1]

[1] *Institute of Medical and Veterinary Science, Adelaide, Australia*

[2] *Novartis Pharmaceuticals Australia Pty Ltd, Sydney, Australia*

BCR-ABL mRNA measurement has become an essential component for assessing treatment response in CML. A major molecular response (MMR) has prognostic significance and is a primary endpoint of clinical trials of BCR-ABL inhibitor therapies. However, the various quantitative PCR methods are not standardized, which precludes comparison of data derived from individual laboratories. Futhermore, values representing MMR are variable and treatment response may be misinterpreted. International standardisation of methods will not only aid clinical decisions for individual patients with CML but also assist the interpretation of clinical studies. We aligned BCR-ABL values generated by 39 international laboratories to an international reporting scale (IS). Alignment was achieved by application of laboratory-specific conversion factors calculated by comparisons performed with patient samples against a reference method in Adelaide. A validation procedure was completed for 20 laboratories. We determined performance characteristics (bias and precision) for consistent interpretation of MMR after IS conversion. When methods achieved an average BCR-ABL difference of ±1.2-fold from the reference method and 95% limits of agreement within ±5-fold, the concordance of MMR was 91%. These criteria were met by 55% of methods. When not met, the MMR concordance was 75% or less. However, irrespective of the precision, when the bias was ±1.2-fold as achieved by 90% of methods, there was good agreement between the overall rates of MMR. This indicates that the IS can deliver accurate comparison of molecular response rates between clinical trials when measured by different laboratories and we identified performance criteria to allow consistent measures of drug response.

CHALLENGES IN PROVIDING CARE FOR ADULTS WITH INBORN ERRORS OF METABOLISM (O60)

J. M. Fletcher,[1,2,4] P. Georgio,[2] M. Netting[1] and I. Chapman[2,3,4]

[1] *Department of Genetic Medicine, Children Youth and Women's Health Service, Adelaide, Australia*

[2] *Department of Endocrinology, Royal Adelaide Hospital, Australia*

[3] *Department of Medicine, Royal Adelaide Hospital, Australia*

[4] *University of Adelaide, Australia*

Introduction: Care of the majority of South Australian adults with Inborn Errors of Metabolism (IEM) has been transferred over the past 11 years to the Royal Adelaide Hospital, a major tertiary adult centre. *Aim:* to describe the challenges to care provision resulting from the availability of new therapies, such as enzyme replacement therapy for lysosomal storage diseases and the longer survival of young adults with life limiting conditions such as Leigh disease and Sanfilippo syndrome. *Service description:* The adult IEM service was initially set up as a 'Carry over care' model, with outpatient care provided by a paediatric IEM specialist and an adult endocrinologist. Inpatient care is provided by the adult physician. A medical food company has provided 0.1 FTE of dietitian input. The endocrinology day unit has been overwhelmed by the workload required to provide fortnightly infusion services to an extended group of patients with lysosomal storage disease: notably 6 Fabry and 1 Gaucher disease and inpatient care for maple syrup urine disease. *Conclusions:* Service demands have outstripped resources.

'NONDIRECTIVE CONTRACEPTIVE ADVICE': SHOULD GENETIC COUNSELLORS OFFER THIS? (P39)

R. Forbes, S. Grover and M. Gardner

Genetic Health Services Victoria and Department of Gynecology, Royal Children's Hospital, Australia

Northern Regional Genetics Service, Auckland, New Zealand

Counsellors and geneticists are used to seeing couples at increased genetic risk for potential children of theirs, and are familiar with the process of conveying genetic information in this situation. However, the discussion does not often explore questions of using contraception in order to avoid having (more) children; perhaps this may be seen as not 'our territory' in Genetics, and perhaps there is a sense that this could be perceived as being directive (or even 'eugenic'). Such an impression, if valid, would seem at odds with the close involvement that genetics professionals have in the reproductive/prenatal clinic, and where it is common to have discussion of, and where necessary to make arrangement for, termination of pregnancy. We suggest that it may be a useful part of the service offered in the genetic clinic, in suitable cases, to raise the issue of contraception, and to outline appropriate methods. We present two illustrative scenarios.

CHALLENGES IN ESTABLISHING A POPULATION CARRIER SCREENING PROGRAM FOR CYSTIC FIBROSIS (O89)

R. Forbes, J. Massie, A. Bankier, B. Chong, D. DuSart, V. Petrou and M. Delatycki

Genetic Health Services, Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Australia

Cystic fibrosis is the commonest life shortening autosomal recessive condition among Caucasians and is due to mutations in the CFTR gene. The carrier frequency in this population is 4% with a disease incidence of 1:2,500. Carriers are healthy and the majority of people are unaware of their carrier status. More than 95% of babies born with CF have no family history of CF. Most parents who have a child with CF elect to utilise reproductive technology for subsequent pregnancies by either prenatal diagnosis (PND) or preimplantation genetic diagnosis (PGD). The US National Institutes of Health and the American College of Obstetrician and Gynecologists recommend offering CF carrier testing to all couples. We have introduced a fee paying prenatal screening program, initially offered through obstetricians in the private sector. Sampling is by cheek brush and we test for the twelve most common severe mutations in CFTR. In the first two years of the program 2175 people were screened of whom 64 were carriers (1:34) and 6 carrier couples were identified all of whom chose either PND if pregnant or PGD if nonpregnant at time of testing. The challenges and difficulties faced include educating health care professionals and the public about CF and the screening program, the requirement for sample recollection in 2.2% of patients screened, the correct collection procedure, patient anxiety regarding not being offered screening until pregnant, reluctance of health professional to offer screening primarily due to time constraints and equity of care when screening is currently only offered in the private sector.

AN INTERNATIONAL ONLINE SURVEY OF GENETIC HEALTH PROFESSIONALS' PRACTICE INVOLVING FAMILY COMMUNICATION (O116)

L. E. Forrest,[1,2,3] M. B. Delatycki,[3,4] L. Curnow,[4] L. Skene[5] and M. Aitken[6]

[1] *Genetics Education and Health Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia*

[2] *Department of Paediatrics, The University of Melbourne, Australia*

[3] *Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia*

[4] *Genetic Health Services Victoria, 10th Floor, Royal Children's Hospital, Melbourne, Australia*

[5] *Melbourne Law School, The University of Melbourne, Australia*

[6] *Research Strategy, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia*

Communicating genetic information in families is becoming increasingly important due to the availability of genetic testing and subsequent low numbers of at-risk family members that contact genetic services for counselling. The responsibility for educating and discussing the familial

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implications of a genetic diagnosis with probands generally lies with genetic counsellors and clinical geneticists (genetic health professionals). However, the area of genetic health professionals' practice that involves family communication is largely unexplored. This is the first international survey to be developed and validated which aimed to explore genetic health professionals' current practice involving family communication. The survey was administered online and genetic health professionals were recruited through membership lists of genetic societies. The survey was completed by 626 genetic health professionals. The results demonstrate that during a consultation with the proband, more than 95% of genetic health professionals always identify which relatives are at-risk and encourage communication about the genetic condition to these family members. Moreover, a comparison between different genetic diagnoses showed genetic health professionals were significantly more likely ($p < .001$) to always discuss these issues for some diagnoses compared to others. Australasian genetic health professionals' were more likely to write letters to probands' at-risk relatives regardless of the genetic diagnosis ($p < .001$) than genetic health professionals from other countries. The results of this survey provide an insight into genetic health professionals' practice internationally and provide information for the development of evidence-based practice for genetic and nongenetic health professionals in the area of family communication.

ANALYSIS OF GENETIC VARIATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA (O131)

R. Fraser, M. Khazab, T. Hillier, J. Beerworth, T. Kuczek, B. Fortunaso, S. Bawden, M. Nicola, J. Suttle, G. Cheetham and S. Moore

SA Cancer Cytogenetics Unit & Molecular Oncology Unit, Division of Molecular Pathology, IMVS, Adelaide, Australia

Chronic lymphocytic leukaemia (CLL) is the commonest type of leukaemia in adults. It is readily diagnosed on the basis of differential white cell counts, blood film morphology and lymphocyte surface markers however the clinical course of CLL is highly heterogeneous. The ability to identify those patients who have stable, indolent disease and those patients who will require early therapeutic intervention because of more rapidly progressive disease, is of major importance. Cytogenetic evidence of genetic variation is a powerful predictor of outcome in CLL, but is hampered by the failure of many patients' cells to divide in culture and so to yield metaphase chromosomes for analysis. To some degree, interphase fluorescence in situ hybridisation (FISH) has overcome this problem although it is an expensive and time-consuming process. Multiplex ligation-dependent probe amplification (MLPA) is a newer, PCR-based technique for copy-number assessment of discrete loci. It is readily applied in the non-mosaic setting and we chose to assess its effectiveness as a replacement for FISH in a busy cancer cytogenetic unit. Over 2 years samples from > 150 CLL patients were received for cytogenetic analysis. Of these 44% showed karyotypic abnormality and 60% of those undergoing interphase FISH showed abnormality. A karyotype was not achieved in 6% and FISH was not successful in 4%. A subgroup of > 40 of these patients' samples was subjected to MLPA, showing similar abnormality rates to the FISH studies. Overall there was good agreement between these methods and we have devised a strategy for optimal use of our resources in genetic analysis of CLL samples.

IDENTIFICATION OF TWO NOVEL MUTATIONS FOR X-LINKED RECESSIVE SPONDYLOEPIPHYSEAL DYSPLASIA TARDA (SEDT) AND REVIEW OF LITERATURE (P81)

K. Friend,[1] L. Sanchez,[1] M. Shaw,[2] E. Thompson,[3] L. McGregor,[3] J. McGraughan[4] and J. Gecz[2]

[1] *Diagnostic Molecular Genetics, Dept of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Neurogenetics, Dept of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[3] *South Australian Clinical Genetics Service, Dept of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[4] *Queensland Clinical Genetics Service, Royal Children's Hospital, Brisbane, Australia*

X-linked recessive spondyloepiphyseal dysplasia tarda (SEDT; MIM 313400) is a late onset progressive skeletal disorder. This disorder is characterized by disproportionate short stature with a short trunk, barrel chest and absence of systemic complications. Other clinical features include degenerative joint disease, which manifests in the early teens. The gene responsible for SED tarda, *SEDL*, is located at Xp22. The open reading frame of 420bp is encoded by 4 exons (designated exons 3,4,5,6). We report two novel *SEDL* mutations identified by routine mutation analysis. The first mutation is a single base substitution (IVS3+1G>A). Although this particular mutation has not been previously detected, other similar splice site mutations have been reported. We also identified a large deletion encompassing exons 4 and 5 of the *SEDL* gene. A deletion involving exons 4, 5 and 6 has been previously published in a patient with SEDT. The identification of these novel mutations in *SEDL* adds to the spectrum of mutations previously reported. A review of all currently known *SEDL* gene mutations will also be presented.

MUTATION DISCOVERY IN THE ARISTALESS RELATED HOMEOBOX (ARX) GENE (O62)

T. Fullston,[1,2] M. Finnis,[1] G. Turner,[3] O. Reish,[4] S. Kieffer,[5] W.T. Gibson,[5] G. Baynam,[6] L. Brueton,[7] J. Morton,[7] A. Norman,[7] G. McGillivray,[8] M. Tan,[1] C. Shoubridge [1] and J. Gecz[1,2]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Department of Paediatrics, University of Adelaide, Australia*

[3] *Genetics of Learning Disability, Hunter Genetics, Newcastle, Australia*

[4] *Asaaf Harofeh Medical Center, Zerifin, Israel*

[5] *Department of Medical Genetics University of British Columbia, Vancouver, Canada*

[6] *Genetic Services of Western Australia, Perth, Australia*

[7] *Clinical Genetics Unit, Birmingham Women's Hospital, Birmingham, United Kingdom*

[8] *Genetics Health Services Victoria, The Royal Children's Hospital, Melbourne, Australia*

Mutations in the ARX gene cause a diverse spectrum of human disorders (MIM#300382), all of which include intellectual disability (ID). The ARX protein has multiple domains, four of which are tracts of uninterrupted alanine residues. The first two polyalanine tracts have been frequently reported as mutated, possibly due to the extraordinarily high GC content of the DNA that codes for them. Polyalanine tract 2 of *ARX* harbours the most frequently observed c.428_451dup (dup24bp) mutation. In our cohort of 500 individuals with ID, genomic DNA samples were initially screened for the recurrent *ARX* mutations. Negative samples were subsequently screened for mutations in the entire *ARX* ORF by either SSCP, dHPLC or direct sequencing. We found seven duplication mutations in polyalanine tract 2 (1.4%), two of which are larger than the recurrent dup24bp mutation (c.435_461dup27bp, c.424_456dup33bp), and one expansion mutation in polyalanine tract 1 (0.2%). Exon 2 of *ARX* represents a mutation 'hot spot' containing 77% (10/13) of all mutations detected, with 54% (7/13) in polyalanine tract 2 alone. We also found three novel point mutations. A segregating c.81G>C point mutation causes a premature termination codon in exon 1, leading to Ohtahara and West syndrome (MIM#308350) in hemizygous male cousins, confirming *ARX* mutations can cause Ohtahara syndrome. Two different point mutations result in an X-linked lissencephaly with ambiguous genitalia phenotype (MIM#300215), probably due to the alteration of homeodomain residues important for either DNA binding or Importin-13 interaction. Studies are underway to asses the molecular and cellular consequences of these novel *ARX* mutations.

HAPLOINSUFFICIENCY FOR COL3A1 RESULTS IN EHLERS-DANLOS SYNDROME WITH VARIABLE PHENOTYPE IN MEMBERS OF A SINGLE FAMILY (P51)

S. Ghedia,[1] A. Turner [1] and P. Byers[2]

[1] *Department of Medical Genetics, Sydney Children's Hospital, Sydney, Australia.*

[2] *Departments of Pathology and Medicine, University of Washington, Seattle, United States of America*

Ehlers-Danlos syndrome, vascular type, is rare, life-threatening autosomal dominant connective tissue disorder characterised by thin, translucent skin, a characteristic facial appearance and arterial and hollow organ fragility. Arterial rupture or dissection and intestinal or uterine perforation are the presenting signs in 70% of adults. The median age of survival is 48 years. COL3A1 is the only gene associated with this form of EDS. Over 400 pathogenic mutations have been identified, the majority of which result in structural alteration in the procollagen III protein leading to impaired collagen function. We present a family with haploinsufficiency for COL3A1 caused by a frameshift mutation (c.1808delG) in exon 26 of the gene. The resultant mRNA is unstable, leading to production of 50% of total protein product. Few such families have been reported in the literature. Previously, because heterogeneous 'null' mouse models have no vascular phenotype, it was thought that people with similar mutations might not be clinically affected. It is now recognised that individuals with COL3A1 null mutations may have a similar clinical course to that typically seen in EDS, vascular type, although they may have a delay in the onset of first symptoms. We have identified four members of this family, who carry the same null mutation. There is great variability in phenotype: two family members have had severe arterial fragility and manifest typical features of EDS, vascular type. Two other family members have very mild musculoskeletal features, comprising of recurrent shoulder dislocation only. The phenotypic variability in our family is unexplained. It has been postulated that the other 'normal' allele may contribute in some way to the overall phenotype.

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ANYTHING I CAN DO, YOU CAN DO TOO? PROFESSIONAL IDENTITY AND GENETIC COUNSELLING (O8)

C. Gaff

Genetic Health Services Victoria, The University of Melbourne, Australia

Professional recognition is a challenge for genetic counsellors in Australia and internationally. This challenge may grow rather than diminish as the genetic basis of common conditions is understood and other health professionals incorporate conveying genetic information into their practice. How can we foster an identity as a profession while genetic counselling is perceived to be an activity performed by many (or any) health professionals who convey genetic information? I will explore this issue by considering genetic counselling as a profession, a practice and a discipline.

LYSOSOMAL STORAGE DISEASE AND BONE MARROW TRANSPLANT: THE NEW ZEALAND EXPERIENCE (P18)

E. Glamuzina[1], L. Teague[1], M. Fietz[2] and C. Wilson[1]

[1] *Starship Childrens Hospital, Auckland, New Zealand*

[2] *National Referral Laboratory for Lysosomal, Peroxisomal and Related Genetic Disorders, Adelaide, Australia*

Background: Bone marrow transplantation (BMT) is used for the treatment of some lysosomal storage diseases. Four children with lysosomal storage disease have received BMT in New Zealand over the past 8 years. *Cases:* Case 1 is a girl with juvenile metachromatic leukodystophy (MLD) underwent BMT at age 10 years. 6 years postprocedure she has experienced marked deterioration in gross and fine motor function and is now fully dependent on carers. Her cognition has deteriorated to a much lesser extent although she has significant problems with mood. Case 2 received a BMT at age 3 years for α-mannosidosis. Currently at age 7 years he has mild orthopaedic, dental and ENT problems but is generally doing well and has normal cognition. Case 3 underwent a BMT at 13 months of age for mucopolysaccharidosis type I. At age 9 years he has relatively mild skeletal manifestations but is otherwise well and has normal cognition. Case 4 is the younger sibling of a patient with MLD who received two presymptomatic BMTs. Unfortunately both of these failed secondary to graft rejection and he has gone on to develop the classical late-infantile form of the disease. *Conclusion:* Bone marrow transplantation, when performed early in the disease, is particularly effective in some forms of LSD's. However in conditions such as MLD the procedure is less predictable and thus the clinical indications less clear.

SKELETAL ABNORMALITIES AND MUCOPOLY-SACCHARIDOSIS TYPE III: TWO BROTHERS WITH MULTIPLE PATHOLOGICAL FRACTURES (P19)

E. Glamuzina, N. Gailer and C. Wilson

Starship Childrens Hospital, Auckland, New Zealand

Background: Mucopolysaccharidosis (MPS) III or Sanfilippo disease is caused by defects in the lysosomal degradation of heparan sulphate. The disease is characterised by developmental regression and unlike the other mucopolysaccharidoses, bone and visceral disease is relatively mild. There has been one previous report of children with Sanfilippo disease and osteoporosis secondary to a combination of diet, vitamin D deficiency, immobility and anti-epileptic drug use. *Cases:* Two brothers, 23 and 28 years of age, with a diagnosis of MPS IIIB present with a recent history of recurrent pathological fractures with excessive callus formation and profound osteopaenia. Their risk factors for osteoporosis included immobilisation and institutionalised care however their bone metabolism parameters including vitamin D were within normal limits. While the patients appeared to experience surprising little discomfort, supposedly due to their severe mental retardation, the fractures significantly affected their care, increasing parental anxiety and impacting on their trust of the institution in which their sons lived. *Conclusion:* Clinicians need to be aware of the risk of bone disease in MPS III, perhaps over and above that of other immobile young adults in institutionalised care.

MICHEL APLASIA AND THE VACTERL SPECTRUM OF CONGENITAL MALFORMATIONS: A RARE ASSOCIATION (P58)

E. Glamuzina and S. Aftimos

New Zealand Biochemical Genetics, Auckland City Hospital, Auckland, New Zealand

Background: Michel aplasia is a rare form of vestibulocochlear dysplasia resulting in complete labyrinthine aplasia with or without failure of the otic placode. Autosomal recessive and dominant familial cases have been described. It is more commonly bilateral and rarely is this anomaly associated with other malformations. There has been one previous report of unilateral Michel anomaly associated with tracheoesphageal fistula. *Case:* 6-year-old girl who presented shortly after birth with an H type tracheo-oesophageal fistula, type I laryngeal cleft, lipomyelomeningocele and tethered cord, thoracic hemivertebra, fused ribs and profound right sided hearing loss. The cause for her hearing impairment was found to be severe vestibulo-cochlear dysplasia associated with abnormal course of the 7th cranial nerve and hypoplasia of the petrous temporal bone consistent with unilateral Michel aplasia. *Conclusion:* We present a case of unilateral Michel aplasia and abnormalities that may fit into the VACTERL spectrum of malformations. The concomitant development of the inner ear and mesoderm differentiation between 3- and 4-weeks gestation, suggests a common insult at a critical period of blastogenesis, resulting in the malformations observed in our patient.

UTILITY OF THE X-TILING PATH AS A DIAGNOSTIC TOOL IN XLMR (P45)

A. Hackett,[1,2] J. Boyle,[1,2] G. Froyen,[3] C. Meldrum,[4] D. Mowat,[5] G. Turner,[1,2] M. Wilson[6] and O. Lawrence[1,4]

[1] *NSW GOLD Service, Hunter Genetics, Newcastle, Australia*

[2] *University of Newcastle, Newcastle, Australia*

[3] *Human Genome Laboratory, Centre for Human Genetics, VIB, Leuven, Belgium*

[4] *Hunter Area Pathology Service, John Hunter Hospital, Newcastle, Australia*

[5] *Sydney Children's Hospital, Sydney, Australia*

[6] *Children's Hospital at Westmead, Sydney, Australia*

In March 2007, our XLMR clinical service introduced testing for microdeletions and duplications on the X chromosome. A proband from 74 undiagnosed probable XLMR families and brother pair families, was screened using the X-tiling path array.[1] This tiling path costs $350 per patient. The resolution of a single clone is ~80 kb and 2 consecutive clones are required to be deleted or duplicated for the change to be classified as significant. Five patients (6.7%) have been identified with copy number changes. All are duplications, ranging in size from 260 kb to 6 Mb. One of these had already been identified by cytogenetic studies and the tiling path was used to define the duplication more precisely. Following segregation analysis in the families, two were determined to be normal copy number variations (one novel). The other 2, representing 2.7% of families, are regarded causal as they (1) contain brain-expressed genes and (2) show segregation with the phenotype (by array-CGH and qPCR). We will present clinical details of these patients and their families, molecular data including potential candidate genes and evidence for the first case of gonadal mosaicism for a chromosome duplication.

1 Bauters, M., Van Esch, H., Marynen, P., & Froyen, G.. (2005). X chromosome array-CGH for the identification of novel X-linked mental retardation genes. *Eur J Med Genet, 48*(3), 263–275.

X-LINKED GRIA3 MUTATIONS CAUSE TWO DIFFERING NEUROLOGICAL PHENOTYPES IN THE HETEROZYGOUS FEMALE AND THE HEMIZYGOUS MALE (O68)

A. Hackett,[1,2] Boyle J.,[1,2] G. Froyen,[3] M. Parsons,[2,4] P. Tarpey,[5] G. Turner[1,2] and J. Gecz[6]

[1] *NSW GOLD Service, Hunter Genetics, Newcastle, Australia*

[2] *University of Newcastle, Newcastle, Australia*

[3] *Human Genome Laboaratory, Centre for Human Genetics, VIB, Leuven, Belgium*

[4] *Neurology Department, John Hunter Hospital, Newcastle, Australia*

[5] *The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, United Kingdom*

[6] *Department Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

Features described in patients with GRIA3 deletions/mutations include moderate mental retardation, aesthenic body habitus, poor muscle bulk, hyporeflexia, myoclonic jerks, seizures, autistic behaviors and bipolar disorder (Wu et al. 2007; Gecz et al. 1999). The GRIA3 gene encodes the AMPA receptor GLUR3, which mediates fast synaptic transmission in the CNS. Two families have been identified in the GOLD service. The W family has a M706T (T2117C) mutation, which lies within a highly conserved region of iGluR3, located within the S2 ligand-binding domain site. Family M has a 0.4Mb deletion at Xq25 that contains the entire GRIA3 gene. The affected males in the two families presented initially with moderate learning disability associated with poor muscle bulk and hypotonia. The majority of carrier females were found to have hand tremor, mild gait ataxia, altered reflexes and pes cavus. This suggests that neurological examination in female relatives of males with suspected X-linked mental retardation may provide a clue to those with GRIA3 gene changes.

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ASSOCIATION STUDIES OF *AR, ER*β AND *CYP19* REPEAT LENGTH POLYMORPHISMS IN MALE-TO-FEMALE TRANSSEXUALS (O99)

L. Hare,[1,2] P. Bernard,[1,2] C. Sanchez,[3] E. Vilain,[3] T. Kennedy[4] and V. R. Harley[1,2]

[1] *Human Molecular Genetics, Prince Henry's Institute of Medical Research, Melbourne, Australia*

[2] *Department of Genetics, Monash University, Australia*

[3] *Department of Human Genetics, University of California, United States of America*

[4] *Gender Dysphoria Clinic, Monash Medical Centre, Melbourne, Australia*

From a very early age, people develop an inner sense of being male or female — known as gender identity, consistent with the sex one was assigned at birth. However, transsexuals develop a strong cross-gender identity and report clinically significant distress. There is a likely genetic component to transsexualism, and genes involved in sex steroidogenesis are good candidates. We hypothesized that male-to-female transsexualism is associated with gene variants responsible for undermasculinisation and/or feminisation. Disease-associated repeat length gene polymorphisms in *androgen receptor* (*AR*), *estrogen receptor beta* (*ER*β), and *aromatase* (*CYP19*) were analysed in 112 male-to-female transsexuals and 258 male controls. Associations and interactions were investigated between CAG repeat length in the *AR* gene, CA repeat length in the *ER*β gene and TTTA repeat length in the *CYP19* gene and male-to-female transsexualism. With respect to allele and genotype frequencies and transsexualism no association was found between the *ER*β gene polymorphisms. A weak association was found between transsexualism and the heterozygous short/long *CYP19* genotype (p = .04). Genotype interaction analyses revealed a significant association between the SL-*CYP19* genotype when in combination with a long *AR* polymorphism (p = .01 after Bonferroni correction). The particular CYP19 and AR variants overrepresented among transsexuals are predicted to raise estrogen signalling and lower androgen signalling. This study provides preliminary evidence that male gender identity may be partly mediated through androgen receptor and aromatase.

IMMUNOHISTOCHEMISTRY TESTING IN COLORECTAL CANCER: WHAT DO NEW ZEALAND SURGEONS KNOW? (P53)

S. J. Harper,[1] A. McEwen,[3] A. Kidd,[3] D. Kenwright,[4,5] and E. R. Dennett[1,2]

[1] *Department of Surgery, Capital and Coast District Health Board, New Zealand*

[2] *Department of Surgery and Anaesthesia, University of Otago, New Zealand*

[3] *Central Regional Genetic Services, Capital and Coast District Health Board, New Zealand*

[4] *Department of Obstetrics and Gynaecology, University of Otago, New Zealand*

[5] *Anatomic Pathology, Capital and Coast District Health Board, New Zealand*

Introduction: Appropriate testing for microsatellite instability (MSI) aims to identify those families who may have syndromic colon cancer. We questioned the current knowledge and practice of general surgeons in New Zealand with respect to MSI testing. *Method:* An anonymous questionnaire was sent to all surgeons registered with the RACS as general surgeons. Combined analysis of all replies was performed and compared against the responses of those who identified themselves to the RACS as colorectal surgeons. The answers were assessed against the revised Bethesda criteria. Fisher's exact and the chi-squared tests were used for statistical analysis. *Results:* Responses were received from 91 surgeons (69 general and 22 colorectal). In 6 of the 10 practice-based questions colorectal surgeons scored higher than general surgeons, but this was not statistically significant. Less than half of all surgeons thought that a family history of renal tract cancer can be linked with HNPCC, and surprisingly, colorectal surgeons were less knowledgeable than their general counterparts about a positive family history of ovarian cancer being an indication for MSI testing (49 vs. 36%). Most surgeons (81%) felt it would be appropriate to discuss the genetic implications of a positive MSI result with the patient. Reassuringly, even more surgeons (91%) would also refer a positive result to a specialist genetics service. *Conclusion:* Surgeons claim to be aware (89%) of the availability of MSI testing in NZ but are inconsistently informed of the indications for this. Education is required though there is a willingness to refer to specialist genetics services.

ROLE OF ORGANIC ACID ANALYSIS IN THE DIAGNOSIS AND MANAGEMENT OF A MILD CASE OF HOLOCARBOXYLASE SYNTHETASE DEFICIENCY (P17)

C. Hart,[1] J. Ang[1] and E. S. Tan[2]

[1] *Biochemical Genetics Laboratory, KK Women's and Children's Hospital, Singapore*

[2] *Paediatric Medicine, KK Women's and Children's Hospital, Singapore*

Patient: The patient is a 2-year-old Chinese boy, first child of nonconsanguineous parents, with a history of atopic dermatitis and mild developmental delay. He presented during an episode of gastroenteritis with hypoglycaemia, encephalopathy and acidosis. Lactate and ammonia were elevated at 3.3 mmol/L (0.7-2.1) and 140 µmol/L (9-33) respectively. *Results:* Organic acid analysis revealed a marked excretion of lactate, ketones, 3-hydroxyisovaleric acid, and 3-methylcrotonylglycine, and significant excretion of 3-hydroxypropionate, propionylglycine, tiglylglycine and methylcitrate consistent with a diagnosis of Multiple Carboxylase Deficiency (MCD). On treatment with biotin (20mg per day) his condition improved rapidly, including complete resolution of the dermatitis within a week. After 1 week of biotin organic acids were reanalyzed and showed complete resolution of propionyl-CoA carboxylase associated metabolites and marked reduction in 3-hydroxyisovaleric acid and 3-methylcrotonylglycine. The lack of total resolution of all metabolites suggested MCD due to holocarboxylase synthetase (HCS) rather than biotinidase deficiency, as was confirmed by the finding of normal biotinidase activity. After 3 weeks of biotin (no protein restriction) organic acid analysis showed complete resolution of all abnormal metabolites indicating a mild variant, consistent with clinical presentation. Full characterization by fibroblast enzyme assays is pending. *Discussion:* Patients with HCS deficiency classically present with severe neonatal symptoms and require protein restriction for management. However, it is clear that a minority of patients present in a manner more usually associated with biotinidase deficiency. Serial analysis of organic acids can allow a degree of characterization and give information on adequacy of treatment pending confirmation of diagnosis.

SUCCESSFUL PREGNANCIES AFTER APPLICATION OF ARRAY-CGH IN PGD ANEUPLOIDY SCREENING (O132)

A. Hellan,[1] K. Abu-Amero,[2] J. Azouri,[3] and S. El-Akoum [1]

[1] *PGD Laboratory, Saad Specialist Hospital, Al-Khobar, Saudi Arabia*

[2] *Shafallah Medical Genetics Center, Doha, Qatar*

[3] *A-Clinic-Mount Liban Hospital, Beirut, Lebanon*

In patients suffering from recurrent IVF failure, implantation failure and early embryo demise can be attributed to the high frequency of chromosomal aneuploidy observed in human embryos. Preimplantation genetic diagnosis (PGD) using multiple displacement amplifications (MDA) and array comparative genomic hybridization (aCGH) was successfully performed on 8 patients with a minimum of 3 recurrent abortions for the aim of detecting aneuploidy and ameliorating pregnancy rate. 41 embryos with 8 or more cells were biopsied by taking two blastomeres from each embryo. The DNA from these blastomeres were amplified and analyzed by aCGH technology. The results showed a complex panel of chromosomal abnormalities, in which 60% of those abnormalities could not be detected by fluorescent in situ hybridization (FISH). 6 out of 8 patients had embryos for transfer with 5 out of those 6 showing positive pregnancy tests. To our knowledge, this report is the first to show a pregnancy after PGD using the aCGH technology. The excellent pregnancy rate obtained here is encouraging and will open the door for enrolment of more patients.

TWO POTENTIAL PMS2 FOUNDER MUTATIONS IN THE AUSTRALASIAN POPULATION (O84)

D. Henry, C. Vakulin, G. Mach, Z. Rudzki and J. Carroll

Division of Molecular Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia

Germline alterations in the DNA mismatch repair genes MSH2, MSH6 and MLH1 predispose to HNPCC with an autosomal dominant inheritance pattern. The PMS2 gene also codes for a protein that is essential for DNA mismatch repair. Diagnostic PMS2 gene screening was introduced at the IMVS in 2003. A total of 118 probands have been analysed by DNA sequencing and MLPA since that time, all with informed consent. To date, we have identified 11 different mutations, of which two in particular stand out as potential founder mutations. We have detected the frameshift mutation, NM_000535.4(PMS2):c.736_741del6ins11, NP_000526.1(PMS2):p.P246CfsX3 in exon 7, in seven probands, accounting for approximately 6% of the total number of patients tested. The other mutation, a deletion of exon 10, (NM_000535.4(PMS2):c.989-296_1144+70del), has been found in four probands, accounting for approximately 4% of all patients screened. Together these two mutations account for 52% of all pathogenic PMS2 mutations identified. Both of these mutations have been detected in conjunction with the same rare, benign variant in exon 11. Given that Australia was colonised in the late 18th century, these 2 mutations are most likely to be of European origin. Indeed, Clendenning et al., in *J. Medical Genetics* (2008) recently estimated that one of these mutations, the indel, arose around 1625 years ago in individuals of British and Swedish ancestry. The high incidence of these 2 mutations and their potential to be founder mutations has raised the issue of whether our current screening strategy should be changed to use MLPA analysis in the first instance.

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IS KARYOTYPING WORTHWHILE IN MYELOPROLIFERATIVE DISORDERS (MPDS)? (O39)

D. Henry, S. Bawden, J. Beerworth, J. Fortunaso, R. Fraser, T. Hillier, M. Khazab, T. Kuczek, M. Nicola, J. Suttle, G. Cheetham and S. Moore

Molecular Pathology, IMVS, Adelaid , Australia

Historically cytogenetics has been of limited use in MPD, other than to serve the major function of separating it into Philadelphia positive disease (CML) and Philadelphia negative disease (PV, ET & MF). CML is now treated by specific kinase inhibitors and it is somewhat irrelevant to identify ancillary mutation by karyotyping when the assessment of BCR-ABL levels accurately demonstrate response to, or failure of, therapy. Q-PCR is probably a better, cheaper test to use in this setting. Therefore cytogenetics is of limited use in CML, being helpful only if the patient develops a Ph-negative disease. Attempts to subclassify the Ph-negative MPDs using cytogenetics have failed abysmally and presentation cytogenetics has not proven particularly useful in stratifying most patients into low- & high-risk groups. Acquired JAK2 V617F mutation was first described in 2005 and is seen in ~95% of PV, ~55% ET & ~45% MF. Additional mutation is required for disease progression, none-the-less JAK2 mutation may be the first genuine genetic risk stratifier in these diseases. We have karyotyped and performed JAK2 mutation analysis on a cohort of ~200 MPD patients and examined cytogenetic patterns in the mutated and non-mutated groups. Our findings suggest that a whole genome screen, such as karyotyping, does remain the only safe way to identify and sub classify the rarer types of Philadelphia-negative & JAK2 V617F-negative MPD, some of which may respond to different therapeutic regimens, but may not be a necessary part of the work-up for all MPD patients.

ESTIMATING THE PREVALENCE & DETECTION RATES OF KLINEFELTER SYNDROME (P75)

A. S. Herlihy,[1,2,3] L. Gillam,[1,4] R. McLachlan,[2,3] M. Cock[2,3] and J. Halliday[1,4]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Monash University, Australia*

[3] *Andrology Australia, Australia*

[4] *University of Melbourne, Australia*

Klinefelter Syndrome (KS) is a genetic condition (47XXY) affecting males and resulting in a spectrum of clinical features. International studies have estimated the prevalence to be 1:650, yet only 30% of these males are diagnosed. In Australia, this translates to 15,000 males with KS, over 10,000 of them remaining undiagnosed. In addition, results from a recent British study suggest that the prevalence of KS may be increasing. Early identification has been advocated for many years, but population-based genetic screening has never been explored. This study aimed to determine the prevalence and detection rates of KS in Victoria, and to provide a context for future studies of postnatal screening strategies. Diagnoses of all relevant karyotypes made in Victoria since 1983 were obtained through multiple sources including the Victorian Birth Defects Register and the four Victorian cytogenetics laboratories. Between 1997 and 2006, there were 63 prenatal diagnoses of 47XXY indicating a prenatal prevalence of around 1:400. 339 postnatal diagnoses of 47XXY were made in this period suggesting 65% of males with KS in Victoria may actually be diagnosed. However, the majority of diagnoses were made in adulthood, probably due to fertility investigations, and often past the point of optimal intervention. This provides the first Australian calculation of prevalence and diagnosis rates for KS and suggests higher detection rates than those seen overseas. Given the high prevalence of KS, and the availability of appropriate medical and psychological interventions, it is vital that awareness is encouraged and detection rates are increased.

THE RISKS AND BENEFITS OF SCREENING FOR KLINEFELTER SYNDROME: A CRITICAL ANALYSIS (O90)

A. S. Herlihy,[1,2,3] J. Halliday,[1,4] R. McLachlan,[2,3] M. Cock[2,3] and L. Gillam[1,4]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Monash University, Australia*

[3] *Andrology Australia, Australia*

[4] *University of Melbourne, Australia*

Background: Klinefelter syndrome (KS) is a genetic condition (47XXY) affecting males and resulting in a spectrum of clinical features, ranging from infertility, androgen deficiency and breast development to varying levels of social, behavioural and learning difficulties. The prevalence has been estimated to be 1:650, yet up to 70% of males remain undiagnosed. Early identification has long been advocated, but population-based genetic screening for KS has never been explored. *Aim:* To identify the potential risks and benefits that could arise from implementing population-based genetic screening for KS at different ages and stages of development. *Method:* A framework was developed to assess the medical (hormone, therapeutic interventions), psychological (self-esteem, relationships) and ethical (autonomy, associated stigma) implications of postnatal genetic screening for KS in four hypothetical age-dependent scenarios — newborn, infancy, primary school entry and high school entry — chosen as providing opportunistic circumstances in which an individual might be evaluated. The outcomes have been considered in relation to diagnosis in adulthood and the most common scenario of lifelong nondiagnosis. Evidence of potential risks and benefits associated with KS diagnosis was collected by analysis of the existing literature. *Results:* Our analysis indicates that while there is information on available medical, educational and psychological interventions, there has been no consideration of the impact of age of diagnosis and the related timing of interventions on psychosocial and other quality of life outcomes. *Conclusion:* Research is needed to inform decisions regarding population-based genetic screening for KS such as our proposed study examining the psychosocial impact of KS.

MICRODUPLICATION OF CHROMOSOME 2Q24 CAUSING FAMILIAL NEONATAL SEIZURES WITH INTELLECTUAL DISABILITY (O123)

S. E. Heron,[1,2] I. E. Scheffer,[3,4] B. E. Grinton,[3] H. Eyre,[1] K. L. Oliver,[3] S. Bain,[1] S. F. Berkovic [3] and J. C. Mulley[1,2,5]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *School of Paediatrics and Reproductive Health, University of Adelaide, Australia*

[3] *Department of Medicine, University of Melbourne, Austin Health, Melbourne, Australia*

[4] *Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia*

[5] *School of Molecular Biosciences, University of Adelaide, Australia*

A family was ascertained with four affected members with neonatal onset of tonic, convulsive and myoclonic seizures. Median age of onset was 2 days (range 12 hours–18 days) in 36–38 weeks gestation infants; jerking in utero was noted in two babies. Seizure offset occurred at median 4 months (range 2 weeks–19 months). Intellectual disability ranged from mild to severe in three children and their affected mother had learning difficulties. A microduplication segregating with the disorder was detected by the observation of three alleles for several microsatellite markers within 2q24. This region contains the sodium channel subunit genes *SCN1A*, *SCN2A* and *SCN3A*. Missense mutations in *SCN2A* cause benign familial neonatal–infantile seizures (BFNIS) while mutations disrupting *SCN1A* cause Dravet syndrome. The duplication of one or more of these genes is presumed to cause the familial disorder described here. The duplication was further characterized using multiplex ligation-dependent probe amplification (MLPA) using probes within *SCN1A* and fluorescence in-situ hybridisation (FISH). These analyses showed that the duplication was approximately 1.36 Mb in size, encompassing 6 intact genes and exons 10 to 26 of *SCN1A*. FISH showed that the duplicated sequence was inverted and inserted at the telomeric duplication breakpoint (nuc ish inv dup(2)(q24.3q24.3)), which is expected to disrupt *SCN1A*. Family members have a more severe phenotype than BFNIS but do not have Dravet syndrome. Determination of the exact breakpoints and insertion point of the 2q duplication to confirm whether or not *SCN1A* is disrupted is required to clarify the genotype–phenotype relationship.

TALKING ABOUT DISABILITY IN PRENATAL GENETIC COUNSELLING SESSIONS: IDENTIFYING TENSIONS AND DEVELOPING STRATEGIES (O112)

J. Hodgson[1] and J. Weil[2]

[1] *Murdoch Childrens Research Institute, Melbourne, Australia*

[2] *University of California, San Francisco, California, United States of America*

To facilitate informed decision-making in prenatal genetic counselling it is essential that counselees and counsellors engage in a process that provides: (a) relevant information concerning the nature of genetic conditions and (b) an opportunity for counselees to consider parenting a child with a disability. This presentation details the findings from two international workshops that were recently held at conferences in USA (National Society of Genetic Counselors) and Spain (European Meeting on Psychosocial Aspects of Genetics) where genetic health professionals were encouraged to discuss and reflect on their experiences of communicating about disability within genetic counselling sessions. Several common themes emerged from the group discussions and participants identified many challenges concerning both 'what to say' and 'how to say it'. There was useful discussion about effective communication strategies that could be used to promote sensitive and ethically appropriate discourse about disability between counselees and counsellors. This presentation will provide valuable information for all professionals who communicate about disability in genetic counselling settings. It is hoped that these findings can be further informed by input from Australasian professionals as well as consumer groups and other stakeholders.

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NEWBORN SCREENING FOR LSD USING PROTEIN PROFILING OF DRIED BLOOD-SPOTS (O52)

C. Dean, D. Lang, J. Pacyna, A. Whittle, Y. Kolev, K. Brion, L. Karageorgos, D. Brooks, E. Parkinson-Lawrence, P. Meikle, M. Fuller and J. Hopwood
Lysosomal Diseases Research Unit, Women's and Children's Hospital, Adelaide, Australia

Lysosomal storage disorders (LSD) are chronic and progressive diseases. Most patients are clinically normal at birth but develop symptoms early in childhood through to adulthood. Despite no curative treatment, a number of therapeutic options are available to improve quality of life and longevity, and this therapy list is expanding. Experience has shown that *therapies are more effective if commenced before the onset of symptoms.* To achieve this, there is a pressing need for newborn screening to identify affected individuals early, before the onset of severe irreversible pathology. We have developed a multiplexed immune-quantification system that is able to assay 11-different lysosomal proteins to generate protein profiles and identify individuals with one of 13-different LSD. Using a single incubation of a 3mm-disc punched from dried blood-spots this method is able to identify mucopolysaccharidosis type I (MPS-I), MPS-II, MPS-IIIA, MPS-IIIB, MPS-VI, metachromatic leukodystrophy, Gaucher, Fabry, Niemann-Pick type A/B, Pompe, multiple sulfatase deficiency and mucolipidosis type II/III patients. The assay also includes a leucocyte-specific marker (CD45) to normalise leucocyte content, one lysosome organelle-specific marker (LAMP-1) to normalise lysosome content, and a marker of inflammation (chitotriosidase) generated from lysosomal storage in macrophages. Importantly, methods to predict the rate of clinical progression in asymptomatic patients — based on amount of storage substrate and genotype assayed with dried blood-spots — are also under evaluation. In combination, this technology will also speed the diagnosis of symptomatic LSD patients and enable accurate prognosis and monitoring of treatment of individual patients.

RETROSPECTIVE ANALYSIS OF PATIENTS ATTENDING AUSTRALIA'S FIRST RETT SYNDROME MULTIDISCIPLINARY MANAGEMENT CLINIC (O78)

Z. Horton,[1] S. Thompson,[2] J. Newsom,[3] J. Cowell,[4] R. Kirkland,[5] E. Jay,[6] E. Lopes,[7] B. Bennetts,[8] J. Christodoulou[9] and C. Ellaway[9]

[1] *Department of Clinical Genetics, Childrens Hospital Westmead, Sydney, Australia*

[2] *Department of Dietetics and Nutrition, Childrens Hospital Westmead, Sydney, Australia*

[3] *Deaprtment of Physiotherapy, Childrens Hospital Westmead, Sydney, Australia*

[4] *The Elinor Wray Department of Speech Pathology, Children's Hospital at Westmead, Sydney, Australia*

[5] *Occupational Therapist, Rett Syndrome Clinic, Childrens Hospital Westmead, Sydney, Australia*

[6] *Special Care Unit, Westmead Centre for Oral Health, Sydney, Australia*

[7] *Nordoff-Robbins Music Therapy Australia at the Golden Stave Music Therapy Centre Kingswood, Australia*

[8] *Department of Molecular Genetics, Childrens Hospital Westmead, Sydney, Australia*

[9] *Western Sydney Genetics Program, Childrens Hospital Westmead, Sydney, Australia*

Established in 2000, the Rett syndrome Multidisciplinary Management Clinic (RMMC) at the Children's Hospital at Westmead (CHW), Sydney, is Australia's first and one of the world's few comprehensive clinics for the diagnosis and long-term management of females with Rett syndrome. Rett syndrome is a neurodevelopmental disorder characterised by normal early development followed by a period of regression. This complex clinical picture demands lifelong input from multiple medical and allied health specialties. To date over 90 females and one male have been diagnosed and supported through the clinic aged between 18 months and 42 years. Currently, members of the clinic team include a clinical geneticist, genetic counsellor, physiotherapist, speech therapist, dietician, occupational therapist, music therapist and dentist. Together, these allied professionals are working towards a retrospective analysis of the patients who attended the RMMC at the CHW between the time when the clinic was established in February 2000, until December 2007. With approval from the CHW Ethics Committee we have reviewed all medical records of females who have attended the clinic since 2000. Demographic data, clinical phenotype and genotype have been entered into a purpose built database. From these analyses we will ascertain the frequency and nature of complications of Rett syndrome in this cohort. We anticipate that this will provide an insight into the services, aids and supports that may be required and help us to provide a better service for these families. We anticipate that early diagnosis and intervention will improve the long-term morbidity of the disorder.

EVALUATION OF THE MANCHESTER SCORING SYSTEM FOR BRCA GENE TESTING IN WESTERN AUSTRALIA (O86)

G. Howarth,[2] A. Bremner,[2] H. Mountain[1] and S. Townshend[1]

[1] *Genetic Services of Western Australia, King Edward Memorial Hospital, Perth, Australia*

[2] *School of Population Health, University of Western Australia, Australia*

A retrospective evaluation of the Manchester scoring system (MSS) was performed at Genetic Services of Western Australia's Familial Cancer Program. The aim was to determine whether the MSS improved the detection rate of BRCA 1 & 2 mutations in our population in comparison to the previously used National Breast Cancer Centre (NBCC) criteria. Case files on 202 individuals offered diagnostic BRCA testing between January 2004 and December 2006 were reviewed. The NBCC and MSS criteria were applied to two groups (115 in the NBCC group January 2004 to June 2005 and 87 in the MSS group July 2005 to December 2006) and the outcomes recorded. Risk factors such as the incidence of ovarian cancer, bilateral disease and male breast cancer were also noted. Testing methods were documented so that differences due to improved laboratory techniques could be accounted for. Mutation detection rates were compared using McNemar tests, logistic regression and sensitivity and specificity analysis. Analysis of the data showed that the mutation detection rate for the NBCC high-risk group was 14% (16/115), and applying the MSS to this group increased the rate to 18.5% with 100% sensitivity and 27% specificity. The mutation detection rate for the MSS group was 17.3% (13/87). The difference of 3.3% was not statistically significant ($p = .5$) however we will show that the Manchester criteria was a more objective risk assessment tool that led to fewer tests with similar, if not higher, detection rate.

A COUPLE'S DECISION TO HAVE PRENATAL TESTING AND THE CONSEQUENCES OF MEDICAL PATERNALISM (P4)

L. Hulston
Sydney Ultrasound for Women, Australia

There is a general consensus that women's decisions regarding prenatal testing should be autonomous. However, studies have shown that, in practice, counsellors and other health professionals can diverge from nondirectiveness. Within the prenatal setting, patients often seek health professionals' opinions regarding whether or not to uptake further diagnostic testing. While shared-decision making is desirable, directive counselling may instead result in paternalism. At SUFW, patients have their nuchal translucency ultrasound with first trimester serology (NT plus), which is followed by a consultation with the genetic counsellor to discuss their results. This poster outlines a case in which a patient and her partner attended our practice for NT plus screening. The results showed an increased risk for aneuploidy (Trisomy 21 and Trisomy 13/18). During post-test counselling the couple chose not to proceed with CVS or amniocentesis, instead electing to wait until the 19-week morphology scan to check for markers of aneuploidy at which time an amniocentesis could be reconsidered. This decision was based on the couple's concern regarding the procedure-related miscarriage risk. However, after consultation with her referring doctor, the patient was advised to have an amniocentesis instead of waiting until the morphology scan. Diagnostic testing revealed that the baby had Trisomy 13. During follow up genetic counselling the couple's grief and frustration was heightened by their lack of involvement in the decision making process. This demonstrates the need for ongoing education within the medical profession towards the benefits of counselling and patient autonomy.

FEEDING THE CHILD WHO IS NOT HUNGRY: A CASE STUDY OF GSD 1B (O24)

M. Humphrey,[1,2] J. Watkins[1,2] and A. Boneh[1]

[1] *Metabolic Service, Genetic Health Services Victoria, Australia*

[2] *Department of Nutrition & Food Services, Royal Children's Hospital Melbourne, Victoria, Australia*

Background: Treatment for GSD1b includes frequent feedings to maintain normoglycaemia and metabolic control. The feeding regime is challenging for infants, as normal appetite and satiety control maybe overridden, resulting in feeding disturbance. Meeting nutritional and glucose requirements without excessive energy intake and weight gain also needs careful manipulation. *Case:* GM presented at 2 months of age with symptoms consistent with GSD1b. Since GM was exclusively breast fed (BF), the initial recommended feeding regime involved BF 3-hourly with additional glucose polymer and overnight continuous nasogastric (NG) feeding. Increasing fussiness with BF resulted in supplemental formula feeds; however bottle refusal meant significant NG feeding was required. Over time, increasing weight gain velocity, total refusal to orally feed, volume intolerance, and hypoglycaemia all worsened. Parental anxiety was significant. At 10 months of age, 2-hourly feeds were required to maintain normoglycaemia. This exacerbated feeding difficulties, and required specialist speech pathology input. At 13 months, hypoglycaemia again worsened and uncooked cornstarch therapy introduced. Dosage increased with tolerance, resulting in improved BSL control, 3-hourly feeding, improvement in oral feeding skills and increased oral diet. However meeting estimated nutrient requirement remains difficult when balancing glucose and energy needs without overfeeding. *Conclusion:* Diets for infants with GSD1b may result in forced or overfeeding and impact on infants' normal feeding cues. Attention is required to balance good metabolic control with normal feeding development. Initiation of specialist help should commence before feeding problems become entrenched. Meeting estimated nutrient and glucose intakes without excessive caloric intake is difficult in totally enterally fed patients.

A FEMALE WITH A SUPERNUMERARY MARKER X CHROMOSOME WITH A DISTINCT PHENOTYPE (P72)

M. Hunter and D. Amor

Genetic Health, Murdoch Childrens Research Institute, Melbourne, Australia.

Supernumerary marker chromosomes (SMC) are quite common, occurring at a frequency of approximately 1 in 2000 livebirths. However there have been few reported patients with 47,XX,+mar(X), where the SMC is present in addition to two normal X chromosomes. We report a 2-year-old female with developmental delay, hypotonia, relative macrocephaly, hypertelorism, down slanting palpebral fissures, low set ears, and small hands and feet. She had a SMC of the X chromosome with breakpoints Xp11.22-p11.1 defined by SNP microarray. Blood karyotype revealed the SMC in all cells examined, however buccal karyotype showed 85 out of a hundred cells with the SMC, and 15 with a normal karyotype. In the cases previously reported in the literature with a similar SMC, there appears to be considerable phenotypic overlap. This girl and the previously reported cases offer a rare insight into the phenotype resulting from functional disomy of genes on the X-chromosome that are usually subject to X-inactivation.

A FEMALE CARRIER OF X-LINKED SPONDYLOEPIPHYSEAL DYSPLASIA TARDA WITH ARTHRITIS MIMICKING ANKYLOSING SPONDYLITIS (P73)

M. Hunter and R. Savarirayan

Genetic Health, Murdoch Childrens Research Institute, Melbourne, Australia

X-linked spondyloepiphyseal dysplasia tarda (SEDT) is a primary skeletal dysplasia characterized by short stature, characteristic radiographic changes and early onset arthritis in affected males. Female carriers are unaffected. Mutations in the TRAPPC2 gene have to been found to be the cause in the majority of patients (approximately 80%). Ankylosing spondylitis (AS) is a rheumatic condition that results in arthritis mainly of the spine and hips. We report a case of a female carrier with X-linked SEDT who had been given a diagnosis of ankylosing spondylitis. She had arthritis of her hips, knee and spine with pain, and stiffness. Mutation analysis showed she was heterozygous for the same mutation as had been found in her 2 affected uncles. There have been rare reports of female carriers manifesting with arthritis. The diagnosis of this patient was changed from AS to SEDT after discussion with her rheumatologist. The postulated mechanism of development of SEDT in a female is by skewed X-inactivation of the normal allele. Clinicians can now be informed that females with a family history of X-linked SEDT, may present with arthritis mimicking ankylosing spondylitis.

MICROARRAY CGH FOR ALL 24 HUMAN CHROMOSOMES ON SINGLE CELLS (O35)

N. Hussey, T. McCarthy, M. Goetz and R. Harris

Reproductive Health Science Pty Ltd, Unley, Australia

Reproductive Health Science Pty. Ltd. (RHS) is a South Australian biotechnology company founded by the University of Adelaide in 2003. RHS has developed a DNA microarray suitable for detecting aneuploidy in Preimplantation Genetic Screening (PGS) and Prenatal Diagnosis (PND) within 24–48 hours starting with as little as a single fetal cell. The RHS array consists of 24 unique probes in 8 replicates, one probe for each of the human chromosomes. The probes were generated by microdissecting individual chromosomes, randomly amplifying them then depleting them of repeat sequences. We have shown the RHS array can successfully diagnose aneuploidy in single lymphocytes, abnormal cell lines, blastomeres from day 3 embryos, fetal cells isolated non-invasively from the cervix, and as little as 100 microlitre amniotic fluid samples. RHS and its collaborators are currently validating our microarray for use in PGD aneuploidy screening and, during 2008, RHS will conduct a large multicentre PND trial on amniotic fluid samples.

THE MOLECULAR GENETICS SOCIETY OF AUSTRALASIA'S LABORATORY BEST PRACTICE METHOD FOR ANALYSIS AND REPORTING OF LABORATORY GENETIC ANALYSES IN THE FRAGILE X MENTAL RETARDATION GENE, FMR1 (O40)

V. Hyland

Pathology Queensland, Australia

The Molecular Genetics Society Of Australasia (MGSA) Best Practice Committee with the Human Genetics Society of Australasia (HGSA) Molecular Genetics Quality Assurance (QAP) Committee shall invite laboratories to submit their FMR1 specific method including any worksheets and process for report writing for the FMR1 mental retardation disorder for consideration to publish their method as one warranting best practice on the MGSA web pages of the HGSA web site. The current best practice method shall be reviewed each year. The MGSA shall archive any previous best practice method for access by members. The MGSA shall consider if the staff from the laboratory with the current best practice method will present an FMR1 mental retardation workshop at a six monthly or annual MGSA meeting. The best practice method will detail the full laboratory analyses. These analyses will include direct genomic DNA only and PCR based analyses. The best practice guidelines will include a mutation nomenclature acceptable to the general community. A set of Australian or New Zealand national FMR1 repeat size standards should be created and be available for use. The range of normal, mutable normal, premutation and full mutation repeats or alleles should be presented. A measurement of uncertainty for the various repeat alleles should be determined. Other mutations that are not identified should be reported. Local, national and Australian/New Zealand FMR1 databases should be established. Standards should apply to the Australian and New Zealand laboratories to use and submit data for FMR1 mutations to national databases.

THE MOLECULAR GENETICS SOCIETY OF AUSTRALASIA'S LABORATORY BEST-PRACTICE METHOD FOR ANALYSIS AND REPORTING OF LABORATORY GENETIC ANALYSES IN THE HUNTINGTON DISEASE GENE, HUNTINGTIN, HTT (O40)

V. Hyland

Pathology Queensland, Australia

The Molecular Genetics Society Of Australasia (MGSA) Best Practice Committee with the Human Genetics Society of Australasia (HGSA) Molecular Genetics Quality Assurance (QAP) Committee shall invite laboratories to submit their HTT specific method including any worksheets and process for report writing for the Huntington disease disorder for consideration to publish their method as one warranting best practice on the MGSA web pages of the HGSA web site. The current best practice method shall be reviewed each year. The MGSA shall archive any previous best practice method for access by members. The MGSA shall consider if the staff from the laboratory with the current best practice method will present a Huntington disease gene analysis workshop at a six monthly or annual MGSA meeting. The best practice method will detail the full laboratory analyses. These analyses will include PCR based analyses. The best practice guidelines will include a mutation nomenclature acceptable to the general community. A set of Australian or New Zealand national HTT CAG repeat size standards should be created and be available for use. The range of normal, mutable normal, reduced penetrance and full penetrance repeats or alleles should be presented. A measurement of uncertainty for the various repeat alleles should be determined. Details re the identification of mutation within the CAG/CAA repeat region should be reported. Local, national and Australian/New Zealand Huntington disease databases should be established. Standards should apply to the Australian and New Zealand laboratories to use and submit data for HTT mutations to national databases.

MUTATION SCREENING IN EPILEPSY AND MENTAL RETARDATION LIMITED TO FEMALES: IDENTIFICATION OF A NOVEL DE NOVO PCDH19 MUTATION IN AN AFFECTED FEMALE (O101)

K. Hynes,[1,2] P. Tarpey,[3] L. Dibbens,[1,4] M. Bayly,[1] S. Berkovic,[5] G. Turner,[6] J. Christodoulou,[7] H. Leonard,[8] J. Mulley,[1,2,4] M. Stratton,[3] I. Scheffer[5,6] and J. Gecz[1,2,4]

[1] *Department of Genetic Medicine, Woman's and Children's Hospital, Adelaide, Australia*

[2] *School of Molecular and Biomedical Science, University of Adelaide, Australia*

[3] *Wellcome Trust Sanger Institute, Hinxton, United Kingdom*

[4] *School of Paediatrics and Reproductive Health, University of Adelaide, Australia*

[5] *Epilepsy Research Centre and Department of Medicine, University of Melbourne, Austin Health, Melbourne, Australia*

[6] *GOLD Service, Hunter Genetics, Waratah, Australia*

Epilepsy and mental retardation limited to females (EFMR) is an intriguing X-linked disorder affecting heterozygous females and sparing hemizygous males. We recently identified mutations in protocadherin 19 (PCDH19) in 7 unrelated families with EFMR. The seizures, which onset in infancy or early childhood cease later in life (mean age 12). While seizures are the hallmark of this disorder, cognitive impairment is found in about 67% and varies in severity. Interestingly, autism spectrum disorder (ASD; 22%) and obsessive features (33%) were also frequently found. We aimed to assess the prevalence of PCDH19 mutations in females with some or all of the features of EFMR by screeneing three different cohorts of patients. The cohorts consisted of 136 females with epilepsy and/or mental retardation, 46 females with Rett syndrome (RS) that were negative for MECP2 and CDKL5 mutations, and 50 females with ASD (selected from the AGRE set, Cure Autism Now foundation, USA). We did not find any changes in the RS and ASD cohorts suggesting that despite some similarities between the symptoms of EFMR, RS and ASD, mutations in PCDH19 are unlikely to be associated with these disorders. We identified one novel missense change in PCDH19 from the cohort of females with epilepsy and/or mental retardation. This change, S276P is predicted to result in a functional knockout of PCDH19 as it affects a highly conserved residue adjacent to the adhesion interface of EC3 of PCDH19.

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GENETIC TESTING FOR INHERITED HEART DISEASES: THE NATIONAL GENETIC HEART DISEASE REGISTRY (O108)

J. Ingles,[1,2] L. Yeates,[1] V. Connell,[3] J. McGaughran,[4,5] A. Davis,[3] J. Vohra,[6] R. Weintraub,[3] J. Atherton[2,5] and C. Semsarian[1,7,8]

[1] *Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney, Australia*
[2] *Department of Cardiology, Royal Brisbane and Women's Hospital, Brisbane, Australia*
[3] *Department of Cardiology, Royal Children's Hospital, Melbourne, Australia*
[4] *Genetic Health QLD, Royal Children's Hospital, Brisbane, Australia*
[5] *Department of Medicine, University of Queensland, Australia*
[6] *Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia*
[7] *Central Clinical School, Faculty of Medicine, University of Sydney, Australia*
[8] *Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia*

Objectives: The National Genetic Heart Disease Registry was established in 2007, with the aim to recruit families with inherited cardiomyopathies and primary arrhythmogenic disorders. The Registry currently recruits from specialised cardiac genetic clinics, with a view to expand this to general cardiology and clinical genetics units. As the genetic basis for these disorders becomes clearer, the number of families undergoing genetic testing continues to increase. We report preliminary recruitment data from the Registry. *Methods:* Recruitment has commenced at Royal Prince Alfred Hospital, Sydney, and Royal Brisbane and Women's Hospital, Brisbane. Recruitment will begin at Royal Children's Hospital, Melbourne and Royal Melbourne Hospital, Melbourne in early 2008. Participation requires informed consent, and eligible individuals include those with disease and their first-degree (at-risk) relatives. Diseases include the inherited cardiomyopathies (e.g., hypertrophic cardiomyopathy [HCM], familial dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) and primary arrhythmogenic disorders (long QT syndrome, catecholaminergic polymorphic VT, Brugada syndrome). *Results:* Since June 2007, 171 individuals from 116 families have enrolled. The mean age of registrants is 48.3 years. To date, 90 (82%) registered families have a history of HCM. Of all families registered to date, 46 (42%) have undergone gene screening with 23 (21%) having a genetic diagnosis, 14 (13%) indeterminate results and 9 (8%) awaiting a result. Over 50% of families have not yet undergone genetic testing. *Conclusion:* Cardiac genetics is emerging as an important subspecialty of clinical genetics. Registry recruitment will increase in 2008 with inclusion of more sites, and become an important resource in raising awareness of cardiac genetics and genetic testing in Australia.

THE PALLIATIVE CARE MANAGEMENT OF A 16-YEAR-OLD FEMALE IN THE END STAGES OF SANFILIPPO SYNDROME 3A (MPS IIIA) (P33)

A. Inwood,[1] D. Phingst,[2] L. Pedersen,[2] L. Lockwood[2] and J. McGill[1]

[1] *Department of Metabolic Medicine, Royal Children's Hospital, Brisbane, Australia.*
[2] *Department of Oncology and Palliative Care, Royal Children's Hospital, Brisbane, Australia*

A 16-year-old female with known MPS IIIA was in the terminal phase of her illness. Seizures had started at 3 years of age and in the last few years had become increasingly refractive to all anticonvulsants. She required full nursing care that was primarily provided by her mother with the support of her father and carers (1 day per week). Her secretions were also resistant to oral medications. The patient's family had recognized that her quality of life was poor and deteriorating and welcomed an active palliative care model. As such care had never been offered at this hospital for patients other than those from oncology, a palliative care oncology model was adopted and the introduction of a subcutaneous continuous infusion of midazolam and glycopyrrolate was initiated, with morphine added 6 months into therapy. Doses were started at low levels and increased with further progression of symptoms. She passed away peacefully 7 months after the introduction of this new therapy. *Conclusion:* We were able to greatly improve her quality of life, which relieved her family's stress and provided them with time to adjust to their grief. They appreciated being empowered with the knowledge and confidence to participate in the decision making process regarding the clinical management of their child's treatment. Interestingly, they were more at ease with their loss than families who have lost children at an earlier phase of the illness, even though these latter families had been spared the most difficult phase of MPS III.

GINI (GENE IDENTIFICATION BY NONSENSE-MEDIATED MRNA DECAY INHIBITION) TO IDENTIFY NEW BREAST CANCER SUSCEPTIBLITY GENES (P46)

J. Johnson, N. Waddell and G. Chenevix-Trench

Queensland Institute of Medical Research, Brisbane, Australia

Approximately one-third of the mutations underlying human genetic disorders are frameshift or nonsense mutations that result in premature terminations codons (PTCs). Mutant messenger RNAs harbouring PTCs are selectively and rapidly degraded by the nonsense-mediated mRNA decay (NMD) pathway. Therefore, blocking the NMD pathway will stabilise these mutant transcripts, and expression profiling to compare mRNA levels before and after NMD inhibition can then be used to identify candidate disease-related transcripts. We are comparing two different methods of GINI: (1) the use of chemicals to inhibit translation, and thus block NMD, and (2) specific inhibition of NMD by RNA interference against an essential NMD component, Upf2. We hypothesize that Upf2 siRNA will reduce the noise in the expression arrays because only NMD, but not Staufen-mediated mRNA decay, will be affected. We will present the results of these comparative approaches on the HT29 colorectal cancer cell line (which has a PTC in SMAD4), and in positive control BRCA1 and BRCA2 lymphoblastoid cell lines (LCLs) The best method will then be applied to LCLs from patients with non-BRCA1/2 hereditary breast cancer and from their unaffected family members, as well as to non-BRCA1/2 breast cancer cell lines. The identification of additional familial breast cancer genes using the GINI technique can lend itself to future breast cancer diagnostic and screening applications.

INTER-LABORATORY VARIATION IN THE MOLECULAR DIAGNOSIS OF TRIPLET REPEAT DISORDERS (P5)

M. Kapps,[2] C. Wise,[3] D. B. Young[1] and S. B. Flanagan[1]

[1] *Molecular Genetics Laboratory, Pathology Queensland, Clinical and Statewide Services, Royal Brisbane Hospital, Brisbane, Australia*
[2] *Molecular Genetics Laboratory, VCGS Pathology, Royal Children's Hospital, Melbourne, Australia*
[3] *Neurogenetics Unit, Royal Perth Hospital, Perth, Australia*

Neurological, neurodegenerative, or neuromuscular disorders associated with trinucleotide repeat expansions include Huntington disease, fragile X syndrome, myotonic dystrophy and several types of spinocerebellar ataxia. Diagnostic services are available in Australia for at least 13 triplet repeat related disorders. In several of these disorders a single repeat unit diagnostically differentiates affected and unaffected individuals, therefore, accurate and consistent sizing of repeat numbers is important clinically, especially in providing presymptomatic diagnoses. The introduction of capillary electrophoresis has vastly improved the precision and accuracy of triplet repeat size estimates, however, inter-laboratory differences in sizing are still encountered in practice. We present several approaches to overcome the technical issues and challenges encountered in accurate molecular characterisation of trinucleotide repeat expansions. These approaches include inter-run allelic ladders, inter-run regression analysis and PCR amplification using primers homologous to the repeat region. We have collaborated to establish the extent of inter-laboratory variation in repeat size estimates for several triplet repeat disorders in Australian diagnostic laboratories. Sets of reference samples for myotonic dystrophy, spinocerebellar ataxia type 1, type 2, type 3 (Machado Joseph disease), type 6, type 7 and dentatorubral pallidoluysian atrophy (DRPLA) spanning the normal and affected range were analysed, enabling direct comparison of repeat sizing. The results presented here will enable comparison between results from different laboratories in the clinical setting. This work will direct investigations to establish the underlying causes of these variations, improve the accuracy of reporting and form the basis of efforts to establish nationally consistent standards in trinucleotide repeat sizing.

IMMUNOHISTOCHEMICAL TESTING FOR HNPCC (LYNCH SYNDROME): CORRELATION WITH GENE SEQUENCING (P54)

D. Kenwright,[1,2] E. Dennett,[3,4] A. McEwen,[5] A. Kidd,[5] S. Lauson[6] and S. Harper[4]

[1] *Department of Obstetrics and Gynaecology, University of Otago, New Zealand*
[2] *Anatomic Pathology, Capital and Coast District Health Board, New Zealand*
[3] *Department of Surgery and Anaesthesia, University of Otago, New Zealand*
[4] *Department of Surgery, Capital and Coast District Health Board, New Zealand*
[5] *Central Regional Genetic Services, Capital and Coast District Health Board, New Zealand*
[6] *Department of Medical Genetics, University of British Columbia, Canada*

Aim: To review the results of immunohistochemical testing for DNA mismatch repair performed at Wellington Hospital between June 2003 and June 2007, and (1) correlate them with the results of gene sequencing (2) review the cost effectiveness of the testing schema. *Introduction:* Inherited abnormalities in DNA mismatch repair are associated with HNPCC (Lynch syndrome). These are commonly referred to as abnormalities in microsatellite instability (MSI). While molecular methods can be used to

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detect the expansion or contraction of mircrosatellite regions, a newer and cheaper method is to use immunohistochemistry to detect loss of expression of the proteins involved in DNA mismatch repair. *Method:* Results from immunohistochemical testing of MLH1, MSH2, MSH6 and PMS2 were compiled and abnormal results were correlated with Genetic Services records of molecular testing. *Results:* 51(29%) of 177 patients tested had an abnormal immunohistochemical result. After genetic clinic review 30 patients were offered either mutation analysis or BRAF testing. Pathogenic mutations were found in 3 patients and mutations of unknown significance in 5 patients. *Conclusion:* All the mutations detected were in tumours that showed loss of protein expression on immunohistochemistry. Mutation testing, even in young patients with a very high risk family history is often negative or gives rise to a mutation result of uncertain significance. The cost of immunohistochemical testing was NZD$2730 per mutation detected. Our testing strategy was cost effective compared to other methods.

ASYMPTOMATIC ISOVALERIC ACIDAEMIA WITH ABNORMAL ORGANIC ACIDS (P20)

D. P. Knoll,[1] C. De Luen,[1] J. Jiang,[1] E.Glamuzina,[2] E.Wiltshire,[3] D.Webster[1] and C. J.Wilson[2]

[1] *National Testing Centre, LabPlus, Auckland Hospital, New Zealand*

[2] *Starship Hospital, Auckland, New Zealand*

[3] *Wellington Hospital, Wellington, New Zealand*

Isovaleric acidemia classically presents in the neonatal period with lethargy and vomiting and biochemically with severe acidosis and variable hypoglycaemia and hyperammonemia. In addition a second group of patients who present in later childhood with episodic symptoms is well described. The advent of expanded newborn screening has allowed for the early diagnosis of the condition with the aim of identifying children and commencing treatment prior to the initial, and often most clinically significant, episode of metabolic decompensation. With screening however a third group of patients has been identified. These children have clearly abnormal C5-acylcarnitine levels but typically only mild–moderately abnormal urinary isovalerylglycine levels. We present a recent patient with these findings. However we have also identified, through screening, another clinically asymptomatic child whereby the organic acids were very abnormal thus suggesting the potential for clinically significant disease. Prophylactic treatment of L-carnitine was commenced. However an older sibling with no history suggestive of metabolic disease was subsequently shown also to have relatively high levels of urinary isovaleric metabolites thus making the clinical picture less clear. We discuss these cases in depth and suggest possible diagnostic and management strategies.

SEX-DEPENDENT CONTRACTION/EXPANSION OF THE HD ALLELE (P74)

V. Kralevski, E. Osborne, T. Davis, C. Beyer, and D. Cram

Monash Reproductive Pathology and Genetics Department, Monash IVF, Melbourne, Australia

Huntington disease (HD) is an inherited neurological disorder caused by an expanded trinucleotide (CAG) repeat in the Huntington gene. CAG repeats demonstrate a relatively stable inheritance until their size exceeds 36 repeats. Large CAG repeats are prone to expansion or contraction in subsequent generations, with expansions and earlier age of onset more commonly seen in paternally inherited HD. Analysis of embryos from HD couples presenting for Preimplantation Genetic Diagnosis (PGD) of HD at Monash IVF from 2000–2008 has demonstrated a clear divergence in the behaviour of the HD allele in human IVF embryos based on parental origin. Analysis of over 130 HD affected embryos has shown that when HD is maternally inherited a contraction of the allele is observed in 71% of embryos (30/42), the repeat size is stable in 19% of embryos (8/42) and an expansion is observed in 10% of embryos (4/42). Conversely when HD is paternally inherited a contraction of the allele is observed in 21% of embryos (19/90), the repeat size is stable in 18% of embryos (16/90) and an expansion is observed in 61% of embryos (55/90). These results confirm previous findings of anticipation (earlier age of onset) in paternally inherited HD and indicate that there may be a sex dependent selection pressure for the HD allele in gametogenesis or prior to Day 3 of embryonic development.

EXTENDED CYSTIC FIBROSIS TESTING: DOES THE END JUSTIFY THE MEANS? (P31)

C. Lau, M. Fietz, T. Pyragius, S. Chin, A. Fellowes and J. M. Fletcher

National Referral Laboratory, Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia

Introduction: Mutation testing of the cystic fibrosis transmembrane conductance regulator (CFTR) gene is often required for a definitive diagnosis of cystic fibrosis, but there are > 1000 known mutations. *Aim:* to compare the mutation detection rate of a 33-mutation panel against the laboratory's standard 11-mutation panel and against direct gene sequencing in patient groups stratified by sweat test/carrier status. *Methods:* 42 patients presenting between 2003 and 2007 whose genotypes failed to be fully characterized by the 11-mutation screen were further evaluated by sequencing and/or comparison with the Abbott-Celera 33-mutation oligonucleotide ligation assay (OLA) kit. *Results:* The 33-mutation screen characterized 12% of patients, compared with 57% by gene sequencing. The 33-mutation screen showed the greatest advantage over the 11-mutation panel in the 'sweat test positive' subgroup, being able to fully characterize 24% of these patients. However it failed to fully characterize any of the 'sweat test equivocal' or 'obligate carrier' patients. In contrast, sequencing is able to fully characterize 47% of 'sweat test positive' patients, 42% of 'sweat test equivocal' patients, and 90% of 'obligate carriers'. *Conclusion:* the 33-mutation screen offers discernible improvement in detection rate over the 11-mutation screen in sweat test-positive patients but sequencing remains necessary for a substantial proportion of tests submitted for other indications.

ANALYSIS OF POSITIONAL AND FUNCTIONAL CANDIDATE GENES FOR FAMILIAL KERATOCONUS (P77)

K. Laurie,[1] D. Coster,[1] J. C. Charlesworth,[2] J. E. Craig [1] and K. P. Burdon[1]

[1] *Department of Ophthalmology, Flinders University, Australia*

[2] *Southwest Foundation for Biomedical Research, San Antonio, Texas, United States of America*

Keratoconus is a debilitating, blinding disease characterised by progressive asymmetrical thinning of the cornea, the clear covering at the front of the eye. The resulting protrusion of the cornea results in severe refractive error, often requiring corneal grafting. It is a complex disease with a genetic component. Despite several reports of linked loci, few genes have been identified. We have previously undertaken a genome-wide linkage scan in a large Australian pedigree and identified digenic linkage to 1p36.23-36.21 and 8q13.1-q21.11, suggesting that two genes may be segregating in this family. Functional candidate genes from these regions were selected based on known function, association with corneal disease or reported interactions between genes in each region. ENO1 is a structural corneal protein. CTNNBIP1 is involved in wnt signalling, important for eye development. UBIAD1 and PLOD1 have been previously associated with corneal phenotypes. SPSB1 and TCEB1 are in different linkage regions and had been shown to interact in vitro supporting the idea of dual segregating disease genes. The expression of each gene was confirmed in mouse cornea by RT-PCR, if not previously reported in humans. All coding and untranslated regions of each gene were directly sequenced in multiple affected individuals. No mutations were identified in any of these plausible candidate genes, although a novel variant encoding G8R was identified in CTNNBIP1. This suggests that these genes are not responsible for keratoconus in this family, although regulatory mutations have not been ruled out. Additional fine mapping and assessment of other positional candidate genes is ongoing.

PATIENTS WITH PHILADELPHIA-POSITIVE LEUKAEMIA WHO ARE RESISTANT TO IMATINIB CAN ALSO DEVELOP RESISTANCE TO THE SECOND GENERATION KINASE INHIBITOR NILOTINIB (O63)

R. Lawrence, Z. Rudzki, T. Hughes and S. Branford

Molecular Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia

Mutations within the BCR-ABL gene are the major mechanism of imatinib resistance for patients with Philadelphia-positive leukaemia. Nilotinib is a more potent BCR-ABL kinase inhibitor. From cell proliferation assays and pharmacokinetic studies imatinib resistant mutations are predicted to be sensitive to nilotinib at therapeutic doses, except T315I. This residue is essential for nilotinib binding. We monitored 68 patients treated with nilotinib after imatinib failure for 2–15 months. BCR-ABL mRNA levels were measured by quantitative PCR. Mutation analysis of the BCR-ABL kinase domain was performed using direct sequencing. Prior to nilotinib, 22 different imatinib resistant mutations were detected in 33/68 patients (1 had T315I). We aimed to determine the effect of these baseline mutations in vivo on the subsequent molecular response and nilotinib resistance. A molecular response was defined as a BCR-ABL reduction to ≤ 1%. For imatinib-treated patients a molecular response is associated with a favourable progression-free-survival. Molecular response occurred in 25/68 patients (37%). The frequency of molecular response was significantly higher in patients without baseline mutations (54% versus 18%), $P = .005$. During nilotinib therapy, 18/68 patients (26%) developed 7 different mutations that were not detectable at baseline. Twelve of these 18 patients had disease progression after the emergence of the mutation. Only one patient developed the highly nilotinib resistant mutation T315I. The other mutations were predicted to be nilotinib sensitive at the doses administered. In conclusion, mutations emerged with nilotinib resistance that were not predicted and may be associated with lower intracellular concentrations of nilotinib than expected from pharmacokinetic studies.

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REPORT ON THE EUROPEAN MOLECULAR GENETICS QUALITY NETWORK (EMQN) BEST PRACTICE MEETING FOR THE MOLECULAR ANALYSIS OF HEREDITARY BREAST AND OVARIAN CANCER, GERMANY 2007 (O41)

J.A. Leary

Familial Cancer Service, Westmead Hospital, Westmead, Australia

It is a widely held view that the use of testing guidelines that direct the practice of genetic testing is of benefit to both practitioners and patients in the delivery of first class genetic services. To some extent the Australian testing community has utilised guidelines from either Europe or America to inform the testing framework. There has been debate as to whether the Australian testing community should develop local guidelines or adopt those used in other jurisdictions. Strong ties have been established between the HGSA and the EMQN via the Quality Assurance program and as a member of that program an Australian delegate was invited to participate in the review of the previously published EMQN Best Practice Guidelines for Molecular Analysis of Hereditary Breast and Ovarian Cancer (2001). The major discussion points of the meeting covered the need for evidence based recommendations; consideration of the number of patient specimens required for testing; models used for pre-selection of patients for testing; the merits of continued testing after finding a pathogenic mutation; the interpretation of unclassified variants; testing for large genomic rearrangements in BRCA2; consideration of susceptibility genes other than BRCA1/2; and the need for a comment on the sensitivity of testing for negative results. The final version of the European guidelines has not yet been released however the debate on whether to simply adopt these, add local caveats or develop Australian guidelines should gain impetus with their imminent release. More details of the meeting and a discussion of the pros and cons of such a decision will be presented at the meeting.

UNEXPECTED DISCREPANT KARYOTYPING AND QF-PCR RESULTS BETWEEN PRENATAL AND POSTNATAL SAMPLES (P7)

J. Lim,[1] S. Wong Kok,[1] F. Wong Lee,[2] S. Lim Seong[2] and R. Quaife[2]

[1] *Thomson Pre-Natal Diagnostics Laboratory Pte Ltd, Singapore*

[2] *Parkway Laboratories Pte Ltd, Singapore*

Patau syndrome is a distinct disorder associated with the presence of Trisomy 13. Its features include craniofacial and limb abnormalities as well as genitourinary, cardiac and central nervous system defects. Growth and mental retardation are invariably present. Most cases succumb in the early weeks of life; 5% to 10% of cases survive up to a year. Rare instances of more prolonged survival have been attributed to variable expressivity, cytogenetic mosaicism and advanced medical care. Prenatal detection is by chromosomal diagnosis or rapid diagnostic methods such as quantitative fluorescent polymerase chain reaction (QF-PCR) and fluorescent in situ hybridization (FISH). A male foetus was diagnosed as a full Trisomy 13 from 15 trisomic metaphases out of 4 vessels in amniotic fluid (AF) by coverslip culture. QF-PCR findings also showed clear triallelic and diallelic trisomic ratios for chromosome 13. Subsequent blood chromosomal analysis at about 1.5 years of age showed mosaicism with 28% of cells exhibiting trisomy 13. FISH showed 33% and 42% trisomic cells in peripheral blood and buccal mucosa cells. Corresponding figures from QF-PCR were ~30% and ~40–50% respectively. A recount of all analyzable metaphases from the original chromosome preparations showed Trisomy 13 in 79 of 80 (98.9%) cells from 35 colonies. Our report demonstrates a previously undescribed possibility that prenatal AF karyotyping may not distinguish full from mosaic Patau syndrome. Variable degrees of mosaicism in different tissues and trisomic rescue mechanisms may be responsible. This has implications on genetic counselling regarding the prognosis of foetuses diagnosed as full Trisomy 13 by AF karyotyping.

THE CLINICAL JOURNEY THROUGH PRESENTATION TO DISCHARGE OF A BABY WITH 6-PYRUVOYL TETRAHYDROBIOPTERIN SYNTHASE DEFICIENCY (P30)

R. Junek, C. Ellaway and B. Wilcken

Western Sydney Genetics Program, The Children's Hospital at Westmead, Australia

This poster outlines the clinical journey, through diagnosis and on to treatment, of a baby found to have 6-pyruvoyl tetrahydrobiopterin synthase deficiency. It follows the patient's journey from birth through the initial hospitalisation in neonatal intensive care and on to management at home at 2 months of age. The purpose of the poster is to show the clinical side of dealing with a patient with a rare disorder of which we have limited experience. This is the fifth baby diagnosed in New South Wales with a disorder of variable outcome. The poster is organised in a chronological manner describing the signs and symptoms, tests and treatments carried out during the neonatal period, of this infant. It describes the dilemmas faced by the metabolic team and our decisions on how we approached them.

DETAILED PHENOTYPE CHARACTERIZATION OF SCHIZOPHRENIA REVEALS CONTRIBUTION OF GENES ASSOCIATED WITH SYNAPTIC PLASTICITY (O97)

L. Kalaydjieva,[1] S. Bouwer,[1] S. Wiltshire,[1] M. Dragovic,[2] K. Peters,[1] D. Chandler,[1] J. Badcock,[2] G. Price,[2] P. Mitchie,[2] G. Montgomery[3] and A. Jablensky[2]

[1] *Western Australian Institute for Medical Research, Australia*

[2] *Centre for Clinical Research in Neuropsychiatry, The University of Western Australia, Australia*

[3] *Queensland Institute for Medical Research, Australia*

Schizophrenia is a complex psychiatric disorder, whose genetic analysis is complicated by the phenotypic heterogeneity inherent in diagnostic classifications. While a large number of genes have been implicated in schizophrenia, association findings have been inconsistent and recent large-scale analyses have failed to confirm any of the top candidate genes. Using a battery of neurocognitive and electrophysiological tests, we have dissected the clinical category of schizophrenia into two major subtypes, one characterized by pervasive cognitive deficit (CD) and the other cognitively spared (CS). The salient features of the CD subtype point to impaired synaptic function as a major contributor to pathogenesis. Using a comprehensive HapMap-based approach, we have investigated the effect of variation in five genes known to contribute to synaptic plasticity, memory and learning in animal models and in vitro systems. Reelin and Apolipoprotein E are extracellular signalling molecules that compete for binding to receptors VLDLR and APOER2, which in turn bind to the common adaptor DAB1. This multimolecular complex acts at the synaptic membrane to recruit and modify glutamate receptors and activate specialized downstream signalling systems. Our analysis revealed a consistent pattern of highly significant association between polymorphisms in Reelin, APOER2 and DAB1 and specific cognitive measures, suggesting a role of these genes in schizophrenia and possibly in normal human cognitive function. The distinct profiles of the two subtypes of the disease support the concept of different pathophysiology and emphasize the role of refined phenotype characterization in facilitating genetic research.

A RARE CASE OF CONFINED PLACENTAL MOSAICISM AND COMPLETE FETAL-PLACENTAL DISCORDANCE (P9)

S. Kerin,[1] R. Hutchinson,[1] E. Haan[2] and A. Baxendale[2]

[1] *Cytogenetics Unit, Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *SA Clinical Genetics Service, Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

Chorionic villus sampling (CVS) was performed on a 37 year old woman at increased risk (1:7) of Down syndrome on first trimester combined screening. Long term cultures of the CVS showed a nonmosaic karyotype, 47,XX,+10. Follow up amniocentesis was recommended as the abnormal result could have represented confined placental mosaicism (CPM) and no abnormalities had been identified in the fetus by ultrasound. FISH was performed on uncultured amniocytes (AneuVysion kit and subtelomeric 10p/10q) and showed only 2 copies of chromosome 10p/10q, but 3 copies of the X centromeric region. Subsequent analysis of the amniotic fluid cultures confirmed the karyotype 47,XXX and no trisomy 10 cells were seen. There had been no suggestion of twinning on early ulstrasound scan. A detailed morphology scan at 18^{+6} weeks did not detect any abnormality in fetal morphology, growth or amniotic fluid volume, and the pregnancy is ongoing. False negative CVS results are extremely rare, and excluding those based solely on direct (uncultured) CVS analysis, only 3 cases reported in the literature have demonstrated a true false negative result from a long term CVS culture. Two of these are postulated to reflect the maternal karyotype. This case demonstrates the unusual combination of a false negative cultured CVS result (47,XXX present in amniotic fluid cells but not in the CVS), together with an abnormal CVS karyotype discordant with a different abnormality in the fetus (47,XX,+10 not present in the amniotic fluid). Such a combination has not been reported in the literature. We will discuss the mechanisms involved with the origin of both CPM and complete fetal-placental discordance and also relate the implications of this rare occurrence to the ongoing pregnancy and its outcome.

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EMBRYONIC STEM CELL DERIVED TRANSMITOCHONDRIAL CYBRIDS: A MODEL FOR STUDYING NEUROPATHOLOGICAL MECHANISMS IN MITOCHONDRIAL DISEASE (O55)

D. M. Kirby,[1,2] A. J. Trevelyan,[2] K. Rennie,[2] R. Acin-Perez,[3] T. K. Smulders-Srinivasan,[2] J. A. Enriquez,[3] D. M. Turnbull[2] and R. N. Lightowler[2]

[1] *Mitochondrial and Metabolic Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia*

[2] *Mitochondrial Research Group, The Medical School, University of Newcastle upon Tyne, United Kingdom*

[3] *Departamento de Bioquímica y Biología Molecular y Celular, Universidad de Zaragoza, Spain*

Neurological involvement, often severe and progressive, is an almost invariant feature of mitochondrial DNA (mtDNA) disease. The exact mechanisms of neuronal damage are unknown, and study of these is severely hampered by the lack of appropriate models that reflect mitochondrial function in the brain. By exploiting the pluripotent nature of embryonic stem (ES) cells, we aimed to develop a cell culture model to investigate the effects of pathological mtDNA mutations on neuronal development. mtDNA sequence variations present in mouse fibroblasts were introduced into murine ES cells by fusion of enucleated fibroblasts with ES cells in which mtDNA had been chemically ablated. Four transmitochondrial lines were generated: one with two mutations (13887Cins in MTND6, 12273G>A in MTND5) and severely reduced complex I activity, two with a mutation in MTCOI (6589T>C) and a moderate complex IV defect and another with a polymorphic variant (9821A del) in MTTR. These retained pluripotency and were able to differentiate into neurons and glia. The neurons expressed typical neuronal markers and demonstrated action and synaptic potentials. A developmental defect was observed in the severe complex I-deficient cybrid. It could generate markedly fewer neurons and there was a paucity of spontaneous synaptic events. These severely affected neurons also demonstrated abnormalities in cellular calcium dynamics, progressively accumulating calcium after stimulation by physiological concentrations of glutamate. This cell culture model will enable study of neuronal function in mtDNA disease, investigation of pathogenic mechanisms and new treatments not only in mtDNA disease, but in other neurodegenerative conditions and ageing.

THE V600E MUTATION IN THE BRAF GENE IN HNPCC (O87)

N. Lerda, G. Cheetham, Z. Rudzki and A. Ruszkiewicz

Divisions of Molecular Pathology and Anatomical Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia

Hereditary non polyposis colorectal cancer (HNPCC) is caused by mutation of a mismatch repair (MMR) gene and tumours found in these patients almost always exhibit microsatellite instability (MSI). However, 15–20% of sporadic colorectal cancers also exhibit MSI, often due to the epigenetic silencing of the MLH1 gene by methylation of the promoter. The BRAF V600E mutation has been shown to be a useful surrogate marker for methylation of the MLH1 gene. Therefore, the presence of this mutation in tumour tissue indicates that the cancer is most likely sporadic and HNPCC is unlikely. Absence of the V600E mutation is consistent with, but not diagnostic of HNPCC. We have developed a single nucleotide primer extension assay for the detection of the V600E mutation. 45 patients were selected for evaluation of the method. DNA was isolated from paraffin-embedded tumour tissue and tested for the 1799 T>A transversion that results in the V600E mutation. 91% of patients with microsatellite stable tumours that showed normal MLH1 immunohistochemistry (IHC) were negative for the V600E mutation. 68% of patients with microsatellite unstable tumours that also showed abnormal MLH1 staining by IHC were positive for the V600E mutation, indicating that these patients are unlikely to have HNPCC and MMR gene screening is unlikely to be of benefit. Used in conjunction with IHC and MSI testing the BRAF V600E mutation is a simple and cost-efficient way to identify those patients who have epigenetic silencing of the MLH1 promoter and are unlikely to benefit from MMR gene mutation screening.

ALLELE SPECIFIC EXPRESSION DUE TO MUTATIONS WITHIN THE CHROMATIN-ASSOCIATED FACTOR ATRX (O64)

K. M. Lower,[1] M. Law,[1] J. Cross,[1] D. Garrick,[1] H. Ayyub,[1] I. Ragoussis,[2] D. R. Higgs[1] and R. J. Gibbons[1]

[1] *MRC Molecular Haematology Unit, Institute of Molecular Medicine, Oxford, United Kingdom*

[2] *The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom*

It is generally accepted that in healthy, noncancerous diploid cells the majority of genes are expressed from both alleles. Exceptions to this include imprinted genes and X-inactivation in a female. We will present data which shows that mutations in the chromatin remodelling protein ATRX result in a shift from biallelic towards monoallelic expression at two identified target genes. ATRX is an ATP-dependent chromatin remodelling protein, and mutations within the gene coding for this protein result in ATR-X syndrome, an X-linked mental retardation syndrome characterised by a characteristic facial appearance, abnormal growth and development, and varying levels of alpha thalassemia. The latter characteristic is highly variable between patients, and is due to down regulation of the alpha globin genes. We have recently identified another gene within 16p13.3 that is also down regulated in ATRX patients. ChIP-Chip of the ATRX protein confirms that both of these genes/loci are direct targets of ATRX. There is an association between the level of down regulation and the haplotype of the alpha globin locus, suggesting allele specific differences in regulation. In addition, the newly identified gene also displays allele specific expression. In many cases, allele specific expression of these genes occurs concomitantly with allele specific DNA methylation of the associated CpG islands. The exact process by which mutations in *ATRX* result in allele specific differences in expression is not yet clear, however preliminary evidence suggests ATRX may recognise abnormal DNA structures which are hypothesised to form within these genes.

NATURAL SELECTION IN WORLDWIDE HUMAN POPULATIONS ON A COMMON GENETIC VARIANT ASSOCIATED WITH MUSCLE PERFORMANCE (O77)

D. G. MacArthur,[1] J. T. Seto,[1,2] J. M. Raftery,[1] G. A. Huttley,[3] M. Lek,[1,2] N. Yang,[1] S. Easteal[3] and K. N. North[1,2]

[1] *Institute for Neuromuscular Research, Children's Hospital at Westmead, Sydney, NSW*

[2] *Discipline of Paediatrics and Child Health, University of Sydney, NSW*

[3] *John Curtin School of Medical Research, Australian National University, Canberra, ACT, Australia*

A common stop codon polymorphism in the human *ACTN3* gene, R577X, results in complete deficiency of the muscle protein α-actinin-3 in more than a billion humans worldwide. α-actinin-3 deficiency is associated with elite athlete status and variation in muscle function in humans, and with altered muscle metabolism and contractile properties in a knockout mouse model. We recently demonstrated that the 577X allele carries a genetic signature of strong, recent positive natural selection in Europeans and East Asians, suggesting that this allele conferred a reproductive advantage to modern humans adapting to the novel Eurasian environment. Here, we extend this analysis by exploring large-scale patterns of genetic variation around the *ACTN3* gene in a sample of 938 humans from 51 populations of the Human Genome Diversity Panel. The 577X null allele is rare (3–18% frequency) in African populations but ranges from 29–90% frequency in non-Africans. 577X is associated with unusually low haplotype diversity in all non-African groups, consistent with widespread positive selection outside Africa. We present a model for the origin and selection-driven movement of the 577X allele through the global human population, and integrate genetic, functional and environmental data to compare scenarios for the selective benefit of α-actinin-3 deficiency.

THE IMPACT OF GENE TESTING FOR HYPERTROPHIC CARDIOMYOPATHY AND LONG QT SYNDROME (O110)

I. Macciocca,[1,2,9] A. Davis,[3] R. Weintraub,[3] V. Connell,[3] J. Ingles,[4,5,8] J. Vohra,[6] A. Aggarwal,[6] J. McGaughran,[7,8] J. Atherton,[8] C. Semsarian,[4,5] T. Thompson,[6] I. Winship,[10] B. Meiser,[6,9] L. Yeates[4,5] and V. Collins[1]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Genetic Health Services Victoria, Australia*

[3] *Royal Children's Hospital, Melbourne, Australia*

[4] *Centenary Institute, Australia*

[5] *Royal Prince Alfred Hospital, Australia*

[6] *Royal Melbourne Hospital, Australia*

[7] *Genetic Health Queensland, Australia*

[8] *Royal Brisbane and Women's Hospital, Australia*

[9] *University of Melbourne, Australia*

[10] *Prince of Wales Hospital, Sydney, Australia*

Hypertrophic cardiomyopathy (HCM) and Long QT syndrome (LQTS) are inherited cardiovascular diseases for which genetic testing has recently become available in the clinical setting. The most concerning feature of these conditions is sudden death. There is good treatment for both conditions and sudden death can be prevented if individuals are aware of their risk. Genetic testing for both conditions has been performed in research laboratories for at least 10 years, but research on the psychological and social impact of such testing has lagged behind. We are conducting a multi-centre prospective questionnaire-based study to examine the psychological responses of individuals undergoing genetic testing for HCM and LQTS and the impact of testing on screening behaviour. The study will contribute to genetic counselling protocols for families with HCM and LQTS. Participants include adults, adolescents and parents of young people who are undergoing either diagnostic or predictive gene testing for HCM or LQTS at four recruitment sites around Australia. Participants complete a baseline questionnaire before gene test disclosure and are followed up at 2 weeks, 3 months and 12 months postgene test disclosure. We will present results collected to date from the baseline and 2 weeks postdisclosure questionnaires for adults undergoing diagnostic (n = 45) and predictive (n = 20) testing.

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DUPLICATE SAMPLING: ARE TWO SAMPLES BETTER THAN ONE? (O43)

G. Mach,[1] B. Mercorella,[1] Z. Rudzki,[1] G. Suthers[2] and J. Carroll[1]

[1] *Division of Molecular Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia*

[2] *Familial Cancer Unit, Department of Genetic Medicine, Children's Youth and Women's Health Service, Adelaide, Australia*

A standardised sample collection protocol is required for genetic testing, as reported results are released in the assumption that the sample collection process was performed correctly. Duplicate sample collection on different occasions is a strategy that addresses this issue and also provides laboratory corroboration for the genetic results obtained. A single blood collection from a patient with breast cancer was obtained in 1997 and split (A and B) between two laboratories. Sequencing of the BRCA genes found no abnormalities. In 2002, when MLPA assays were made available, a BRCA1 duplication of exons 16 to 19 was identified in sample A. Presymptomatic testing was offered to at-risk relatives and the proband DNA which was included each time as a positive control, consistently showed the mutation. However, in 2007, a confirmation test in an affected family member failed to detect the expected duplication. Two possibilities were proposed; either the affected individual was a phenocopy or the initial proband result was a false–positive. Sample A and B were thus tested independently in two laboratories. Both confirmed the duplication of exons 16–19 in sample A; however, neither laboratory identified the duplication in sample B. A human ID panel confirmed that the two split specimens originated from the same person. Fresh DNA samples were collected in 2007, and neither laboratory was able to identify the duplication. Though no light has been shed on how the same specimen yielded different results, had duplicate sampling been policy, this discordant result would have been apparent immediately thus sparing the family the psychological burden of a false result.

LOCALISED HIGH-LEVEL AMPLIFICATION AT 20Q11.2 IN AML WITH DEL(20)(Q12) POINTS TO AN ONCOGENE IN THE REGION OF AMPLIFICATION (O82)

R. N. MacKinnon,[1] E. Baker,[2] H. Nandurkar[3,4] and L. J. Campbell[1,4]

[1] *Victorian Cancer Cytogenetics Service, St Vincent's Hospital, Melbourne, Australia*

[2] *Pathwest Dept of Cytogenetics, King Edward Memorial Hospital, Perth, Australia*

[3] *Immunology Research Centre, St Vincent's Hospital, Melbourne, Australia*

[4] *Department of Medicine, University of Melbourne, Australia*

Deletion of the long arm of chromosome 20 is one of the most common cytogenetic abnormalities in acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). A 2.6Mb common deleted region (CDR) at band 20q12 has been defined and L3MBTL has been proposed as the deleted tumour suppressor gene. We have identified a range of unbalanced chromosome 20 abnormalities in AML/MDS. In 20 cases with deletion of the CDR, five had localised amplification of 5Mb or less at band 20q11.2, on the same chromosome arm as the deletion but closer to the centromere. Such amplification usually indicates an active oncogene. This region was usually preserved on the deleted chromosome. Additional copies of the abnormal chromosome were present in another six of the 20 cases, supporting our suggestion that a retained chromosome 20 gene plays a role in the disease. Cases with extreme amplification of the CRR tended to have an AML-M6 subtype. We defined the amplified and retained regions using multicolour chromosome banding, BAC clones from band 20q11.2 and array CGH. The maximum 600kb overlap between the shortest amplified region and the common retained region (CRR) on 20q11.2 contains 14 genes. We suggest that a tumour suppressor gene in the deleted region normally suppresses an oncogene on the same chromosome. Deletion of the tumour suppressor gene alters the balance between it and the oncogene, up-regulating the oncogene. Amplification of the oncogene creates greater imbalance, increasing the oncogene's activity. This model may also apply to other chromosome deletions.

USING MZ TWINS IN GENOME-WIDE ASSOCIATION STUDIES (O80)

N. Martin

Queensland Institute of Medical Research, Brisbane, Australia

By studying our variable of interest, for instance blood pressure or asthma, in MZ twins who have been typed for genes implicated in disease causation, we can see not only whether some genotypes have higher levels of risk, but whether some genotypes are more variable, having larger differences between MZ co-twins for blood pressure, or a higher discordance rate for asthma. Identifying such variability genes can flag genotypes that may be most susceptible to environmental modification, for example, by exercise regimes, behavioral therapy, or drug treatments. The promise of this approach, therefore, is not just in identifying the genes causing levels of disease that lead us into the biochemical and physiological pathways in which we may be able to intervene with new drug treatments. Using MZ twins to identify variability genes will help target treatments to genetically susceptible individuals whose risk is most modifiable.

A DIFFERENT APPROACH TO KARYOTYPING MALES PRESENTING FOR THE INVESTIGATION OF INFERTILITY (O91)

N. J. Martin, K.L. Harrison and D. Molloy

Queensland Fertility Group, Brisbane, Australia

Azoospermia and oligospermia are recognized clinical indications for karyotyping males presenting with infertility, with many publications showing an increase in numerical and structural chromosome abnormalities. Karyotyping has not been regarded as part of the routine work up in patients undergoing assisted reproductive technologies (ART). QFG has adopted routine karyotyping as part of the initial work up for any couple presenting for the investigation of infertility. We present the first 4 years of data for males. Semen parameters (count, motility and morphology) and clinical presentation were also recorded. Clinical presentation included failed IVF else where, know karyotype, primary infertility, male factor, idiopathic, and female factor. The detection rate for chromosome abnormalities was 1.75% — this included both numerical and structural abnormalities. 40% of all chromosomally abnormal cases had a normal semen count; there was also no correlation with sperm morphology or motility. Translocations accounted for approximately half the abnormalities detected: reciprocal translocations were found in 30.5% and Robertsonian translocations in 17.6% of cases — the reverse of that reported in the literature. Of the sex chromosome abnormalities (31.7% of cases), the majority were 47,XXY, but 12% were sex reversals due to the translocation of SRY to one X chromosome — a detection rate much higher than the population incidence. The remaining 20% of cases comprised inversions, insertion and extra small marker chromosomes. Detection of additional cases of chromosome abnormalities in an ART setting allows for appropriate counseling and the development of clinical strategies to maximize the chance of a normal pregnancy.

DECISION-MAKING FOR YOUNG ADULTS IN PREDICTIVE GENETIC TESTING (O113)

K. Mattingley,[1] G. Betts,[2] M. Freckmann[1] and R. Sachdev[1]

[1] *Clinical Genetics, St George Hospital, Australia*

[2] *Sydney Children's Hospital, Australia*

In recent years a number of articles have discussed the predictive testing process in minors and young adults. A young individual's ability to make an informed and responsible decision regarding predictive testing and the potential harm this may cause has been a contentious issue. A more recent view[1] argues that assessment of the individual's maturity of judgement in the decision making process, should be a consideration in predictive genetic testing protocols. Should this not also be applied to young adults? Not all adults by the nature of their age are 'mature' in their decision-making ability. Cognitive but also psychosocial factors influence decision making whether in adolescence and adulthood. Legally 'mature' by age may not mean cognitive or psychosocial maturity and can result in immature decision-making. Should we then deny young adults who don't have a mature outlook access to testing? The case of three sisters, 18 to 22 years of age, at 50% risk for Huntington disease (HD) and their journey through the predictive testing process is presented and discussed.

1 Richards, F. H. (2006) Maturity of judgement in decision making for predictive testing for nontreatable adult-onset neurogenetic conditions: a case against predictive testing of minors. *Clinical Genetics, 70,* 396–401.

CLINICAL SUPERVISION IN GENETIC COUNSELING: MAXIMIZING THE PROCESS AND OUTCOMES (O1)

P. McCarthy Veach[1] and B. S. LeRoy[2]

[1] *Department of Educational Psychology, University of Minnesota, United States of America*

[2] *Department of Genetics, Cell Biology, and Development, Institute of Human Genetics, University of Minnesota, United States of America*

Clinical supervision is the lynchpin of student preparation in human service professions, ensuring that: students develop adequate clinical skills; clients receive appropriate care; and only those individuals with adequate skills enter the profession. This 3-hour workshop is designed to achieve four outcomes: (1) Differentiate four supervisor roles and four student roles; (2) Identify parameters for establishing the supervision relationship; (3) Review strategies for managing feedback and evaluation; and (4) Address challenging clinical supervision issues. The workshop will consist of a series of interactive exercises, discussions, supplemented with didactic information. The content is drawn from genetic counseling and psychological literatures and based on the presenters' experience as supervisors, educators, and researchers. The workshop is intended for supervisors of all experience levels.

A COMPARATIVE ANALYSIS OF ETHICAL AND PROFESSIONAL CHALLENGES EXPERIENCED BY AUSTRALIAN AND NORTH AMERICAN GENETIC COUNSELLORS (O114)

P. McCarthy Veach,[1] B. S. LeRoy,[2] D. M. Bartels,[3] C. James,[4] F. Lian[1] and S. Alliman[5]

[1] *Department of Educational Psychology, University of Minnesota, United States of America*

[2] *Department of Genetics, Cell Biology, and Development, Institute of Human Genetics, University of Minnesota, United States of America*

[3] *Center for Bioethics, University of Minnesota, United States of America*

[4] *Queensland Clinical Genetics Service, Toowoomba Base Hospital, Toowoomba, Australia*

[5] *Signature Genomics, Spokane Washington, United States of America*

Ethical issues are an inevitable part of genetic counseling practice. Prior research has identified 16 major domains of ethical and professional challenges encountered by practitioners in North America. In order to further validate these domains, the present study surveyed a sample of Australian genetic counselors. 63 respondents rated the frequency with which they encountered each domain, and 39 of these individuals also provided personal anecdotes detailing their most challenging ethical and professional dilemmas. Every ethical and professional domain reportedly was experienced by the Australian sample. However, there were some differences between the Australian respondents and North American genetic counselors in frequencies of their occurrence, and in strategies they would recommend to resolve them. Several of the present sample's anecdotes illustrate unique aspects of ethical challenges due to Australia's geography, universal healthcare system, and evolution of the profession in that country. The results provide validation of the domains identified for North American genetic counselors. They further suggest that certain ethical issues may manifest in ways unique to a given country, and therefore they must be addressed in a culturally appropriate manner.

CYSTIC FIBROSIS CASCADE CARRIER TESTING IN VICTORIA, AUSTRALIA: AN AUDIT OF CLINICAL SERVICE (O88)

B. J. McClaren,[1,2,4] M. A. Aitken,[1] R. J. Massie,[1,2,3,4] S. A. Metcalfe[1,4] and D. J. Amor[1,2,4]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Genetic Health Services Victoria, Australia*

[3] *Royal Children's Hospital, Melbourne, Australia*

[4] *The University of Melbourne, Australia*

In Victoria, carrier testing for cystic fibrosis (CF) is performed by a single state-wide laboratory and counselling service. CF carrier testing is offered free of charge to relatives of babies diagnosed with CF through newborn screening. Although cascade testing is known to detect carriers for CF, its effectiveness has been questioned because most babies with CF are born to couples who do not have a family history. Uptake of cascade testing following a child's diagnosis of CF by newborn screening has not been previously described. We investigated cascade testing in the families of Victorian children with CF. Uptake of cascade carrier testing was studied by examining pedigrees of 96 newborns diagnosed with CF between 2000 and 2004, and performing data linkage to the laboratory database records. Uptake of carrier testing amongst adult relatives was 17% (289/1658). Parents were the most likely to have been tested, followed by aunts/uncles, then grandparents. 12 pedigrees contained another affected child however only four of these children were diagnosed prior to the proband. The majority of relatives have not had cascade carrier testing despite being at high risk. We conclude that cascade testing, as currently offered, is not an effective strategy for detecting carriers for CF. An alternative is population-based screening, however quite variable uptake is reported. Therefore factors influencing uptake of CF carrier testing need to be explored. We are conducting an evaluation of the barriers and facilitators to CF carrier testing to inform both clinical service delivery and population-based CF screening.

FORENSIC DNA TESTING OF DATABASES AND DISCLOSURE (O103)

B. McDonald

DNA Consults, Australia

The trial of an Aboriginal elder in Australia involved paternity testing using short tandem repeat testing at 9 loci and the use of various databases representing various subpopulation data. Before the trial a search was conducted of a general database that produced two 9/9 loci matches and 1 8/9 loci matches. The database contained 214 profiles of which half were female and not searched. The two 9/9 locus matches were Aboriginal and the 8/9 locus match was Caucasian. The database was lost and not available to the defence team. Subsequent to the trial it was maintained that in fact different database consisting of 2659 Caucasians, 658 Aborigines and 115 Asians were searched and not the 214 given in evidence. Request for the database were denied in the following thre years however the Caucasian data was diclosed though the National Institutes of Forensic Science which had initiated a study of Australian Aboriginal data. In contrast to the single male with an 8/9 loci match this data revealed 18 males with 8/9 loci matches suggesting the assertion that this was the data originally searched was not correct. The trial proceeding with the use of a subpopulation model to calculate paternity index. The model assumes linkage and Hardy Wienberg equilibrium within the subpopulation which make up a total population which is not expected to be in equilibrium. An Fst correction is then used to acknowledge sharing of alleles within the subpopulation compared with the total population.In the 1994 trial a 3% Fst was considered conservative for Aborigine population groups and is the figure used for Caucasian calculations. Caucasian data in Australia is shown to be in HWE and LE however it is not assumed whereas Aboriginal data demonstrates lack of HWE (p = .008) and LE (p = .007) which is ignored on the basis that reliance on p values less than 0.05 is outdated. The Fst required to explain the matches which have been disclosed is more than 13% a figure which would effectively decimate certainly any evidence comparing a relative of the accused man. This data requires open access and a wider philosophical input to the analysis of Aboriginal data for use in Australian courts.

NEGOTIATING DUAL ROLES: COMBINING RESEARCH AND CLINICAL PRACTICE (O11)

A. McEwen

Central Regional Genetic Services, Wellington Hospital, New Zealand

Background: An insider is an individual who has a priori knowledge of the group they are researching whereas an outsider is not a priori familiar with the setting and group. Genetic counselors involved in research projects that recruit people they have previously seen as clients bring an insider perspective to the research. Using an independent interviewer (an 'outsider'), we have almost completed a qualitative, interview-based project looking at New Zealand women's experiences of being at increased risk for ovarian cancer. *Aim:* Using an insider–outsider framework I consider the impact the dual roles of 'practicing genetic counselor' and 'clinical researcher' have on both clinical work and research. *Case report:* Anna, one of the first young women I counseled through a BRCA predictive testing process, and among the first women in NZ to have a positive predictive test, participated in our ovarian cancer project and was interviewed by the independent (nongenetic counselor) interviewer employed by the project. Her memories of the genetic testing experience and the details recorded in her file differ significantly at key points. *Discussion:* This paper discusses the tensions that arise from a genetic counselor's dual role when conducting clinical research. Anna's experiences, and the experiences of other client-research participants, are used to illustrate some of these tensions. *Conclusion:* Genetic counselors undertaking research must be aware of the tensions that exist between their separate yet linked roles as clinical counselor and researcher. They must have strategies for managing these tensions.

MLPA ANALYSIS FOR THE DETECTION OF LARGE DELETIONS AND CONVERSIONS IN THE 21-HYDROXYLASE GENE (P64)

I. McGown,[1] T. Munce,[1] A. Cotterill[2] and D. Cowley[1]

[1] *Departments of Molecular Genetics, Mater Hospital, Brisbane, Australia*

[2] *Paediatric Endocrinology & Diabetes, Mater Hospital, Brisbane, Australia*

Congenital adrenal hyperplasia (CAH) is a common autosomal recessive disease caused by a deficiency of one of the five enzymes involved in the biosynthesis of cortisol. About 90-95% of CAH cases are caused by defects in the steroid 21-hydroxylase gene (CYP21A2). The disease is unusual in that the majority of mutations that are found in the CYP21A2 are found in a closely related pseudogene (CYP21A1P). Most mutations occur by either gene deletions or gene conversions, whereby mutations are transferred from the nearby pseudogene. Approximately 30% of mutant alleles have large deletions or conversions with the majority being a 30 kb deletion that has been generated by unequal meiotic crossing-over producing a nonfunctional chimeric pseudogene. Previously methods such as Southern blot analysis, homozygosity testing for single nucleotide polymorphisms (SNPs) and semi-quantitative GeneMapper analysis have been used to detect large deletions. In order to better characterise large deletions and conversions we undertook a study of CAH cases using multiplex ligation-dependant probe amplification (MLPA). We performed MLPA analysis on 35 samples that had previously been found to have large deletions/conversions by GeneMapper analysis and DNA sequencing. MLPA analysis confirmed large deletion/conversions in all 35 samples.We conclude that MLPA is a highly sensitive and cost-effective alternative to the previously described methods.

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DETECTION OF A NOVEL 15Q SUBTELOMERIC DELETION IN A CHILD WITH SHORT STATURE, DEVELOPMENTAL DELAY AND DYSMORPHIC FEATURES (P79)

L. McGregor,[1] L. Sanchez,[2] K. Friend[2] and S. Yu[2]

[1] *SA Clinical Genetics Service, Women's and Children's Hospital, Adelaide, Australia*

[2] *Diagnostic Molecular Genetics, Women's and Children's Hospital, Adelaide, Australia*

The aetiology of mental retardation and dysmorphism remains elusive in over 50% of affected individuals. The advent of MLPA and array CGH to assess submicroscopic chromosomal aberrations is providing answers in a growing number of cases, but often it is difficult to determine whether the copy number variation detected is pathologic or a normal variant. We present here a novel observation of an approximately 3.0Mb deletion at 15q11. The deletion encompasses a region at the BP1 / BP2 breakpoint (of the PWS/AS locus), distal to C15ORF12 and proximal to SNRPN. This was identified in an 11-year-old girl referred with proportionate short stature, mild to moderate developmental delay, a duplex kidney, a thyroglossal cyst and dysmorphic features including hirsuitism, downslanting palpebral fissures, a prominent nasal columella, broad thumbs and bifid deviated great toes. Routine karyotype analysis was otherwise normal. Further testing determined that the same deletion was carried by the phenotypically normal mother and maternal grandfather. The extended pedigree is large and there are no other similarly affected cases although extensive clinical evaluation has not been possible to date. We suggest that this is likely to be a polymorphic variant and not causative of the phenotype either by a deletion or imprinting mechanism.

HOMOCYSTINURIA: MORE THAN JUST A MULTIDISCIPLINARY TEAM CHALLENGE (P14)

C. McMahon, E. Wiltshire, B. Randall, N. Clark and C. Wilson

Auckland, Capital Coast and Canterbury District Health Boards, New Zealand

Homocystinuria is a well-documented disorder of methionine metabolism. While the biochemical theory and best clinical management are well understood, the actual 'lived experience' of this disorder is not well documented. We present the recent experiences of a young adult whose chosen lifestyle resulted in a serious deterioration of health and serious threat to life. The multidisciplinary team approach continues to include intensive liaison between nursing, medical, metabolic, surgical, and dietetic disciplines in various New Zealand centres and has occurred over several years. Most importantly the patient's and the patient's immediate family experiences will be presented. The patient's willingness to accept their disorder, to build skills for adult life and to participate fully in the self-management of their own disorder, is discussed. The process remains ongoing, as further changes and challenges occur in 2008.

'IT'S CHALLENGING ON A PERSONAL LEVEL': EXPLORING GENETIC COUNSELLORS' EXPERIENCES AND SUPPORT IN A PRENATAL SETTING (O6)

M. Menezes,[1,2] M. Sahhar,[1,2,3] J. Hodgson,[1] M.A. Aitken[1,2] and S.A. Metcalfe[1,2]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Department of Paediatrics, The University of Melbourne, Australia*

[3] *Genetic Health Services Victoria, Australia*

Prenatal genetic counsellors see clients who are at risk of having, or who have received a diagnosis of, a fetal anomaly in their pregnancy. For many clients this is a time of crisis, which may have varying impact upon the counsellor. Professional support through formal individual and group supervision is one process offered to genetic counsellors in Victoria, although may not be available universally. The aim of this study was to explore the experiences of genetic counsellors in the prenatal setting and to identify the types of support systems used by genetic counsellors. Semi-structured interviews were conducted with 14 prenatal genetic counsellors: 9 from Victoria, Australia and 5 from Ontario, Canada, countries with similar healthcare models. Participants discussed their experiences of working as a prenatal genetic counsellor and the methods of support used. Interviews were analysed using thematic analysis. Participants identified a range of challenging situations where they needed support, including the impact of counselling while pregnant themselves as well as issues of countertransference that may have affected the counselor–client relationship. In discussing how to deal with the challenges of prenatal genetic counselling, Australian counsellors discussed use of both formal and informal supports whereas Canadian counsellors accessed more informal supports. Working in the prenatal area appears to have a substantial impact on genetic counsellors. While formal supervision and peer support is helpful in managing this impact, there needs to be a greater awareness of additional supports that may be required in the prenatal setting especially when counsellors are themselves pregnant.

CDH1 TESTING FOR HEREDITARY DIFFUSE GASTRIC CANCER AND OTHER RELATED CANCERS AT THE INSTITUTE OF MEDICAL AND VETERINARY SCIENCE (IMVS), ADELAIDE (P57)

B. Mercorella,[1] L. Rawlings,[1] Z. Rudzki,[1] G. Suthers,[2] N. Poplawski[2] and J. Carroll[1]

[1] *Institute of Medical and Veterinary Science, Adelaide, Australia*

[2] *Familial Cancer Unit, Department of Genetic Medicine, Children, Youth and Women's Health Service, Adelaide, South Australia*

Hereditary diffuse gastric cancer (HDGC) is inherited in an autosomal dominant manner and confers susceptibility for diffuse gastric cancer, a poorly differentiated adenocarcinoma that infiltrates into the stomach wall without forming a distinct mass. These diffuse carcinomas display a prominent cytological abnormality with there being defective intracellular adhesion. In most cases, this results from a loss of expression of the cell adhesion protein E-cadherin, encoded by the gene CDH1. Individuals who carry germline mutations in CDH1 are at a significantly increased risk of diffuse type gastric cancer and lobular type breast cancer. The CDH1 gene mutation detection rate for patients with HDGC has been reported as 30%. In 2007 the Familial Cancer Laboratory at the IMVS introduced screening of the CDH1 gene for sequencing variations and large-scale deletions and duplications. To date we have performed seven gene screens on patients referred to us by the South Australian Familial Cancer Service. These patients presented with lobular breast cancer, diffuse gastric cancer or a family history of breast and colorectal cancer. We detected a pathogenic nonsense mutation, NM_004360.2(CDH1):c.1309A>T, NP_004351.1(CDH1):p.Lys437X, in one patient who presented with a personal history of diffuse gastric cancer. Identification of this mutation allowed presymptomatic testing to be conducted. Testing of the proband's parents identified a paternal mode of inheritance. Availability of this diagnostic test in a NATA-accredited laboratory will enable mutation carriers to be identified therefore eliminating unnecessary surveillance of non-mutation carriers.

A SYSTEMATIC APPROACH TO GENETIC INVESTIGATION OF PATIENTS WITH ANOPHTHALMIA AND MICROPHTHALMIA (O127)

M. Mihelec,[1] P. Abraham,[1] R. Susman,[2] M. Flaherty,[3] J. Grigg,[1] L. St Heaps,[1,4] G. Peters,[4] A. Colley,[5] K. Gibson[6] and R. Jamieson[1,2,7]

[1] *Eye Genetics Research Group, The Children's Hospital at Westmead, Children's Medical Research Institute and Save Sight Institute*

[2] *Clinical Genetics, The Children's Hospital at Westmead, Sydney, Australia*

[3] *Ophthalmology, The Children's Hospital at Westmead, Sydney, Australia*

[4] *Cytogenetics, The Children's Hospital at Westmead, Sydney, Australia*

[5] *Clinical Genetics, Liverpool Hospital, Sydney Australia*

[6] *Genetic Health Queensland, Royal Children's Hospital, Brisbane, Australia*

[7] *Discipline of Paediatrics & Child Health, Faculty of Medicine, University of Sydney*

Theme: Molecular Genetics, Clinical Genetics Anophthalmia and microphthalmia are severe ocular disorders with significant impact for affected individuals and their families. Associated ocular features may include ocular colobomata, as well as anterior segment abnormalities such as sclerocornea and cataract. There is marked variability in expression so that an apparently isolated case may be found to be familial on detailed parental and sibling ophthalmic examinations. Mutations in a relatively small proportion of anophthalmia/microphthalmia cases are identified in a number of genes including SOX2, RAX, CHX10, OTX2, PAX6, STRA6 and BMP4. A systematic approach considering such features as: the inheritance pattern in familial cases (e.g., autosomal recessive, CHX10); the eye phenotype (eg sclerocornea, RAX, SOX2); particular dysmorphic features (eg diaphragmatic defects, STRA6) and ethnic background (e.g., CHX10), helps prioritise the genes for molecular investigation. CGH microarray investigation may also be used in those with associated developmental delay and nonspecific dysmorphic abnormalities. In using this approach we have identified a novel mutation in SOX2 and further investigation has revealed novel phenotypic associations. CGH microarray has revealed a novel microdeletion in one patient. A systematic approach to patient and family investigation is useful to prioritise the genes for investigation in this genetically heterogeneous disorder.

IMATINIB RESISTANCE BY T315I AND ITS PREVALENCE IN CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH IMATINIB MESYLATE (P86)

M. Rashid, S. Sazawal, R. Chobey, B. Bohra, B. Sharma, R. Mehraj, Y. Quereshi, Mudasir, P. Mishra and R. Saxena

Department of Haematology, All India Institute of Medical Sciences, New Delhi, India

Background: The BCR-ABL mutations is the main mechanism of Imatinib resistance. So the early detection of T315I mutations may allow timely treatment intervention to prevent disease progression or overcome resistance in CML patients. *Lacunae:* ASO-PCR based detection and prevalence of T315I mutation in Indian populations. *Aims:* To detect T315I mutation in

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CML patients by Allele specific-oligonucleotide- PCR. To study prevalence of T315I mutation in Indian CML patients. *Methodology:* Chronic myeloid leukemia patients at presentation patients were diagnosed by RT-PCR. Imatinib (400mg/day) was the frontline therapy. ASO-PCR was done for all 160 patients for BCR-ABL mutations (T315I). The patients were evaluated for hematologic and molecular responses, time to progression, survival and toxicity. *Results:* The study included 170 newly diagnosed CML patients. A fraction of CML patients develop hematological and molecular resistance (35/170) against Imatinib. 15/170 were in late chronic phase and in AP/BC CML. All 170 CML patients were screened for T315 mutation by ASO-PCR. T315I mutations had proven to be fatal & a main cause of Imatinib resistance in our CML patients. It was detected in 80% to 85% of our relapsed cases. Survival and time-to-progression curves were obtained from Kaplan-Meier method. The prevalence of T315I mutations in our CML population was 25.22% after a follow-up of more than 4 years. *Discussion:* India is a developing country, the patients cannot afford expensive tests like sequencing for T315I mutation. So we had standardized ASO-PCR for routine screening of T315I mutations in our patients. *Conclusion:* ASO-PCR proved to be very economical, sensitive and rapid technique for detection of known BCR-ABL mutations like T315I and is even sensitive than mutation detection by sequencing. T315I has turned out to be a multi-tyrosine kinase inhibitor resistant mutation and a bad prognostic marker in CML patients. The early detection by ASO-PCR assay proved to be helpful in clinical management of therapeutic decisions in CML patients.

AUSTRALIAN EVIDENCE OF A LITERACY GAP IN LAY KNOWLEDGE OF GENETIC SCIENCE AND RELATED CONCEPTS (P62)

C. Molster,[1] T. Charles,[1] A. Samanek[1] and P. O'Leary[1,2,3]

[1] *Office of Population Health Genomics, Health Policy and Clinical Reform Division, Department of Health, Perth, Western Australia*

[2] *School of Women's & Infants' Health, University of Western Australia, Perth, Western Australia*

[3] *School of Public Health, Division of Health Sciences, Curtin University of Technology, Perth, Western Australia*

This study collected data on lay knowledge of genetic issues such as risk of disease, inheritance, biology and genetic determinism, and identifies factors that predict relatively higher genetic knowledge within the general adult population. A cross sectional telephone survey of 1009 respondents suggests that most members of the Western Australian community understand basic genetic concepts and the fact there is a link between genes, inheritance and risk of disease. Significantly fewer understand the biological mechanisms underlying these concepts. The relative odds of higher genetic knowledge were significantly greater among females, younger members of the public, those with higher socioeconomic status as measured by education and household income and those who had talked with someone or searched the internet for information on genes and health. Providing evidence of a socially inequitable 'genetic literacy' gap in public understanding of genetics and human health, further research is being undertaken to determine in the Australian context, whether this gap needs closing or whether current public understanding of genetics is sufficient to allow for effective community participation in decisions regarding human genetics and health.

ETHICAL COMPLEXITIES FOR WESTERN GENETICS EDUCATION PROGRAMS IN ASIA

V. Morrigan

University of Queensland, Australia

Recently, there has been a burst in activity of various genetics health professionals in the East and West who are successfully constructing a lack of clinical genetics in Asia as a problem, and the provision of genetics education to Asian health professionals as the solution. Ethicists, social, cultural and policy theorists have been involved in some cases. I argue that such cross-cultural education programs are more than simply the transfer of information and/or technology. Experiences in genetics education within the West already show many complexities. Cross-cultural genetics education involves a greater complexity of relations within local, national and global assemblages of bodies, scientific knowledge claims, and technologies. Some examples I explore in detail raise questions about particular cultural assemblages, such as: particular conditions for regulating populations, and organising genetics and other health professionals within and beyond dedicated genetics services; differences and similarities in meanings of the goal of 'having a healthy baby' for prenatal testing assemblages; and beliefs, institutions and communicative practices that guide understandings about which technologies will work in particular conditions.

DETECTION OF GENE MUTATIONS CAUSING MATURITY-ONSET DIABETES OF THE YOUNG IN AUSTRALIAN PATIENTS (P63)

T. Munce,[1] I. McGown,[1] M. Harris,[2] A. Cotterill[2] and D. Cowley[1]

[1] *Department of Molecular Geneticsm Mater Hospital, Brisbane, Australia*

[2] *Department of Pediatric Endocrinology & Diabetes, Mater Hospital, Brisbane, Australia*

Maturity-onset diabetes of the young (MODY) is a heterogenous form of diabetes mellitus characterised by an early age of onset, impaired insulin secretion and autosomal dominant inheritance. This form of diabetes accounts for 1% of all cases of diabetes. Mutations in six different genes have been identified in MODY patients, including genes encoding glucokinase (*GCK*), hepatocyte nuclear factor *(HNF)-4* , *HNF-1* , insulin promoter factor 1, *HNF-1* and *NeuroD1*. The majority of MODY patients have mutations in either *HNF-1* (70%) or *GCK* (15%) genes. 25 probands with strong family histories of diabetes mellitus were genotyped for mutations in *HNF-4* , *HNF-1* and *GCK* by DNA sequencing and multiplex ligation-dependent probe amplification (MLPA). We report on the identification of mutations in both the *GCK* and *HNF-1* genes in 6 probands (25% detection rate). Within the *HNF-1* gene, three previously described MODY mutations (P291fsinsC, P447L and R229Q) were identified in three families. Each of these mutations results in a loss of function of the *HNF-1* gene product. Two previously described MODY mutations were found in the *GCK* gene (C129Y and G299R). One novel *GCK* mutation was identified (E256D), which through family studies was shown to segregate with the presentation of diabetes mellitus. This is the first report of MODY genotyping in Australia.

APOLIPOPROTEIN C-III ISOELECTRIC FOCUSING IN PRADER-WILLI SYNDROME (P23)

T. Munce[1,2] and F. Bowling[2]

[1] *Mater Children's Hospital, Brisbane, Australia*

[2] *School of Molecular and Microbial Sciences, University of Queensland, Australia*

Prader-Willi syndrome (PWS) is a contiguous gene disorder characterised by a range of neurological and endocrine abnormalities. Genetically, PWS arises from a loss of paternal chromosome 15q11-q13 with associated maternal imprinting of genes in this region. The most common molecular mechanisms are either paternal interstitial deletions or maternal uniparental disomy. During investigations into protein post-translational modifications in PWS, we performed isoelectric focusing (IEF) of the serum O-linked glycoprotein, apolipoprotein C-III (apoC-III) in our cohort (n = 23, age range = 1–18 yrs). Through apoC-III IEF, three isoforms differing in sialic acid content may be resolved. Healthy individuals typically contain relatively equal amounts of the disialylated and monosialylated isoforms with low levels of the asialylated isoform. Our study revealed nine PWS patients (~40%) had an abnormal apoC-III IEF profile with increases in the asialylated isoform (9.1–16.9%; normal range 0–8.0%) and decreases in the disialylated isoform (22–39%; normal range 26–59%). The abnormal apoC-III IEF patterns observed in our study were independent of genotype. Although no genes involved in glycosylation are situated in 15q11-q13, there are two genes that have been given putative roles as ubiquitin E3 enzymes. We propose the increase in asialylated apoC-III isoforms in PWS is a reflection of an abnormality in the clearance of abnormal proteins rather than from a defect in glycan biosynthesis.

ROLE OF CDKL5 IN RETT SYNDROME (O126)

V. L. Nelaturi, S. L. Williamson, H. Lahooti and J. Christodoulou

NSW Centre for Rett Syndrome Research, Western Sydney Genetics Program, Children's Hospital at Westmead & Discipline of Paediatrics and Child Health, University of Sydney, Australia

In recent years CDKL5 (cyclin-dependent kinase like 5) has been shown to be a rare cause of the Hanefeld variant of Rett Syndrome (RTT). In most cases, RTT is caused by mutations in the MECP2 (methyl-CpG binding protein 2) gene that accounts for up to 95% of classical cases and a further 40-60% of atypical cases. The following study aims to shed some light into the role of CDKL5 in the pathogenesis of RTT. We have discovered a novel CDKL5 isoform with an alternative C-terminus that exhibits a different tissue distribution and subcellular localisation to the formerly identified transcript. The novel transcript is expressed ubiquitously in human tissues while the recognised transcript only in the testis. The two CDKL5 isoforms show different subcellular localisation profiles. In addition, we have shown that both CDKL5 isoforms are capable of phosphorylating histone-1 and myelin basic protein, but not MeCP2. These results suggest that the two isoforms have very different cellular properties and functions. Interestingly, we have found that CDKL5 interacts with tubulin, much like MeCP2. This interaction with tubulin seems to be of particular importance and could offer a common molecular pathway for the two proteins. The interaction with tubulin is made even more significant by our finding that fibroblasts from patients with CDKL5

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mutations show impaired tubulin polymerisation following treatment with nocodazole. These studies lead us to speculate that abnormalities in the interaction between MeCP2, CDKL5 and tubulin could be contributing to the neurophysiology of RTT.

NUTRITIONAL MANAGEMENT OF CYTOCHROME C OXIDASE DEFICIENCY COMPLICATED BY FOOD ALLERGY, PANCREATITIS AND DIABETES: A CASE STUDY (O28)

M. J.Netting,[1] J. M. Fletcher,[2] D. Ketteridge[2] and A. L. Sweeney[1]

[1] *Nutrition Department, Women's and Children's Hospital, Children's, Youth and Women's Health Service, Adelaide, Australia*

[2] *Metabolic Unit, Women's and Children's Hospital, Children's, Youth and Women's Health Service, Adelaide, Australia*

We describe the nutritional care of a 12-year-old girl with Cytochrome C Oxidase Deficiency, insulin dependent diabetes and pancreatic insufficiency requiring enzyme supplementation. Our case was born at term, but had interuterine growth restriction (birth weight 2.23kg). She has mild intellectual disability. Feeding issues led to her diagnosis and have been on going, and a gastrostomy tube was placed at 1 year of age. At the age of three she was diagnosed with a probable IgE mediated egg allergy, but this has never been tested with food challenge due to her poor oral intake. At 4 years of age she had a prolonged admission due to pancreatitis and after a stormy 4 months was discharged on home total parenteral nutrition – 12 months later she had been weaned back to enteral feeds of FS Monogen (SHS) but oral intake remained problematic. Insulin was commenced at 9 years of age due to persistent hyperglycemia and raised HBA1C levels. Pancreatic enzyme replacement therapy (Creon 10 000) commenced at 11 years of age, has resulted in an improvement in fat absorption and subsequent weight gain. At 12 years of age she continues to obtain most of her nutritional requirements from enteral feeds of 1 Cal/ml Monogen with a small but consistent oral intake. Weight and length have tracked around the 3rd to 10th percentile lines. Her head circumference is less than the 3rd %ile. This case demonstrates the complexities of nutritional management of a child with multiple issues impacting on intake and absorption of nutrients essential for growth and development.

A COMPARISON OF CGH-MICROARRAY AND CYTOGENETIC ANALYSIS IN PRENATAL DIAGNOSIS (P41)

T. K. Nguyen, J. Cross, A. Darmanian, A. Daniel and G. Peters

Cytogenetics Department, Western Sydney Genetics Program, The Children's Hospital at Westmead, Sydney, Australia

The extent to which CGH-microarray can replace conventional cytogenetics is a current topical issue in prenatal diagnosis. To address this, we reviewed cases received in our lab over the period Jan 2004–Dec 2007. In this period, we received 4195 amniotic fluid and chorionic villus samples. For a hypothetical 50,000-probe oligo array platform, we estimated the numbers of cases where array-CGH would have yielded a normal result, but where cytogenetics could detect a clinically significant abnormality. [Economic and copy number variant (CNV) issues, although important, have not been considered in the context of this review]. From reviewing incidence figures and population studies for various syndromes, we conclude that over this period we could have expected approximately 7 cases in which array-CGH would have detected a clinically significant genetic abnormality, not detectable by cytogenetics. Such unforseen anomalies may present significant problems in counselling. Over the same period we received 13 actual cases in which array-CGH alone would have given a false negative (normal) result. These include cases with triploidy, de novo apparently balanced translocations and inversions, and low-level mosaicism for autosomal trisomies. Three of these cases were retrospectively subjected to array testing and will be presented. From our data, we believe that cytogenetic analysis can currently detect such above chromosome abnormalities prenatally and, supported by FISH, it remains the gold standard.

IDENTIFICATION OF GENOME-WIDE TARGETS OF THE UPF3B DEPENDENT NONSENSE-MEDIATED MRNA SURVEILLANCE PATHWAY BY EXON ARRAY EXPRESSION PROFILING AND THEIR RELEVANCE TO THE PATHOGENESIS OF INTELLECTUAL DISABILITY (O65)

L. S. Nguyen, A. Gardener, L. Vandeleur, C. Shoubridge, M. Corbett and J. Gecz

Women's and Children's Hospital, Adelaide, Australia

Non-sense mediated mRNA decay (NMD) is a universal RNA surveillance pathway that among other functions degrades mRNAs bearing premature termination codons (PTC). We recently showed that mutations in UPF3B, an important member of this pathway, caused syndromic and nonsyndromic mental retardation.[1] To assess the impact of UPF3B null mutations and to identify relevant genes regulated by NMD, we performed expression profiling using RNA isolated from control and patient lymphoblastoid cells using both Affymetrix HU133 Plus 2.0 and Human Exon 1.0 ST arrays. Using HU133 and Exon arrays, we identified that 595 probesets (70% up, 30% down, false positive rate (FPR) = 30% by real time validation) and 633 genes (30% up, 70% down, FPR = 10%) were significantly dysregulated respectively. 27 genes were reported by both arrays, among them UPF3B itself (~2 folds down regulated). Hence, NMD is only partially compromised in the absence of UPF3B as its own PTC containing mRNA is NMD degraded. Comparison with previous microarray studies from UPF1, UPF2 or UPF3B knock down cell lines in human, fly and yeast generated minimal overlap. Such low correspondence could mean that these studies did not reflect the real situation of a knock out study, but it could also be due to the differences in the tissue types and platforms used. Applying KEGG pathway analysis, we found disruption in regulation pathways of cytoskeleton and axon guidance, as well as purine and pyrimidine metabolism in the patients. Our results have identified the bona-fide targets of the UPF3B dependent NMD pathway and shed light into the understanding of the pathogenic mechanism of the disorder.

1 Tarpey, P. S. et al. (2007). Mutations in UPF3B, a member of the nonsense-mediated mRNA decay complex, cause syndromic and nonsyndromic mental retardation, *Nat. Genet., 39*, 1127–1133.

ARRAY CGH DETECTS CRYPTIC CHROMOSOME ABNORMALITIES IN PATIENTS WITH INTELLECTUAL DISABILITY: THE ADELAIDE EXPERIENCE (O128)

J. Nicholl,[1] D. Bratkovic,[2] E. Haan,[1,2] S. Brown[1] and S. Yu[1]

[1] *Department of Genetic Medicine, Children, Youth & Women's Health Service, Australia*

[2] *South Australia Clinical Genetics Service, Australia*

Array CGH has developed as a useful adjunct technology for improving the detection rate of submicroscopic copy number changes in patients with idiopathic intellectual disability. Development of the technology is at an early stage and the demand for testing exceeds capacity. To address this, patients have been prioritised using an in-house scoring system based on four criteria:

- Developmental delay/ mental retardation is scored 0–2.
- Dysmorphic features are scored 0–2.
- Malformations are scored 0–2.
- The presence of an apparently balanced karyotype (with an abnormal phenotype, inherited or de novo) is scored 2.

The maximum possible score achievable is 8. A custom-built whole genome BAC array with a resolution of 0.2-1Mb (consisting of approximately 4,700 clones) has been used to study those with the highest scores among 100 patients awaiting array CGH screening. Two FISH confirmed cryptic imbalances were detected among the first twenty patients screened; a ~1Mb duplication of 1p36.12 and a 4.7Mb deletion of 9q22.31-q22.32. These patients had scores of 6 and 5, respectively. Array CGH screening is continuing, and will assess the diagnostic yield of the technology and the ability of the scoring system to predict the presence of a pathological cryptic chromosome imbalance.

CONFIRMATION OF GLYCOGEN STORAGE Ia IN SIBLINGS BY MUTATION ANALYSIS (P52)

C. M. Nicholls,[1] M. J. Fietz,[1] D. Ketteridge,[1] Y. S. Choy[2] and J. M. Fletcher[1]

[1] *Women's and Children's Hospital, Adelaide, Australia*

[2] *Subang Jaya Medical Centre Sdn. Bhd, Malaysia*

Introduction: Glycogen storage disease Ia (GSDIa) is an autosomal recessive disease caused by a deficiency of liver glucose-6-phosphatase which catalyses the terminal step in glycogenolysis and gluconeogenesis. Glucose-6-phosphatase is encoded by the G6PC gene (17p21) which contains 5 exons and has a short coding sequence of just over 1 kb. The patients studied here had clinical presentation typical of GSDIa. Both sibs (of nonconsanguineous parents), presented with doll-like facies, gross hepatomegaly, short statue, lactic acidosis, raised liver enzymes, hyperuricaemia, hypertriglyceridaemia, hypercholesterolaemia and impaired platelet function. Glucose challenge showed a reduction in lactate levels on administration of glucose. *Aim:* To confirm the enzymatic diagnosis of GSDIa by the determination of the causative mutations in the G6PC gene. *Methods:* Primer pairs were developed for each of the five exons in the G6PC gene and sequence analysis was performed on DNA extracted from liver lysate. *Results:* Sequencing revealed the presence of two heterozygous mutations, c.597T>C (p.L172P) in exon 4, and c.743G>A (p.G222R) in exon 5 of the G6PC gene. Both are located in conserved regions of the gene. *Conclusion:* This study has confirmed the ability to readily detect the causative mutations for GSDIa. Given the invasive nature of collecting a liver biopsy for enzyme analysis, mutation analysis in DNA extracted from a small volume of peripheral blood may provide an alternative means of diagnosing this disorder. Detection of the causative mutations also facilitates carrier testing and prenatal diagnosis in affected families.

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AUDIT OF THE NORTH EAST THAMES REGIONAL GENETICS SERVICE CANCER GENETICS TELEMEDICINE CLINICS (O93)

S. Nisbet, E. Williams and J. Soloway

Central and Southern Regional Genetics Services, Capital & Coast District Health Board, Wellington Hospital, Wellington South, New Zealand

Aim: To audit consultant-led telemedicine clinics for cancer genetics cases to determine whether these clinics were utilised appropriately and the cost effectiveness of offering this service. *Background:* The telemedicine clinic was piloted in one centre in 2003. Patient satisfaction questionnaires were analysed and 3 further monthly half-day telemedicine clinics were established. These clinics offer consultant-led appointments to patients living outside London, without the need for the consultant or patients to travel longer distances. *Method:* The counsellors responsible for each of the telemedicine clinic reviewed the records for patients who attended these clinics and the appointment availability over a 12-month period to determine:

- Could the patient have been seen by only a genetic counsellor/nurse?
- Was the appointment for a new referral or follow-up?
- Who followed up the family e.g. requesting confirmations of diagnoses and samples for testing?
- Unfilled appointment slots.

Results: 55 (72%) of the 76 patients seen in the telemedicine clinics could have been seen by genetic counsellor only. Follow-up was required for around 2/3 of the patients and the genetic counsellors were arranging the majority of this. 38 (33%) of the 114 available clinic slots remained unfilled. The cost of running these clinics over a 12 month period was £5000 ($12,700NZD, $10800AUD), which does not include the cost of the clinician's time. *Conclusions:* The audit has led to a change in practice for the service, with all new patients now meeting with a counsellor and follow-up appointments offered where consultant contact is required.

EPIGENETIC MODIFICATION IN HUMAN PLACENTATION: PARALLELS TO HUMAN TUMOURIGENESIS AND POSSIBLE ROLE IN ADVERSE PREGNANCY OUTCOMES (O61)

B. Novakovic,[1] N. Wong,[1] V. Rakyan,[2] S. Beck,[2] T. Down,[2] Craig Jeff[1] and R. Saffery[1]

[1] *Epigenetics Research Group, Murdoch Childrens Research Institute, Melbourne, Australia*

[2] *The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, United Kingdom*

The eutherian placenta regulates exchange of nutrients, oxygen, and waste between maternal and fetal circulations and helps protect the developing embryo/fetus from rejection by the maternal immune system. There are striking similarities between placental trophoblasts and some cancer cells including; growth in a low oxygen environment, lack of cell-contact inhibition, immune privilege, and invasive potential. The key difference lies in the spatial and temporal limitations of trophoblast growth in normal pregnancy. Mounting evidence suggests that epigenetic disruption in utero may play an important role in adverse pregnancy outcomes and modulation of disease risk later in life. We have identified a range of specific gene-promoter methylation events in human placental cells that are likely to contribute to this process. These include the selective methylation of the maintenance DNA methyltransferase DNMT1, Wnt signalling pathway inhibitors (and tumour suppressors) SFRP2 and APC, and genes regulating vitamin D metabolism. These cumulative data suggest that a series of specific DNA methylation events play a fundamental role in the process of human placentation. We are currently examining the distribution and function of this methylation within specific trophoblast cell populations of the placenta with the goal of identifying novel mechanisms contributing to the unique properties of human placentation. This has the potential to identify novel epigenetic targets for preventative or therapeutic intervention for disorders involving placental dysfunction (such as pre-eclampsia), and to identify the underlying mechanisms that produce a coordinated series of DNA methylation events common in human tumours.

ABSENCE OF TYPICAL EYE FINDINGS IN A MALE WITH JUVENILE X-LINKED RETINOSCHISIS: CLINICAL GENETIC IMPLICATIONS FOR THE FAMILY (P67)

E. C. Oates,[1] K. Friend,[2] L. Burrows,[2] J. Mulley,[2] A. Colley,[3] J.R. Grigg[4] and R.V. Jamieson[1,5]

[1] *Clinical Genetics, The Children's Hospital at Westmead, Sydney, Australia*

[2] *Women's and Children's Hospital, Adelaide, Australia*

[3] *Clinical Genetics, Liverpool Hospital, Sydney, Australia*

[4] *Save Sight Institute, Sydney, Australia*

[5] *Discipline of Paediatrics & Child Health, Faculty of Medicine, University of Sydney, Australia*

Juvenile X-linked retinoschisis (XLRS) is the most common cause of early onset macular degeneration in boys. Males with XLRS develop microcystic 'spoke-wheel'-like changes that disrupt the retina particularly in the macular region, causing progressive visual loss. Affected individuals are also at risk of sight-threatening complications such as vitreous haemorrhage and retinal detachment. RS1 is the only known causative gene. Female carriers do not usually have clinical abnormalities; however affected males are generally believed to show retinal features of the condition with impaired visual acuity. We report a 73-year-old male with 3 affected brothers, but had no clinical evidence of XLRS on initial ophthalmological examination. His clinical status was reevaluated when his daughter's 3-year-old son was unexpectedly diagnosed with the condition. Again he did not have typical retinal changes, however his ERG showed reduction in b-wave amplitude, a typical ERG finding in XLRS. Mutation testing of affected members within the family has since identified the presence of a splice site mutation in RS1 that segregates with the disease phenotype. Findings in this family emphasise the importance of requesting detailed ophthalmic examination, including full clinical and electrophysiological examination, in male individuals at risk for inheritance of an abnormal RS1 allele. It also shows the value of RS1 mutation testing in providing accurate genetic information in this condition. As in this family, this information can have significant implications for a grandson at risk of a potentially severe vision disorder.

A POLYMORPHISM AT THE *MDR*1 GENE LOCUS IS SIGNIFICANTLY ASSOCIATED WITH NON-SYNDROMIC ORAL CLEFTING IN FAMILY-BASED ASSOCIATION STUDY (P83)

A. Omoumi,[1] Z. Wang,[2,3] C. G. L. Lee[2,4,5] and S. S. Chong[1]

[1] *Department of Pediatrics & Obstetrics/Gynecology, National University of Singapore, Singapore*

[2] *Department of Biochemistry, National University of Singapore, Singapore*

[3] *Graduate Programme in Bioengineering, National University of Singapore, Singapore*

[4] *Division of Medical Sciences, National Cancer Center, Singapore*

[5] *DUKE-NUS Graduate Medical School, Singapore*

Aim: Oral clefts are one of the most common birth defects and create significant medical and emotional burdens for affected individuals and their families. Non-syndromic oral clefts are considered 'complex' or 'multifactorial' in that both genes and environmental factors contribute to the etiology. Current research suggests that several genes are likely to control risk, as well as environmental factors such as maternal smoking. The ATP-binding cassette (ABC) super-family transporters play important roles in the regulation of the traffic of drugs/xenobiotics across cells. These genes are expressed in many tissues, especially those with barrier functions such as liver, brain, kidney, intestine, and placenta. Hence, alteration in ABC genes expression especially in placenta may increase the risk for fetal exposure to teratogenics and fetotoxics during organ formation. Functional sequence variations in ABC genes might influence their expression or function in protecting the cells and organs against toxic compounds. We present our approach to study the association between genetic variations of ABCB1 at positions e12/1236 (C>T), e21/2677 (G>T, A), and e26/3435 (C>T), ABCC1 at position 5'FR/-260 (G>C), ABCC2 at positions e1/-24 (C>T), e10/1249 (G>A), and ABCG2 at positions e2/34 (G>A), e5/421 (C>A), and I9/-357 (T>C) and non-syndromic oral clefting. Given the abundance of SNPs within the human genome, identification of functionally important SNPs is difficult. We chose SNPs that have been reported to be under recent positive selection as well as potentially functional non-synonymous coding SNPs within these ABC genes for this association study. *Method:* 150 nuclear families with oral cleft child were recruited from Singapore and Taiwan for a family-based association study which is immune to confounding effects caused by population stratification/admixture. This study was approved by the Institutional Review Board (IRB). Both parents and affected offspring were genotyped for the selected SNPs within the above-mentioned ABC genes using multiplex minisequencing, and TaqMan® SNP Genotyping Assay. Whenever necessary, the genotyping results were validated by sequencing. We utilized extended transmission disequilibrium test to analyze the genotype data for association with oral clefting. *Results:* The results were statistically analyzed using TDT-McNemar and Extended TDT test. Only SNPs within the ABCB1 gene (SNPs e12/1236, e21/2677, and e26/3435), but not SNPs in other ABC genes were found to be significantly associated with oral clefting ($P < .05$). However, after Bonferroni correction, only SNP e12/1236 remained significantly associated with oral clefting. *Conclusion:* This result suggests that ABCB1 polymorphism appears to be associated with susceptibility to oral clefting and supports the hypothesis that its expression in placenta which about four-fifths of that is of fetal origin can influence the barrier role of this organ against teratogenics.

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CASE REPORT: TWO ASYMPTOMATIC INFANTS WITH CITRULLINAEMIA TYPE 1 (O23)

C. O'Neil,[1] R. Price,[2] V. Wiley,[3] B. Wilcken,[3] L. Norton,[4] J. Gavranich,[5] A. Inwood[6] and J. McGill[6]

[1] *Department of Nutrition and Dietetics, Royal Children's Hospital, Brisbane, Australia*

[2] *Newborn Screening Section, Pathology Queensland, Australia*

[3] *NSW Newborn Screening Program, Children's Hospital at Westmead, Australia*

[4] *Department of Nutrition and Dietetics, Gold Coast Hospital, Australia*

[5] *Department of Paediatrics, Ipswich Hospital, Department of Metabolic Medicine, Royal Children's Hospital, Brisbane, Australia*

We report two infants with citrullinaemia type 1 who were detected by newborn screening with elevated citrulline. Patient 1 had citrulline of 2000 µmol/L (Day 13 card!) (< 60 µmol/L). Confirmatory tests showed citrulline of 3400 µmol/L which was her highest citrulline. She has never had an elevated glutamine or ammonium and has never been symptomatic, even with intercurrent illnesses. Now 12 months of age, she has maintained good growth, health and development with protein restriction of 1.8–2.0 g/kg/day. Citrulline has decreased to 820 µmol/L. Patient 2 was detected in NSW with newborn screening citrulline 430 µmol/L (< 75 µmol/L). Confirmatory tests showed citrulline of 480 µmol/L and his highest citrulline was 1300 µmol/L. He has never had an elevated ammonium but by 3 months of age his glutamine had increased to 940 µmol/L (450–750) on 2 gm/kg/day of protein and 95 cals/kg/day. We therefore elected to restrict his protein and his glutamine normalised on 1gm/kg/day. At 7 months of age he is growing well on 1gm/kg/day of protein and 80 cals/kg/day. Citrulline is 190 µmol/L and glutamine 500 µmol/L. We have been trying to increase his protein to 1.5 gm/kg/day but he is reluctant to eat solids. *Conclusion:* Both patients are asymptomatic and growing and developing normally, but it is not clear that protein restriction is definitely required. We have chosen to monitor with glutamine as for other urea cycle disorders. Although patient 2 is protein restricted, he is growing well with normal ammonium so we have not considered any medications.

BIOBANKS: NEXT STEPS IN COMPLEX DISEASE DISCOVERY (O81)

L. J. Palmer

Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Australia

Common, chronic diseases continue to rise in incidence across all age groups and their diagnosis, prevention, and treatment continue to increase in complexity. Concomitantly, debates over effective resource utilization in the Australian and other health systems are becoming more common. New diagnostic, therapeutic, interventional, and health promotion strategies are urgently needed given our ageing populations. An increasing number of genes and modifiable environmental factors associated with complex diseases have been discovered. The escalating utilization of genomic data in clinical, epidemiological and public health investigations in novel and creative ways represents fresh hope for disciplines beleaguered by the potential for reverse causality, confounding and many forms of bias. These data may also help to explain the causes of current widespread variations in health within our population and inform strategies to deal with ill health at the level both of populations and individuals. However, in many ways we are right at the beginning of our ability to discover and use complex disease genes. For most complex human diseases, the reality of multiple disease-predisposing genes of modest individual effect, gene–gene interactions, gene–environment interactions, heterogeneity of both genetic and environmental determinants of disease and low statistical power mean that both initial detection and replication will likely remain difficult. Defining modifiable environmental determinants of complex disease has proven an equally difficult task. It has become increasingly clear that there is a critical need in epidemiology and genetic epidemiology for large, well-characterized, population-based resources. The development of such resources for the joint investigation of environmental and genetic hypotheses is a key advance for the growing integration of epidemiology with genetics and for personalized medicine to become a public health reality. Numerous population-based studies that include DNA banking are currently ongoing around the world, or have been completed in the last 10 years. New large, national cohorts such as the MRC/Wellcome Trust UK Biobank have been funded, with planned or ongoing initiatives for national cohorts in a number of countries in Western Europe, Scandinavia, North America and Australasia. These exceptional cohort resources are another step on the long road to discovering and utilizing the genes and modifiable environmental factors underlying common human diseases.

STRATEGIES FOR ACCESSING ONLINE GENETICS HEALTH INFORMATION (P71)

G. Parasivam,[1] E. Mastrocostas,[1] D. Petrie[2] and K. Barlow-Stewart[1]

[1] *The Centre for Genetics Education, NSW Department of Health, Royal North Shore Hospital, Sydney, Australia*

[2] *Association of Genetics Support of Australasia, Sydney, Australia*

In delivering online health information through NSW Health's Centre for Genetics Education (CGE) website (www.genetics.edu.au), it is important that information is highly relevant and easily accessible by our target audience, namely, families affected by a specific genetic condition, health professionals, teachers and students, and other members of the community with a general genetics health question. The aims of the 'Online Information Access Project' are to explore if, how, why and when women:

- in the general community access general genetics health information online (Phase 1)
- with a personal or family history of a known genetic condition, access genetics health information online (Phase 2).

In Phase 1, women in two focus groups will not have a personal or family history of a specific genetic condition. These women may not have tried to access genetics health information before, and searching strategies will be explored using hypothetical scenarios. A market research company will be contracted to recruit, conduct and analyse these focus groups. Issues may include the use of specific search terms such as 'inherited' or 'family', and use of search engines or health portals such as 'HealthInsite'. Themes from Phase 1 will inform the approach to focus groups in Phase 2. In Phase 2, two focus groups will be recruited through the Association of Genetics Support of Australasia (AGSA). Emerging themes from groups where there are specific genetics concerns will be compared and contrasted with those where concerns may be more general. Findings will inform future developments of the CGE website.

DEVELOPMENT OF NOVEL THERAPIES FOR THE TREATMENT OF METABOLIC DISORDERS USING METHYLMALONIC ACIDURIA (MMA) AS A DISEASE MODEL — WHERE ARE WE AT (O59)

H. L. Peters[1], N. Buck[1], R. Hui[1] and J. Pitt[2]

[1] *Cell & Gene Therapy Group, Melbourne, Australia*

[2] *VCGS Pathology, Murdoch Childrens Research Institute and Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia*

Currently conventional treatment for organic acidaemias and in particular MMA is limited and despite such treatment, morbidity and mortality remains high with many long-term complications. Realistically there have been no new advances in the treatment of this devastating chronic disease indicating a clear need for the development of alternative therapies. We have established a research program focusing on mutase deficient MMA with the aim of developing new therapies. In order to achieve this goal we first produced a number of novel animal models that recapitulate the human MMA disorder at both a biochemical and molecular level. We have begun initial studies on liver and stem cell transplantation, viral gene therapy and pharmacological gene manipulation. A major aspect of this work concentrates on the identification and testing of novel compounds that may be beneficial in either (A) *upregulating residual enzyme activity* or (B) *inducing stop codon readthrough* in individuals affected by mutase MMA. It is anticipated that a small improvement in enzyme activity, which is feasible with the proposed approaches, will result in significant clinical benefit. This fact is supported by our animal studies where a 5% increase in enzyme activity allows our neonatally lethal mice to survive long term whilst a 10% increase results in mice with minimal biochemical and clinical phenotype. We have identified a number of FDA approved compounds that have resulted in between 100–105% increase expression of the MUT gene. We plan to use these models to trial different therapeutic approaches prior to ultimately translating this work into clinical practice.

ARRAYCGH AND SNP ARRAYS IN DIAGNOSIS OF GENOMIC DISORDERS: SOME APPLICATIONS IN A CLINICAL CYTOGENETICS LABORATORY (O130)

G. Peters, A. Darmanian, D. Hung and J. Cross

Cytogenetics Dept, Western Sydney Genetics Program, Children's Hospital at Westmead (CHW), Sydney, Australia

In late 2006, our lab in the Children's Hospital at Westmead introduced 'comparative genomic hybridisation by microarray' as a diagnostic service, to investigate constitutive changes in gene copy number, excluding referrals in prenatal settings. This service began with BAC (bacterial artificial chromosome) arrays, at around 1Mb resolution, and has progressed to a higher resolution format, at ~0.3Mb resolution (44,000 oligomeric probes per genome). Although not available 'in house', we have also used SNP arrays, in rare and research applications. To date (March, 2008), we have processed 500 diagnostic specimens by CGH

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(competitive genomic hybridisation) array, and these now comprise 25% of the total constitutive, postnatal case load, within this 'cytogenetics' department. The significant findings will be presented, among them being five cases of the recurring 'del17q21.31' syndrome, and two cases of the problematic 1q21.1 microdeletion, currently described within the Decipher Consortium database (UK) as recurrent, but 'of uncertain significance'. Problems associated with such potential CNVs (copy number variants) will also be considered. Abnormalities have been detected in around 12% of our referrals to date. Using these as examples, we will consider the range of anomalies detectable with the differing array platforms, and likely future developments in the field.

AN EVALUATION OF TANDEM MASS SPECTROMETRY URINE METABOLIC SCREENING (O29)

J. Pitt,[1,2] A. Mishra,[1] M. van Werkhoven [1] and M. Eggington[1]

[1] *VCGS Pathology, Murdoch Childrens Research Institute, Australia*

[2] *Department of Paediatrics, University of Melbourne, Australia*

We have developed a high throughput method for urine screening by tandem mass spectrometry (MSMS) in which samples are analysed in positive and negative ion mode and 104 metabolic markers are targeted using multiple reaction monitoring. Diagnoses made by our biochemical genetics laboratories (including newborn screening) over a 3.3-year period were reviewed to evaluate the effectiveness of this screening method. Mitochondrial and lysosomal storage disorders were excluded. 7091 urine samples were analysed and results were available from 129 patients with diagnoses. 123 of these patients gave abnormal MSMS screening results, all of them highly suggestive of the final diagnosis. 26 patients had disorders that would not be detected by conventional amino or organic acid testing. The 6 false negatives comprised two cases of OTC deficiency and one each of NKH, AADC, thiamin-responsive PDH and citrin deficiencies. However, 4 of these had nondiagnostic metabolite levels when tested by other methods. Our experience has been that MSMS urine screening can replace conventional amino acid screening. There was excellent agreement for most organic acids between MSMS and GC-MS but the detection limits for some organic acids such as orotic and vanil-lactic were poorer using MSMS. MSMS is a useful and rapid initial screen for organic acidurias but GC-MS analysis is still required in some situations.

FAMILIAL HYPERCHOLESTEROLAEMIA (FH) PILOT CASCADE SCREENING PROJECT (O119)

S. Poke,[1] G. F. Watts,[2,3] M. A. Powell,[2] J. Emery[4] S. Maxwell,[1] K. Brameld,[1,2] T. Bates,[3] J. Burnett,[2,3] F. van Bockxmeer,[2,3,5] S. Dimmitt,[2,3] T. Redgrave[3,6] and P. O'Leary[1,7,8]

[1] *Office of Population Health Genomics, Department of Health, Western Australia*

[2] *School of Medicine and Pharmacology, University of Western Australia*

[3] *Royal Perth Hospital, South Metropolitan Area Health Service*

[4] *School of Primary, Aboriginal and Rural Health Care, University of Western Australia*

[5] *School of Surgery and Pathology, University of Western Australia, Australia*

[6] *School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Australia*

[7] *School of Women's and Infant's Health, Faculty of Medicine and Dentistry, University of Western Australia, Australia*

[8] *School of Public Health, Curtin University of Technology, Australia*

Familial hypercholesterolaemia (FH) is an inherited disorder of cholesterol metabolism leading to premature coronary heart disease (CHD). The early diagnosis and treatment of FH can delay or prevent the onset of CHD. The Office of Population Health Genomics in collaboration with the Department of Internal Medicine (RPH), and the UWA School of Medicine and Pharmacology are supported by the Australian Better Health Initiative to run a pilot program of family cascade screening of FH cases in WA. A model of care has been developed for screening adults and children at risk of FH. Index cases are identified through lipid and cardiology clinics, as well as through selected general practices. Once participants consent to the cascade-screening program, their relatives may be recruited into the program. All cases have an initial consult with the RPH Lipid Disorders Clinic, with ongoing medical care through their GP. So far, 69 index cases have been assessed by the FHWA clinic and 28 relatives are under clinical review. This is the first report of an Australian FH program that has the potential to prevent 26 heart attacks in every 100 cases identified and treated, with a potential cost-effectiveness of $14,000 per life year gained. This program provides information on appropriate service frameworks, support for FH families and opens issues of targeted genetic screening, sharing family health information and the translation of research into improvements in community health.

THREE-YEAR RETROSPECTIVE REVIEW ON PRENATAL MOSAIC KARYOTYPES (P69)

S. Polihronis, S. Robinson and D.C. Wright

Sydney Genetics, Sydney, Australia

A retrospective review from Jan 2005 to Dec 2007 was performed on prenatal samples (n = 6412) encompassing the Sydney metropolitan area, including chorion (CVS) (n = 2806) and amniotic fluid (AF) (n = 3606) samples. Our aim was to determine the frequency of mosaics, the utilisation of interphase fluorescent in-situ hybridisation (FISH) follow-up studies and impact on counselling and patient management. Follow-up studies involved amniocentesis or fetal blood sampling (FBS) and included karyotyping and FISH to clarify the fetal karyotype. Overall, mosaic karyotypes were identified in 49/6412 (0.76%) samples, however the frequency in CVS was 43/2806 (1.5%) and in AF was 6/3606 (0.17%). Mosaicism involved +2, +4, +7 +8, +9, +12, +13, +15, +16, +18, -18, +20, +21, +22, 3n, 4n, XXX, XO, XX/XY, +mar and a double aneuploidy. For CVS, follow-up AF was received in all 43 cases however FISH was performed in only 39 cases. FISH detected the abnormality in 7/39 (18%) cases but only 3 of these were confirmed in 3 long-term cultured karyotypes. For AF, follow-up AF was received in all cases with 2 cases progressing to additional fetal blood sampling. The abnormality was confirmed by FISH and karyotyping in 4 (67%) cases. In summary, FISH was utilised in 45/49 (92%) mosaic cases and the abnormality detection rate was 18% for CVS and 67% for AF. This data can be useful for patient counselling and further management.

TP53 MUTATIONS IN YOUNG WOMEN WHO EXPERIENCE BREAST CANCER (O83)

N. K., Poplawski,[1] J. Armstrong,[1] G. Suthers,[1] J. Gardner[2] and S. Grist[2]

[1] *Familial Cancer Unit, Women's and Children's Hospital, Adelaide, Australia*

[2] *Genetic Pathology Laboratory, Flinders Medical Centre, Adelaide, Australia*

Introduction: The prevalence of germline TP53 mutations in women presenting with young-onset breast cancer (YBCa; 30 years or younger at diagnosis) is unknown. *Aim:* A retrospective analysis of TP53 mutations in women with YBCa. Case selection: 238 women with YBCa, from 228 pedigrees, were reported to the South Australian Familial Cancer Unit (SAFCU). The SAFCU had contact with 72, 68 of whom had BRCA1/2 testing. Mutations were identified in 16 (9 BRCA1; 7 BRCA2). 52 had no BRCA1/2 mutation identified and in 45 appropriate consent and DNA samples were available for TP53 testing. *Results:* On 14/03/2008 TP53 analysis was completed in 23/45 tests ordered and 4 pathogenic sequence changes identified. *Case 1:* YBCa at 20 and 28; 2 cousins with non-Li-Fraumeni cancers (1 maternal, 1 paternal). *Case 2:* YBCa at 27, 28 and 30; her mother experienced YBCa at 27. *Case 3:* YBCa at 24; her paternal grandmother experienced BCa at 46, her maternal grandfather CRC at 68. *Case 4:* YBCa at 29; her brother experienced synchronous CRC and sarcoma at 28, her father gastric cancer at 31, her father's half-sister BCa at 50, and her paternal grandfather ureteric and prostate cancers. *Conclusion:* TP53 mutation screening is appropriate in women with YBCa, including women with no family history of Li-Fraumeni cancers, or a family history of Li-Fraumeni component cancers where the 'Chompret criteria' are not met (see ref). Identification of a mutation aids decisions regarding breast cancer surveillance (mammography vs MRI) and risk-reducing surgery.

PMS2 AND CANCER: THE AUSTRALASIAN EXPERIENCE (P78)

N. K. Poplawski,[1] K. Phillips,[1,2] C. Vakulin,[3] D. Henry,[3] J. Carroll,[3] L. Andrews,[4] M. Gattas,[5] C. Groombridge,[6] J. Kirk,[7] C. Lintott,[8] A. McEwen,[9] J. McGaughran,[5] G. Mitchell,[10] A. D. Spigelman,[6,11] R. Ward,[12] A. Zankl[5] and G. Suthers[1]

[1] *Familial Cancer Unit, Women's and Children's Hospital, Adelaide, Australia*

[2] *Australasian Colorectal Cancer Family Study, Melbourne, Australia*

[3] *Division of Molecular Pathology, IMVS, Adelaide, Australia*

[4] *Hereditary Cancer Clinic, Prince of Wales Hospital, Sydney, Australia*

[5] *Genetic Health Queensland, Royal Children's Hospital, Brisbane, Australia*

[6] *Hunter New England Family Cancer Service, Hunter Genetics, Newcastle, Australia*

[7] *Familial Cancer Service, Westmead Hospital, Sydney, Australia*

[8] *Central and Southern Regional Genetics Service, Christchurch Women's Hospital New Zealand*

[9] *Central Regional Genetic Service, Wellington Hospital, Wellington, New Zealand*

[10] *Familial Cancer Centre, Peter MacCallum Institute, Melbourne, Australia*

[11] *University of New South Wales, Australia*

[12] *Prince of Wales Clinical School, University of New South Wales, Australia*

Aim: A retrospective review of Australasian families with identified mutations or unclassified variants in the PMS2 gene. Results: 31 families were identified, 19 with a monoallelic pathogenic mutation and 12 with an unclassified variant(s). In families with pathogenic mutations, 9 probands experienced colorectal cancer (CRC) under 50, with 6/9 reporting a family history (FmHx) meeting Amsterdam II criteria, 2/9 a FmHx which included 1 or more Lynch Syndrome cancers (LSCa) and 1/9 a FmHx

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containing no known LSCa. Six mutation probands experienced CRC over 50; 2/6 Amsterdam II, 2/6 a FmHx of LSCa and 2/6 no FmHx of LSCa. Two mutation probands experienced endometrial carcinoma under 50; 1 Amsterdam and 1 no FmHx of LSCa. One mutation proband experienced multiple LS-primaries and 1 jejunal cancer at 63 (both with a FmHx of LSCa). Immunohistochemistry showed isolated absence of PMS2 in 16/19 (84%) proband cancers, absence of both MLH1 and PMS2 in 2/19, and patchy loss of MSH6 with complete loss of PMS2 in 1/19. Two mutations were recurrent; c.989-296_1144+70del (5 families) and c.736_741del6ins11 (7 families). *Conclusion:* Mutations in PMS2 are an important cause of Lynch Syndrome, familial colorectal cancer and young onset bowel cancer. The paucity of cancer-affected family members in some pedigrees suggests that PMS2 mutations may be less penetrant than mutations in other genes associated with LS, although analysis of additional pedigrees and extended genetic testing in recognized families would clarify this. Early mutation results suggest a small number of relatively more common mutations may be important.

FAMILY CASE STUDY OF AN INHERITED T(9;16) INVOLVING AN INTERESTING SUBTELOMERIC REARRANGEMENT (P8)

F. Price, E. Baker, J. Peverall and other members of the Cytogenetics Department, KEMH

Cytogenetics, King Edward Memorial Hospital, Australia

A case study of a family that carries a t(9;16)(p?24.3;p13.3) involving an interesting subtelomeric rearrangement and FISH pattern. Subtelomeric FISH analysis reveals a translocation involving the short arms of chromosomes 9 and chromosome 16. Of interest is that the subtelomeric 9p probe was not relocated, and the translocation breakpoint lies distal to the probe region. That is, both the 9p subtelomeric probe as well as the 16p subtelomeric probe were present on the short arm of the derivative 9, with the 16p being in a position distal to the 9p subtelomeric region. An extensive family history has been collected and includes both a liveborn child of a family member (carrier) as well as a pregnancy loss of a different family member (carrier), both of which had the same unbalanced karyotype containing the der(9), resulting in trisomy 16p. Fluorescent in situ hybridisation pictures as well as karyotypes will be presented in poster form.

THREE CASES OF MATERNAL 3-METHYLGLUTACONIC ACIDURIA DETECTED BY NEWBORN SCREENING IN QUEENSLAND (P15)

R. Price,[1] C. Gurnsey,[1] D. Cowley,[2] A. Inwood,[3] M. Henman,[1,2] D. Coman[3] and J. McGill[1,2,3]

[1] *Department of Chemical Pathology, Pathology Queensland, Central Laboratory, Herston, Brisbane, Australia*

[2] *Department of Biochemistry, Mater Pathology, Brisbane, Australia*

[3] *Department of Metabolic Medicine, Royal Children's Hospital, Brisbane, Australia*

The Queensland Newborn Screening laboratory has detected three cases of maternal 3-methylglutaconic aciduria by routine newborn screening. The newborn screening results of the babies were characterized by mild elevations in 3-hydroxyisovalerylcarnitine (C5OH) and an elevated C5OH/C0 ratio, while two also had an elevation in the C5OH/C8 ratio. The infants' urine organic acid analyses were all essentially normal and plasma acylcarnitine studies showed elevated C5OH in both of the tested infants. Two of the mothers had elevated C5OH in their plasma acylcarnitine studies and all had moderate elevations in both 3-methylglutaconate and 3-methylglutarate in their urine. Increased 3-methylglutaconate in the urine of pregnant women is well recognized but the aetiology is unknown. The suggestion, that the 3-methylglutaconate and 3-methylglutarate resulted from increased production via the mevalonate shunt, has been disproved. Another hypothesis is that the 3-methylglutaconate originates from the 'isoprenoid' shunt in the placenta. All 3 women were asymptomatic and had persisting urinary metabolites several months after delivery suggesting that the metabolites were not related to pregnancy. Asymptomatic women with these metabolites have been reported before. None of the women had any features to suggest a mitochondrial disorder. We propose that 3-methylglutaconic aciduria is yet another example of a 'non-disease' detectable by newborn screening although we cannot exclude the possibility of later onset mitochondrial disease.

FREQUENCY OF CFTR-RELATED INFERTILITY IN SOUTH AUSTRALIAN MALES (O48)

T. Pyragius, S. Chin, C. Nicholls, K. Whenan, J. M. Fletcher and M. Fietz

Department of Genetic Medicine, Child, Youth and Women's Health Service, Adelaide, Australia

Background: Cystic Fibrosis (CF) is a common autosomal recessive disorder, presenting with pulmonary disease and in more severe cases pancreatic insufficiency. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, with the severity of the disease being dependent in part on genotype. CFTR mutations have also been shown to cause male infertility (obstructive azoospermia), predominantly with a severe mutation on one allele and a mild mutation on the other. Studies have also shown that the 5T (c.1210-12T[5]) polymorphism in intron 8, in trans with a severe mutation, can result in obstructive azoospermia. *Aim:* To perform a retrospective analysis of males referred to the National Referral Laboratory for infertility, examining the frequency of CFTR mutations and the presenting clinical phenotype. *Methods:* CFTR mutation analysis results were examined for males referred for infertility, dating from 1998 to the present. All patients have been screened for 7-11 CFTR mutations and examined for their polyT genotype. *Results:* In this patient cohort, we have detected 14 patients (3.7%) with a genotype suggestive of CFTR-related obstructive azoospermia. Within the remainder of patients, the frequency of p.F508del heterozygotes (5.4%) was higher than the general population (3%) and the frequency of 5T alleles (5.7%) was similar to the general population (5.2%). Conclusion: Based on genotype we have identified 14 patients (3.7%) with probable CFTR-related infertility. Given the higher than expected frequency of p.F508del heterozygotes, it remains possible that a proportion of these carry a second undetected CFTR mutation responsible for their infertility.

USE OF ARRAY CGH IN PRENATAL DIAGNOSIS (P84)

H. Raussi,[1] P. Miny,[2] K. Heinimann,[2] F. Wenzel,[2] I. Filges,[2] A. Godenhjelm[1] and P. Ollikka[1]

[1] *PerkinElmer LAS, Wallac, Turku, Finland*

[2] *Division of Medical Genetics, University Children's Hospital, Basel, Switzerland. Presented by Dr Chuang-Fong Kong, PerkinElmer Australia*

Objective: Microarray based comparative genomic hybridization (aCGH) is relatively widely used in genetic diagnosis of children, but true potential is still unexplored in prenatal diagnosis. The objective of our study is to evaluate the feasibility of BAC arrays in the analysis of prenatal samples. *Methods:* Chorionic villus and amniotic fluid samples are obtained using standard clinical procedures. DNA is extracted and labelled for the aCGH analysis. For samples with limited amounts of DNA, we perform whole genome amplification (WGA). Two types of arrays are used: arrays targeted to constitutional syndromes (Constitutional Chip® 3.0), and 1 Mb resolution-arrays covering whole genome (Spectral Chip™). The arrays are scanned with ScanArray®, and data is analyzed with SpectralWare®. All samples are also analysed by conventional karyotyping. Potential aCGH findings are confirmed with FISH using the corresponding BAC DNA as probe. *Results:* To reduce the turn-around time, DNA is extracted directly from the samples. For direct amplification, we have compared 3 suppliers for their WGA performance. In addition, some cases have been tested both with native and amplified DNA to address potential bias caused by amplification. Results are promising, and a larger set of samples will confirm the best practices. *Conclusion*: The use of samples without cell culturing combined with simultaneous detection numerous genomic imbalances can have great benefit to prenatal diagnosis. The difficulty in discriminating the pathologic and benign copy-number variations and the possibility to detect potentially unwanted information will undoubtedly be challenging for the professionals interpreting the data but also for array manufactures.

LABORATORY QUALITY IMPROVEMENT OF NEWBORN SCREENING BY TANDEM MASS SPECTROMETRY (O13)

P. Rinaldo

Mayo Clinic College of Medicine, Rochester, United States of America

This project started in 2004 with seven US states and has grown to 44 states and 55 additional laboratories in 32 countries. The goals of this project are to develop evidence-based standards and metrics for laboratory performance in newborn screening and to create a culture of data sharing, constructive inter-laboratory comparison, and exchange of specimens. Data posted by participants on our website (www.region4genetics.org) include: (1) system definition (reagents, instrumentation, derivatization and acquisition parameters); (2) percentiles of normal population for all markers and calculated ratios (15,339 data points as May 10, 2008); (3) cutoff values (2,998 values); (4) anonimized results of true positive cases (5,742 cases, 308,386 data points); and (5) performance metrics (detection rate, positive predictive value, and false positive rate; 33 labs). Submissions are added to databases and processed automatically to generate project tools and reports, including the compilation of cutoff target ranges, defined as the interval between the cumulative 99%ile of the general population and the 5%ile of the disease range. The cutoff tool compares each individual value used by a given participant to the target range and to the values of all other labs. A cutoff value is considered validated if it remains within the target range (clinical validation) and is also comprised between the 25%ile–75%ile range of all submitted values (peer comparison). For each analyte, the highest and lowest values among all participants are referred to as 'outliers'. By doing so participants are given the opportunity to recognize and, if appropriate, correct their cutoff outliers to improve overall sensitivity and specificity of their program.

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PRENATAL DIAGNOSIS OF SIMPSON-GOLABI-BEHMEL SYNDROME: THE IMPORTANCE OF ULTRASOUND AND FAMILY HISTORY IN MAKING THE DIAGNOSIS (P70)

R. Robertson, R. Fleischer and M. Field

Royal North Shore Hospital, Sydney, Australia

This case report describes a couple that initially presented for pre-conception genetic counselling regarding their self-reported family history of Beckwith-Wiedermann syndrome (BWS). A clinical examination did not support the diagnosis of BWS in the consultand. The family history was thought to be significant, however her more severely affected brother declined an appointment to be assessed. Following 2 pregnancy losses, the couple presented with a dichorionic twin pregnancy. Ultrasound identified a cystic hygroma, polydactyly and renal pyelectasis in one fetus. Chorionic Villus Sampling (CVS) was performed and indicated normal male and female karyotypes. These clinical findings in conjunction with the family history prompted the diagnosis of Simpson-Golabi-Behmel syndrome to be considered. Mutation analysis of the GPC3 gene was performed on the CVS tissue, consultand and her brother. A deletion in exon one of the GPC3 gene was identified and the couple counselled regarding this finding. Further ultrasounds showed the male fetus had a diaphragmatic hernia. The babies were delivered at 35 weeks gestation. The affected male died shortly after birth. The surviving female twin had clinical features including relative macroglossia and polydactyly suggesting that she has inherited the familial GPC3 mutation. This case demonstrates:

- the combined value of clinical information and family history in reaching the correct diagnosis
- the importance of considering X-linked conditions in families with a male with developmental delay
- the value of thorough ultrasound for the identification of abnormalities
- the complexities of managing a twin pregnancy where abnormalities are detected in one twin.

KAROTYPE EVOLUTION AND CENTROMERE REPOSITIONING (O115)

M. Rocchi

Dip. di Genetica e Microbiologia, Via Amendola, Bari, Italy

Karotype evolution in primates was first studied as morphological comparisons using gross straining and banding techniques. Subsequently, molecular cytogenetics began with whole chromosome paints (WCP) and reciprocal chromosome painting to better delineate primate karotypic evolution on the basis of DNA content. WCPs while efficient in resolving interchromosomal rearrangements (translocations), were not suitable for detecting intrachromosomal changes in marker order. The use of small probes of cloned DNA, bacterial artificial chromosomes (BAC) in particular, now allows detailed studies on marker order between prmates. A detailed reconstruction of the Hominoidea Ancestor (HA) karotype will be presented, along with the flow of chromosomal changes linking the HA to the extant great apes and lesser apes. These comparative studies, in addition, have disclosed novel phenomena such as pericentrometric plasticity and evolutionary centromere repositioning. The latter phenomenon consists of the emergence of a new centromere along a chromosome during evolution, while the order of flanking physical markers remains unchanged. The impact of centromere repositioning events in shaping the architecture of primate chromosomes will be discussed.

CENTROMERE REPOSITIONING (O32)

M. Rocchi

Dip. di Genetica e Microbiologia, Via Amendola, Bari, Italy

Human neocentromeres are perfectly functioning, analphoid centromeres which emerge epigenetically in ectopic chromosomal regions. In the majority of cases, neocentromeres appear to rescue the mitotic stability of acentric chromosomal fragments, often giving rise to aneuploidy. Centromere repositioning, also indicated as evolutionary new centromere, is a recently discovered biological phenomenon consisting of the emergence of a new centromere along a chromosome during evolution, while the order of flanking physical markers remains unchanged. These two phenomena are more frequent than has been suspected up to now. Interesting examples of human clinical neocentromeres and evolutionary novel centromeres will be presented. They point to the conclusion that they are two faces of the same coin.

NOVEL *JARID1C* MUTATIONS IN TWO FAMILIES WITH X-LINKED MENTAL RETARDATION (O107)

S. Rujirabanjerd,[1,2] J. Nelson,[4] G. Turner,[6] PS. Tarpey,[5] M. R. Stratton [5] and J.Gecz[1,3]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Department of Pathology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*

[3] *Department of Pediatrics and School of Molecular and Biomedical Science, University of Adelaide, Australia*

[4] *Genetic Service of Western Australia, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia*

[5] *Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom*

[6] *GOLD Service, Hunter Genetics, Waratah, Australia*

Mental retardation (MR), is a genetically heterogeneous condition characterized primarily by cognitive impairment with IQ < 70. The ~30% excess of affected males versus females suggests above average contribution of the X chromosome. Recently, our group has participated in the identification of several mutations in the Jumonji AT-rich interactive domain 1C (*JARID1C*) gene on Xp11.2 in families with X-linked mental retardation (XLMR). Currently, there are 14 mutations of *JARID1C* reported. As part of a systemic re-sequencing of 737 genes in 225 XLMR families of the IGOLD consortium, we identified two novel nucleotide changes in *JARID1C* coding region, which we speculate to be causative in these XLMR families. The first mutation is a single nucleotide insertion in exon 21 (c.3258_3259insC p.K1087fs*43) causing a frameshift and resulting in a premature termination codon (PTC). Generally, such PTC containing mRNAs are efficiently degraded by nonsense-mediated mRNA decay (NMD) surveillance. However, our results show that this is not the case with this mutation. The other change is a single nucleotide substitution in exon 12 (c.1160C>A) in a published family with non-syndromic mental retardation, MRX13. This change occurs at a highly conserved amino acid, proline (P) which is substituted by threonine (T), in the JmjC domain of *JARID1C* (p.P544T). This is the first report of the JmjC domain mutation. This substitution is predicted to disrupt the histone demethylase activity of the JmjC domain. Both nucleotide changes segregate with disease phenotype in respective families. We conclude that the two novel *JARID1C* changes are disease-causing mutations in these families.

FAMILY HEALTH HISTORY: A MODEL FOR INCREASING BEHAVIOUR CHANGE? (O118)

A. Samanek,[1] J. Brisbane,[1] G. Kyne[1] and P. O'Leary[1,2,3]

[1] *Office of Population Health Genomics, Health Policy and Clinical Reform Division, Department of Health, Western Australia*

[2] *School of Women's & Infants' Health, University of Western Australia, Australia*

[3] *School of Public Health, Division of Health Sciences, Curtin University of Technology, Australia*

To increase awareness among the community of family health history to provide a cue to action for modifying behaviour that will reduce the risk of common chronic diseases. A pilot project was undertaken in a Perth suburb in 2008 to gauge community interest in family health history and determine if awareness of family health history and potential increased risk of common chronic diseases resulted in behaviour change. Family health history represents a largely nonmodifiable risk factor and applying the Protection Motivation Theory may prove useful to ensure that the information obtained from a family health history results in attendant behaviour change. 133 people over the age of 18 years attended seminars on family health history during the pilot project; the majority of attendees were women. The perceived importance of family history replicated the results of international studies with 85% of attendees responding that family history was 'very important' (25% response rate). Despite the perceived importance of family health history, few respondents had actively collected their family history. All respondents (except community health nurses) stated that if they became aware of a family health history that indicated increased risk of a chronic disease they would be 'very' or 'somewhat' likely to modify their behaviour. Family health history can be used to indicate an increased risk of common chronic disease but represents a significant challenge for implementation of large scales programs aimed at modifying behaviours to reduce their risk.

EDUCATING HUMAN RESEARCH ETHICS COMMITTEES ON GENETICS: IS IT ETHICAL? (P61)

A. Samanek,[1] L.Youngs [1] and P. O'Leary[1,2,3]

[1] *Office of Population Health Genomics, Department of Health, Western Australia.*

[2] *School of Women's & Infants' Health, University of Western Australia, Australia*

[3] *School of Public Health, Division of Health Sciences, Curtin University of Technology, Australia*

With the increasing emphasis on genetic research, how much information do HREC members require to adequately review complex questions of genetic privacy, discrimination, familial information and large-scale biobanking activities? We investigated the appeal and effectiveness of

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undertaking education for HREC members. Two education seminars and one interactive workshop were held for researchers, HREC members, genetic support group members, HREC administrators and Department of Health policy officers. 156 people from the target groups attended these events. The first seminar, 'Using human tissue for genetic research', explored ownership, management, governance and consumer perspectives of tissue banks, the 26 respondents (35% response rate) stated the information provided at the seminar was useful. The second seminar, 'Consumer attitudes to genetics and databases', considered the National Statement, lay understanding of consent, consumer attitudes to genetics and health data and the ethical perspectives that might guide tissue banking. Most (90%, $n = 23$) respondents indicated the information provided in the seminar would be useful to their HREC activities. The more complex topic of 'familial comity' was undertaken in a facilitated workshop format with four case studies used to explore the ethical principles that were applied in reviewing them. Analysis indicates the generally accepted ethical principles of autonomy, beneficence, non-malificence and justice were not routinely applied. HREC members undertake a complex task, reviewing numerous and varied applications to carry out research. These seminars and workshops supplemented the limited training otherwise provided for HREC members. Our findings suggest further guidance about undertaking ethical review of genetics-related research is warranted.

SUBTELOMERE MLPA: DETAILED ANALYSIS OF POLYMORPHIC CNV (P68)

L. Sanchez,[1] A. Correll,[1] E. Douglas,[1] K. Cox,[1] P. Nelson,[1], S. Brown,[1] L. Teicher,[1] M. Harbord,[2] E. Haan,[1] J. Liebelt,[1] K. Friend[1] and S. Yu[1]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Strathmont Centre, Oakden, Australia*

Copy number variation (CNV) of chromosomal subtelomeric regions has been found to be a frequent cause of idiopathic mental retardation. Commercially available MLPA kits (MRC-Holland) provide an efficient means of detecting these abnormalities (deletions and duplications). Since mid-2005 we have screened in excess of 1500 patients by subtelomere MLPA, identifying 69 abnormalities in 67 individuals. The data from our study indicate that we have identified 9 de novo CNVs, 25 inherited CNVs and 35 currently unclassified CNVs. The most frequently identified abnormalities are apparent deletions at the 4q (10%) and 15q (6%) probes. Detailed analysis (by sequencing) of these regions indicate that not all MLPA anomalies represent true copy number imbalances. The 4q region appears to be particularly prone to sequence variants adjacent to the MLPA probe ligation site. These variants have been identified as the likely cause of abnormal MLPA results in a number of our patients and are considered to be most likely polymorphic.

PERINDOPRIL REDUCES LARGE ARTERY STIFFNESS AND AORTIC ROOT DIAMETER IN A RANDOMISED, DOUBLE BLIND STUDY OF PATIENTS WITH MARFAN SYNDROME (O69)

R. Savarirayan,[3] A. Ahimastos,[1] A. Aggarwal,[2] K. D'Orsa,[1] M. Formosa,[1] A. Dart[1] and B. Kingwell[1]

[1] *Baker Heart Research Institute, Melbourne, Australia*

[2] *Royal Melbourne Hospital, Australia*

[3] *Murdoch Children's Research Institute, Melbourne*

Objective: Given the beneficial effects of angiotensin converting enzyme inhibitors on arterial stiffness we sought to determine whether perindopril therapy would reduce aortic stiffness and attenuate aortic dilatation in patients with Marfan syndrome. *Design, Setting and Participants*: 17 patients with Marfan syndrome (aged 33 ± 6 years) on standard β-blocker therapy were randomized to also receive perindopril (8mg once daily, $n = 10$) or placebo ($n = 7$) for 24 weeks in a double blind study. *Main Outcome Measures*: Indices of arterial stiffness were assessed via systemic arterial compliance, and central and peripheral pulse wave velocity. Aortic root diameters were assessed at 4 sites via transthoracic echocardiography. *Results:* Perindopril reduced arterial stiffness as indicated by increased systemic arterial compliance (by 0.2 ± 0.1mL/mmHg, $p < .0001$ all p values relative to placebo), reduced central (by 1.6±0.2m/s, $p < .0001$) and peripheral (by 2.2 ± 0.2m/s, $p < .0001$) pulse wave velocity. In addition, perindopril significantly reduced aortic root diameters relative to placebo in both end-systole and end-diastole (by 2–6 mm, $p < .0001$). While perindopril marginally reduced mean blood pressure (by 1.3 ± 0.2mmHg, $p = .004$), importantly, the observed changes in both stiffness ($p = .001$–$.006$) and left ventricular outflow diameter ($p < .001$) remained significant when mean pressure was included as a covariate. Transforming growth factor-βsignalling contributes to aortic degeneration in Marfan syndrome and both latent (by 14±4.5ng/ml) and active (by 4±1ng/ml) forms were reduced by perindopril when compared to placebo ($p < .05$). *Conclusion:* Perindopril reduces both aortic stiffness and aortic root diameter in patients with Marfan syndrome on standard β-blocker therapy, and might decrease the incidence of aortic rupture in this condition.

GENETIC REFERRALS: THE QUEENSLAND EXPERIENCE (O49)

L. Scott, J. Bjorkman, A. Duffy and V. Hyland

Pathology Queensland, Royal Brisbane and Women's Hospital, Australia

With the rapid development of DNA based tests for human disorders, it is impossible for any pathology provider to undertake in-house testing for all available tests. Pathology Queensland provides a service to our clinicians and patients which affords easy access to genetic testing across Australia and internationally. We present a brief analysis of this service and the results obtained. In 2006 Pathology Queensland referred 509 genetic tests, with 914 referred in 2007. Here we discuss the 2006 data. Mutations were reported for 33% of domestic and 53% of international referrals. This compares favourably with genetic analyses completed in-house. Clinician's knowledge and quality genetic counselling are a major contributor to a high discovery rate. Approximately half of the genetic referrals in Queensland originate from Genetic Health Queensland, who had a discovery rate of 46.5% for domestic and 55.2% for international referrals. By contrast, non-GHQ referrals had a discovery rate of 29.2% for domestic and 27.8% for international referrals. Challenges in providing an effective genetic referral service include identifying which laboratory should receive a specimen and establishing an effective funding model to support relatively expensive testing. A particular challenge is to ensure that tests are reported; more than 50% of international tests were unreported at the end on 2007. Despite these challenges, the provision of an effective genetic referral service allows Queensland patients and clinicians to access cutting edge genetic diagnoses, irrespective of where that testing may be performed.

MOLECULAR INVESTIGATION IN AN X-LINKED CATARACT SYNDROME (O104)

S. Sharma,[1] A. Dave,[1] K. S.Y. Koh,[2] C. Collin,[2] A. K. Voss,[2] D. A. Mackey[3] and J. E. Craig[1]

[1] *Department of Ophthalmology, Flinders University, Australia*

[2] *The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*

[3] *Centre for Eye Research Australia, Royal Victorian Ear and Eye Hospital, East Melbourne, Australia*

Nance-Horan syndrome (NHS) is a rare X-linked genetic disorder characterised by severe bilateral cataracts, dental anomalies, dysmorphic facial features and mental retardation in some male cases. We identified the causative gene, NHS, located on Xp22.13, in a large affected Australian family through linkage analysis and candidate gene approaches. Mutations in the NHS gene, in affected individuals, lead to premature truncation of the protein. Others have also reported similar mutations in their families affected with this syndrome. The NHS gene is expressed during development in the organs affected in individuals with Nance-Horan syndrome. It encodes two protein isoforms, NHS-A and 1A. These isoforms are differentially expressed and localized in a cell type dependent manner. The NHS-A isoform expressed in the lens and brain, the tissues affected in the syndrome, associates with the cell membrane in epithelial cells. Data showing how various regions of this protein play a role in its targeting to the cell membrane will be presented. Evidence supporting the role of NHS-A at epithelial tight junctions will also be presented. These data suggest the involvement of tight junctions in causing the developmental defect in Nance-Horan syndrome.

CHOLESTEROL BIOSYNTHETIC DEFECTS: 2 AUSTRALIAN CASES OF X-LINKED CHONDRODYSPLASIA PUNCTATA MALE MOSAICS (O20)

P. Sharp,[1] J. Liebelt,[1] L. Sheffield,[2] J. Pitt,[3] K. Carpenter,[4] L. Greed,[5] C. Gurnsey[6] and M. Fietz[1]

[1] *Department of Genetic Medicine, Women's & Children's Hospital, Adelaide, Australia*

[2] *Genetic Health Services Victoria, Murdoch Childrens Research Institute, Melbourne, Australia*

[3] *VCGS Pathology, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia*

[4] *NSW Biochemical Genetics Service, Children's Hospital Westmead, Sydney, Australia*

[5] *Dept of Clinical Biochemistry, Princess Margaret Hospital, Perth, Australia*

[6] *Dept of Chemical Pathology, Pathology Queensland, Central Laboratory, Brisbane, Australia*

There are approximately 30 enzymatic reactions required to synthesize cholesterol from its starting material, acetate. In 1993 Smith-Lemli-Opitz Syndrome (SLOS) became the first post-squalene defect of cholesterol biosynthesis to be biochemically described. Since that time a number of other inherited defects in the pathway have been elucidated. Studies of these disorders have resulted in a new understanding of the importance of cholesterol, its biosynthetic intermediates and metabolites in a number of biological roles particularly in signaling pathways. A number of Biochemical Genetics laboratories in Australia offer diagnostic services, ranging from routine plasma testing through to prenatal diagnosis, for dis-

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orders of cholesterol biosynthesis. The most common means of testing is metabolite detection but more recently molecular techniques have also been introduced. This study reviews the results from these laboratories and, consistent with international experience, SLOS is the most common disorder of the pathway. Molecular studies have shown that a single mutation (c.964-1G>C) accounts for >50% of alleles in tested SLOS patients. The only other post-squalene defect of cholesterol biosynthesis to be described in the Australian laboratories surveyed is type 2 X-linked dominant chondrodysplasia punctata (CDPX2). Although CDPX2 has been presumed to be male lethal, two Australian laboratories have diagnosed a male patient affected by the disorder. In each case, molecular studies have confirmed that the patients are somatic mosaic for a mutation in the EBP gene. These patients will be presented in greater detail.

INTEGRATING PHARMACOGENOMIIC TESTING INTO CLINICAL PRACTICE IN TEACHING HOSPITALS (O72)

L. Sheffield,[1] P. Irving,[2] P. Gibson,[2] T. Catto-Smith,[3] F. Macrae,[5] A. Gupta,[5] K. Byron,[5] M. Dooley,[6] S. Poole,[6] R. Gearry[7] and M. Sparrow[2]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *Department of Gastroenterology, Box Hill Hospital, Australia*

[3] *Department of Gastroenterology, Royal Children's Hospital, Australia*

[4] *Department of Gastroenterology Royal Melbourne Hospital, Australia*

[5] *Healthscope Molecular, Melbourne, Australia*

[6] *Department of Pharmacy, Alfred Hospital, Melbourne, Australia*

[7] *Department of Gastroenterology, Christchurch, New Zealand*

There are a number of recent studies showing that pharmacogenomic testing is often not used. There are many reasons given for this such as cost and lack of clear advice about interpretation of the results from a knowledgeable colleague. We have we have studied a molecular test for common variants of the thiopurine methyltransferase gene (TPMT). A single base extension method was used to test for TPMT 3A, TPMT3C and TPMT*2, using blood samples and cheek brush sample. We combined this with a study measuring 6-thioguanine levels (6-TGN) and 6-MMP. We are enrolling IBD patients taking a thiopurine drug for at least 3 months and being on a stable dose for at least 4 weeks. We aim to enrol 200 patients from 4 teaching hospitals and compare thiopurine drug doses, 6-TGN levels and 6-MMP levels for different genotypes. The results on the first 68 patients show 6 heterozygotes (9%), the mean heterozygote 6-TGN level was above the desired therapeutic range and dosages were the same in heterozygotes as normal. There was one homozygote deficient patient who developed neutropenia. This study is expected to familiarise clinicians with the concept of TPMT testing within a relatively short period of time and comments will be made on the effect of clinician awareness. It may lead to preliminary data that could be used to mount a more widespread prospective study of the health value of TPMT testing. We have recently started a similar study on testing for warfarin dosage.

MUTATIONS IN IQSEC2, A GUANINE NUCLEOTIDE EXCHANGE FACTOR FOR ARF6, CAUSE NONSYNDROMIC MENTAL RETARDATION (O122)

C. Shoubridge,[1] P. Tarpey,[2] J. Boyle,[3] A. Gardner,[1] G. Turner,[3] A. Hackett,[3] L. Raymond,[4] C. Schwartz,[5] R. Stevenson,[5] A. Futreal,[2] M. Stratton[2] and J. Gécz[1,6]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia.*

[2] *Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom*

[3] *GOLD Service, Hunter Genetics, Waratah, Australia.*

[4] *Cambridge Institute of Medical Research, Cambridge, United Kingdom*

[5] *JC Self Research Institute of Human Genetics, Greenwood Genetic Center, Greenwood, South Carolina, United States of America*

[6] *Department of Paediatrics and School of Molecular and Biomedical Science, University of Adelaide, Adelaide, South Australia 5001, Australia*

Mental retardation (MR) is a frequent clinical condition of considerable medical importance affecting ~1/50 individuals across the world population. To identify novel genes involved in these disorders a systematic screen of the X-chromosome coding sequences in > 200 families with predominantly nonsyndromic X-linked mental retardation (XLMR) was undertaken. As part of this effort we identified unique changes in the guanine nucleotide exchange factor (GEF) for the Arf family of GTP-binding proteins, IQSEC2 gene. We identified single nucleotide substitutions c.2587C>T in the MRX1 family, c.2402A>C in family MRX18 and c.2273G>A in a family from the USA, all three predicted to lead to missense amino acid changes p.R863W, p.Q801P and p.R758Q, respectively. All 3 changes occur within the Sec7 domain of IQSEC2. Another change was identified in an unpublished family, c.1075C>T/p.R359C, which lies in the IQ domain of IQSEC2. All four changes segregate with the MR phenotype in respective families. These sequence variants were not found in the > 200 case cohort nor in > 200 controls. Based on this data we speculate these changes to be deleterious to the function of IQSEC2 and suggest that IQSEC2 is a novel XLMR gene. IQSEC2 has been found at excitatory synapses as part of the post-synaptic protein complex with PSD-95 and NMDA receptors and may function as a GEF for Arf61. We predict that these mutations compromise GEF function of IQSEC2 and impact on the Arf6 mediated regulation of actin cytoskeleton organization and dendrite differentiation.

A NEW NOMENCLATURE FOR OSTEOGENESIS IMPERFECTA SYNDROMES 2008 (O71)

D. Sillence

Centre of Children's Bone Health and Department of Medical Genetics, The Children's Hospital at Westmead, Sydney, Australia

To facilitate care of patients with Osteogenesis Imperfecta, it is important to understand the nomenclature and the advances in the genomic basis of Osteogenesis Imperfecta. In the latest nomenclature of OI syndromes eight (8) numerical types of OI and 3 named syndromes are listed. Two of these, OI type V and type VI, are clinically delineated but their genomic basis is not understood. OI type II is usually perinatally lethal although we now recognise a spectrum of severity in OI type II resulting in part from genetic heterogeneity. Five gene loci are known to contribute to the pathogenesis of these 11 clearly delineated syndromes and there phenotypic subtypes. These gene loci are COL1A1, COL1A2, CRATP, P3H1/LEPRE1(coding for Leprecan) and PLOD2. Other gene loci are yet to be identified. The description of severity has been a significant confounder in making a diagnosis of a particular type of OI. A scale has been developed for the assessment of severity and mobility outcomes. While this phenotypic characterisation is very valuable in terms of diagnosis severity alone is not a classification of OI. Our present estimate of the frequency of brittle bone disorders in various populations is that they are present in 1/5000–1/8000 newborns. Heterozygous mutations in type I collagen genes account for the majority of mutations in many European populations but in some African and Asian populations autosomal recessive types of OI are more prevalent.

ACCELERATED AMINO ACID QUANTITATION USING BIOCHROM 30 ANALYSER (P25)

K. Sim,[1] E. Blakeman[1] and K. Carpenter[1,2]

[1] *NSW Biochemical Genetics Service, The Children's Hospital at Westmead, Australia*

[2] *Departments of Paediatrics & Child Health and Genetic Medicine, University of Sydney, Australia*

Ion exchange amino acid analysis remains the gold standard for physiological fluid analysis but run times are long reducing throughput and monitoring amino acid levels in patients with inborn errors of metabolism demands reasonably quick return of reports, especially during metabolic crisis. The Biochrom 30 is a dedicated amino acid analyser employing lithium ion exchange chromatography with post column ninhydrin colorimetric reaction. We compared the performance of the factory standard method that has a turn-round time of 3 hours with a factory approved accelerated method with a turn-round time of 2 hours. The accelerated method employs a higher buffer flow rate (31.3 vs 25 mL/hr), nihydrin flow remains at 20 mL/hr. Results obtained from the 2 methods were compared using old ERNDIM QAP samples and internal QCs with values established on our previous instrument. For most analytes, the values were comparable and chromatographic separation adequate using the accelerated method. There were 2 analytes that the accelerated method did not give satisfactory results for. Methionine sulphoxide does not separate from Threonine and Argininosuccinic acid co-elutes with leucine but the resolution of the standard method was satisfactory. We resolved to employ the accelerated method routinely and use the factory standard method when there is request for ASA quantitation. This strategy meets the requirement of higher throughput and so far has not resulted in any noticeable deterioration in column life after 8 months of use.

MULTIPLEX LIGATION-DEPENDENT PROBE AMPLIFICATION (MLPA) IS A PROMISING TECHNOLOGY FOR CARRIER DETERMINATION AND PRENATAL DIAGNOSIS IN HAEMOPHILIA A CAUSED BY EXON DELETION/ DUPLICATION OF THE FACTOR VIII (F8) GENE (P55)

A. Simsek, G. Casey and M. Holloway

Department of Molecular Genetics, Institute of Medical and Veterinary Science, Adelaide, Australia

Haemophilia A is an X-linked recessive bleeding disorder affecting one in 5000 males, resulting from mutations in the factor VIII gene. The majority of patients are found to have point mutations, small deletions/duplications or inversions in the factor VIII gene. Our current strategy for mutation detection in severe patients involves initially testing for the intron 22 and intron 1 inversions, followed by direct sequencing of all exons and exon/intron boundaries of the factor VIII gene. In male patients with large deletions involving one or more exons, the defect can be inferred by the failure of the relevant exons to amplify on repeated PCR. In the case of

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female relatives however this technique does not provide any useful information for distinguishing carriers and for performing prenatal diagnosis. MLPA is a simple method that amplifies up to 45 DNA fragments in a single tube. Because the method uses a common set of primers to amplify all fragments, under a common set of conditions, it can be used for the relative quantification of all the fragments in the mix. Here we present the results from 8 male patients in whom we used MLPA to confirm deletions of one or more exons suggested by previous PCR amplification and 4 female patients in whom we were able to determine carrier status. MLPA is a reliable and easy to perform method for large deletion screening, and is a promising technology for carrier determination and prenatal diagnosis.

HOMOZYGOUS DELETION ON 13Q ASSOCIATED WITH DELETION OF P53 IN CLL: REPORT OF 44 CONSECUTIVE CASES (O37)

N. R. Singh,[1] L. A. Pereira [1] and S. P. Mulligan[2]

[1] *Cytogenetics Laboratory and Department of Haematology, Australia*

[2] *Royal North Shore Hospital, PaLMS, Sydney, Australia*

The most common genetic aberrations that determine prognosis in chronic lymphocytic leukemia (CLL) involve del(13q), +12, del(11q) and del(17p) with increasing risk respectively. Detection of these aberrations by routine karyotyping has been limited due to the low proliferative rate of the malignant B cells. Fluorescent in-situ Hybridization (FISH) is widely used as it can be applied to either blood or bone marrow in CLL and does not require metaphase spreads. 44 cases were evaluated by both karyotyping and FISH using the Vysis CLL panel of probes. 66% of cases were abnormal by FISH vs 18% by karyotyping. 40% [16] of cases showed a del(13q) with 44% [5] being homozygous interstitial deletions. All cases with homozygous del(13q) in this series also showed deletion of 17p. 2 cases showed evidence of progression from a single 13q deletion to a double 13q deletion. All 5 cases correlated with a high WCC and high lymphocyte count. There was no correlation with disease stage or CD38 expression in these 5 patients. Karyotypes were either normal or failed to grow. Homozygous del 13q has been described mainly in association with del(11q). Involvement of unbalanced translocations has been postulated in some studies. Further investigation using DNA and gene expression arrays may yield further insights into the possible associations between homozygous 13q- and 17p-, given the importance of alternate therapeutic regimens required for patients with del(17p) in CLL.

THE DETECTION OF PROGNOSTIC FACTORS IN MULTIPLE MYELOMA BY CYTOPLASMIC IMMUNOGLOBULIN FISH (CIGFISH) (P6)

R. Singh and K. Dun

Cytogenetics Laboratory, Royal North Shore Hospital, PaLMS, Sydney, Australia

Multiple myeloma arises from the proliferation of malignant plasma cells. The disease progresses in a stepwise manner with a patient survival of 2–3 years. Genetic abnormalities have been described in association with plasma cell disorders and have helped to define prognosis and therapeutic management. Abnormal karyotypes have been detected in the earliest stages of the disease and have shown increased karyotypic instability with disease progression. However, the detection rate by routine chromosome analysis is only ~20%. Also, subtle abnormalities with important prognostic significance such as the t(4;14) are not detectable by chromosome analysis. A plasma cell specific FISH technique was further modified in our laboratory and applied to 65 consecutive patients referred for multiple myeloma. Monotypic plasma cells were stained with fluorescent antibodies specific to the restricted Kappa or Lambda light chains. FISH probes for the t(4;14),t(11;14) and p53 were subsequently hybridised to all cells and visualised simultaneously with the immuno-stain. cIgFISH identified abnormalities in 70% of cases. 20% of cases showed an abnormal karyotype. 55% of abnormal karyotypes showed loss of 13/del13q and this was not restricted to non hyper diploid cases. cIgFISH is a powerful robust technique and is currently regarded as an essential part of first line testing for multiple myeloma.

CORNEAL DYSTROPHY IN ASSOCIATION WITH AN INTERSTITIAL DELETION OF CHROMOSOME 12Q21.2-Q21.33 ENCOMPASSING THE DECORIN (DCN), LUMICAN (LUM), AND KERATOCAN (KERA) GENES (P44)

R. D. Susman,[1] F. Collins,[1] L. St Heaps[2] and G. Peters[2]

[1] *Department of Clinical Genetics, The Children's Hospital at Westmead, Sydney, Australia*

[2] *Department of Cytogenetics, The Children's Hospital at Westmead, Sydney, Australia*

We report a 7-year-old boy with corneal dystrophy, developmental delay and seizures who was found to have a deletion of 12q21.2-q21.33. This region contains three genes (DCN, LUM, and KERA) that are expressed in the cornea. We review the literature that includes two families with autosomal dominant congenital stromal corneal dystrophy (CSCD) associated with mutations within DCN. This is the first case reported of a complete deletion of the DCN gene associated with corneal dystrophy. Although mutations in KERA have been identified in cases of recessive cornea plana, there are no previous reports in humans of mutations in LUM or KERA associated with corneal dystrophy.

PREDICTIVE GENETIC TESTING AND RISK MANAGEMENT (O74)

G. Suthers[1] and D. Ravine[2]

[1] *Familial Cancer Unit, SA Clinical Genetics Service, Children's Youth & Women's Health Service, Adelaide, Australia*

[2] *PathWest/ Western Australian Institute of Medical Research, Centre for Medical Research, University of Western Australia, Australia*

Predictive genetic testing is available for an increasing number of genetic disorders. Although the goal of any medical diagnostic laboratory is to provide the right result for the right patient in a timely fashion every single time, the reality is an unavoidable background risk of error. By definition, a predictive genetic test lacks any clinical corroborating evidence that might unmask an erroneous result. In view of the possibility of error, what precautions should be taken regarding such results that are so important for both the patient and relatives? There is no published consensus on the measures required to minimise the risk of a predictive genetic testing error. A survey in 2005 of directors of HGSA-listed molecular genetic diagnostic laboratories identified a variety of protocols that varied within and between laboratories. A new Australian laboratory accreditation guideline has since been published (NPAAC 2006), but this does not address the specific issue of genetic tests results that cannot be corroborated. The Royal College of Pathologists of Australasia has recently adopted a policy regarding sample requirements (http://www.rcpa.edu.au/applications/DocumentLibraryManager2/upload/Sample%20requirements%20for%20medical%20testing.pdf). Guidelines for laboratories may contribute to quality improvements for predictive genetic testing. However, professional responsibility for decisions about generating independent corroborating evidence must rest with the clinician ordering the test. Predictive genetic tests are increasingly requested by a diverse range of specialists. Clinical professional organisations, including the HGSA, should reassess the currently recommended professional standard for predictive genetic testing.

GUIDELINES FOR REPORTING MEDICAL GENETIC TESTS (P37)

G. Suthers[1,2]

[1] *Familial Cancer Unit, SA Clinical Genetics Service, Children's Youth & Women's Health Service, Adelaide, Australia*

[2] *Consultant Genetic Pathologist, QUPP Project, Royal College of Pathologists of Australasia, Australia.*

The provision of high quality medical testing rests on the quality of each step in the process, from test selection through to analysis, reporting, and subsequent medical decision-making. It is clear that the laboratory report is not always a secure means of transferring a result from the laboratory to clinical decision-making. Essential information is often missing from reports, and clinicians often fail to identify these deficiencies. Even when the necessary information is provided, clinicians can misinterpret pathology reports 30% of the time. This miscommunication occurs with reporting in long-established disciplines such as histopathology and radiology, and so it is not surprising that similar issues have been identified in genetic testing. Clinicians from diverse disciplines prefer structured, itemised reports that summarise the information that they need for decision-making. Their principle concern is the clinical relevance of the test result, with the inclusion of an interpretation in the report saving time and reducing the risk of misdiagnosis. Brevity is not necessarily regarded as a key attribute of a 'good report', with clinicians preferring more comprehensive reports that address both the primary result and incidental findings. Consistent report structure is both essential and effective in ensuring that key elements are always included. The Royal Australasian College of Pathologists, in conjunction with the HGSA, has developed guidelines for the reporting of medical genetic tests. These guidelines encompass report content and report style. These guidelines incorporate recommendations and requirements of NPAAC, NATA, EMQN, OECD, NCCLS, ACMG, and CAP.

WHAT IS BEING ORDERED? GENETIC TESTING ACROSS AUSTRALIA IN 2006 (O117)

G. Suthers[1,2]

[1] *Familial Cancer Unit, SA Clinical Genetics Service, Children's Youth & Women's Health Service, Adelaide, Australia*

[2] *Consultant Genetic Pathologist, QUPP Project, Royal College of Pathologists of Australasia, Australia.*

There is an increasing gap between the genetic testing that laboratories would like to provide and the resources available. Discussions about the

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delivery of genetic testing have been hampered by a lack of data regarding the current level of demand and supply. The Royal College of Pathologists of Australasia received funding from the Australian Department of Health & Ageing for a survey to fill this gap. The project has been overseen by the RCPA and HGSA. The principle aim of this survey and the resulting report is to provide data to inform research and policy developments; the report will not provide commentary or make recommendations. 58 separate genetic testing laboratories were identified from NATA, HGSA, University, Red Cross, and personal sources. Thus far, 90% have provided data on the level of genetic testing in 2006, with projections for 2007. The analysis has incorporated the volume of Medicare-funded genetic tests. The following issues will be presented:

- the variety of medical genetic tests offered in 2006
- the proportion of tests provided as NATA-accredited assays
- the extent to which laboratories provided testing for local versus interstate subjects
- the type and volume of tests sent overseas
- the volume of tests for purposes, that is, diagnostic, predictive, screening, somatic assay
- anticipated change in test volume in 2007
- rate of testing per 100,000 people in different states.

FAMILIAL LEUKAEMIA (O10)

G. Suthers and M. Altree
Familial Cancer Unit, CYWHS, Adelaide, Australia

Referrals regarding familial cancer account for approximately half of the referrals to the South Australian Clinical Genetics Service. Over 90% of such referrals deal with familial breast/ovarian cancer and familial bowel cancer. The remaining referrals deal with much rarer familial cancer syndromes, such as retinoblastoma and von Hippel-Lindau syndrome. Haematological malignancies (such as leukaemia and lymphoma) are common cancer diagnoses, with a lifetime risk of 2-3% (similar to bowel cancer). But they are not usually considered to have a significant familial component. However, first-degree relatives of patients with haematological malignancies have a 2- to 6-fold relative risk of similar cancers. ~8% of patients have one or more affected relatives, and ~5% of those with such a family history have multiple affected relatives.

We can estimate that

- 98% of population have no close relatives with a haematological malignancy, are at *standard risk* of such a cancer, and account for ~92% of cases;
- ~2% of population have one affected relative, are at *moderate risk* (4-fold), and account for ~8% of cases.
- ~0.04% of population have multiple affected relatives, are at *high risk* (10-fold), and account for ~0.4% of cases.

In other words, familial haematological cancer is uncommon — but real. The Australian Familial Haematological Cancer Study has now been running for 4 years. We will present the clinical, genetic, social characteristics of some of the families identified in the course of this study.

MLL DUPLICATION AND 5Q- IN ACUTE MYELOID LEUKAEMIA (P47)

P. Sutton-Davies, J. Anderson, R. Brookwell, E. Jones, B. Lundie, M. Trentin and C. Ward
Department of Cytogenetics, Sullivan Nicolaides Pathology, Australia

A 47-year-old male patient presented with a full blood count picture indicating the presence of an acute leukaemia. A bone marrow aspirate and trephine were collected and the Haematology results supported the diagnosis of an Acute Myeloid Leukaemia with maturation (WHO classification). Urgent FISH and PCR testing for the PML/RARA translocation and Cytogenetic analysis were requested. Both the FISH and PCR results were negative for the PML/RARA t(15;17) rearrangement. FISH analysis did however indicate the loss of one copy of the RARA locus region in 80% of interphase cells examined. Cytogenetic analysis showed the presence of multiple karyotypic abnormalities including additional material of unknown origin attached to the long arm of one chromosome 5, loss of one chromosome 7, the presence of a derivative chromosome 9, loss of material from the long arm of one chromosome 11, loss of one chromosome 17 and the presence of one to two marker chromosomes. Interphase FISH and M-FISH were used to further elucidate the observed karyotype. Reports in the literature indicate that our final result was consistent with a particularly poor prognosis.

A CRYPTIC TRANSLOCATION IN ACUTE PROMYELOCYTIC LEUKAEMIA IDENTIFIED BY FISH (P48)

P. Sutton-Davies,[1] J. Anderson,[1] R. Brookwell,[1] C. Chhuon,[2] C. Christison,[1] K. Evans,[1] B. Garrone,[1] E. Jones,[1] E. M. Lew,[1] C. McCarthy,[2] L. Smallhorne[1] and M. Trentin[1]
[1] *Department of Cytogenetics, Sullivan Nicolaides Pathology, Queensland, Australia*
[2] *Pathology Queensland, Royal Brisbane and Womens Hospital, Herston, Australia*

A 46-year-old female presented with a peripheral blood film suggestive of acute promyelocytic leukaemia, M3 variant. PML/RARA FISH was performed urgently on the peripheral blood sample and a variant positive signal pattern was observed. Subsequent cytogenetic analysis showed the presence of an apparently standard t15;17). Further FISH techniques were carried out to correlate the original variant FISH result with the cytogenetic result.

COMPUTATIONAL PREDICTION OF CANDIDATE GENES ASSOCIATED WITH SPECIFIC PHENOTYPES (O98)

E. Teber, J. Y. Liu, R. A. George, S. Ballouz, R. J. Bryson-Richardson, G. Guo, R. Otway, D. Fatkin and M. A. Wouters
Victor Chang Cardiac Research Institute, Australia

Gentrepid(1) is a computational system to prioritize genes associated with specific diseases or traits within genomic loci. The system adopts two novel algorithms: Common Module Profiling (CMP) and Common Pathway Scanning (CPS). CMP is based on the hypothesis that genes of similar function will lead to the same phenotype and identifies likely candidates using a domain-dependent sequence similarity approach. The CPS method assumes that specific phenotypes are associated with proteins that participate in the same complex or pathway and applies network data derived from protein–protein interaction and pathway databases to identify relationships between genes. Both CMP and CPS use two forms of input data: known genes or multiple loci. The system has been tested for its ability to predict disease genes on a test set of 29 diseases with 3 or more known disease genes. When using known disease genes as input, our combined methods have a sensitivity of 0.52 and a specificity of 0.97 and reduce the candidate list by 13-fold. When using multiple loci, our methods successfully identify disease genes for all benchmark diseases with a sensitivity of 0.84 and a specificity of 0.63. These results are competitive with other methods of candidate gene prediction and Gentrepid offers several advantages over other methods. The Gentrepid webserver is available to identify genes associated with particular diseases and traits in user-specified intervals. Gentrepid[1] is a computational system to prioritize genes associated with specific diseases or traits within genomic loci. The system adopts two novel algorithms: common module profiling (CMP) and common pathway scanning (CPS). CMP is based on the hypothesis that genes of similar function will lead to the same phenotype and identifies likely candidates using a domain-dependent sequence similarity approach. The CPS method assumes that specific phenotypes are associated with proteins that participate in the same complex or pathway and applies network data derived from protein-protein interaction and pathway databases to identify relationships between genes. Both CMP and CPS use two forms of input data: known genes or multiple loci. The system has been tested for its ability to predict disease genes on a test set of 29 diseases with 3 or more known disease genes. When using known disease genes as input, our combined methods have a sensitivity of 0.52 and a specificity of 0.97 and reduce the candidate list by 13-fold. When using multiple loci, our methods successfully identify disease genes for all benchmark diseases with a sensitivity of 0.84 and a specificity of 0.63. These results are competitive with other methods of candidate gene prediction and Gentrepid offers several advantages over other methods. The Gentrepid webserver is available to identify genes associated with particular diseases and traits in user-specified intervals.

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TETRASOMY 18P: A COMPARATIVE STUDY (P80)

B. Telford-Herdman, L. Baratta, J. Anderson, D. Bale and L. Smallhorne
Sullivan Nicolaides Pathology, Brisbane, Australia

Tetrasomy 18 is a clinically recognised syndrome caused by a supernumerary isochromosome 18p. It is a rare chromosomal abnormality occurring 1 in 140,000 live births, affecting males and females equally. The majority of i(18p) cases are sporadic due to de novo formation, while familial and mosaic cases are infrequent. The clinical manifestations include moderate to severe mental impairment, psychomotor retardation, delayed speech, feeding difficulties and dysmorphic facial features. However, a degree of variation exists within the clinical spectrum. We present two de novo cases in children with i(18p) detected by conventional cytogenetics and FISH, both displaying concordant features of the tetrasomy 18p syndrome as described in the literature.

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THE NF1 MICRODELETION SYNDROME IN A 5-YEAR-OLD GIRL: THE IMPORTANCE OF FOLLOW-UP IN MAKING A SYNDROME DIAGNOSIS (P87)

E. M. Thompson, K. Friend and L. Sanchez

Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia

We describe a 5-year-old girl with delayed development, pulmonary stenosis, strabismus, hypermetropia, severe gastro-oesophageal reflux, a right dacrocystocele and hypsarrythmia requiring treatment. Dysmorphic features included epicanthic folds, convergent strabismus, telecanthus, short palpebral fissures, short nose, full cheeks and inverted nipples. Birth weight and length were above the 97th centile and all growth parameters remain at that level. No overall diagnosis was made when she was first seen by the clinical genetics team at 6 months of age. At clinical genetics review at 2 1/2 years, two café au lait patches on the abdomen were noted. At 5 1/2 years, freckling in the axillae, groins and neck had appeared. MLPA revealed a deletion within the NF1 gene at 17q 11.2 which indicates a diagnosis of neurofibromatosis type 1 microdeletion syndrome. About 5% of NF1 patients carry a heterozygous deletion that includes the entire NF1 gene. NF1 microdeletion patients usually have a more severe phenotype than in the general NF1 group with intellectual disability, variable dysmorphic features and increased numbers of neurofibromas for age. They are at increased risk of developing malignant tumours and may have short or tall stature, microcephaly or macrocephaly, large hands and feet, scoliosis, iris coloboma and pulmonary stenosis. Connective tissue abnormalities are also common. This case report highlights the need for ongoing assessment in the dysmorphic child with malformations, medical problems and developmental delay. In the case of the NF1 microdeletion syndrome, the classical pigmentary signs of NF1 may not be present initially but when they appear, the correct diagnosis can be made.

A TEENAGER WITH LONG CHAIN 3-HYDROXY-ACYL-COA DEFICIENCY (LCHAD): COMPARISON OF DIETARY INTAKE WITH NUTRIENT REFERENCE VALUES (NRV) FOR AUSTRALIA AND NEW ZEALAND (O25)

S. Thompson

Western Sydney Genetics Program, Children's Hospital at Westmead, Sydney, Australia

JT, now 15 years, was diagnosed with LCHAD at 8 months of age and commenced on a very low long chain fat diet with medium chain triglycerides (MCT). He initially presented with failure to thrive (weight *Z* score –5.92 and height *Z* score –5.11) but is now within normal range (height 11th percentile, *Z* score –1.26; weight 25th percentile, *Z* score –0.38; BMI Z score 0.24). A 2-day diet diary, analysed by Foodworks 2005, shows a high carbohydrate intake (74% energy) and poor tolerance for MCT oil (total fat intake 10% of energy). Despite an appropriate energy intake he does not meet acceptable macronutrient distribution ranges for adolescents for total fat, n-3 or n-6 intake. Dietary intake of fibre and micronutrients, excepting fat soluble vitamins, met recommended or adequate intakes (RDI, AI) but he only achieved the suggested dietary target for folate. Compliance with supplements (walnut oil, fish oil and multivitamins) is intermittent. Monitoring of plasma essential fatty acids previously showed adequate levels of n-3 fatty acids but n-6 below the normal range. Dietary vitamin A intake was 59% RDI and intake of vitamins E and D, estimated from NUTTAB 2006 were < 20% RDI. Poor plasma vitamin E status has been demonstrated recently but Vitamin D status (plasma 25-OH calciferol) is normal. JT's diet illustrates that energy intake can be achieved on a very low fat diet but that achieving RDI, AI and dietary targets is influenced by compliance with supplements and food choice within the diet prescription.

MOUSE MODELS FOR MITOCHONDRIAL COMPLEX I DEFICIENCY (O76)

D. R. Thorburn, B-X. Ke, J. Komen, A. Laskowski, B. Hardman, D. Grubb, F. Rodda, M. McKenzie and M. T. Ryan

Murdoch Childrens Research Institute, Australia

Mitochondrial respiratory chain complex I is a ~1,000kDa complex comprised of 45 subunits. Complex I deficiency is the most common mitochondrial enzyme defect in humans. We describe two mouse models for complex I deficiency generated by knockout of subunits chosen on the basis of known human mutations and evolutionary conservation. Ndufs6gt/gt mice were generated from GeneTrap embryonic stem cell lines and represent a partial knockout of the NDUFS6 subunit, with small amounts of wildtype mRNA detected in all tissues studied. For the first 6 months of life Ndufs6gt/gt mice have no obvious phenotype, with normal growth rates and survival. Ndufs6gt/gt mice develop cardiomegaly, which can lead to sudden weight loss and lethargy after 6 months of age. Ndufs6gt/gt mice have marked Complex I deficiency in heart with more modest decreases in other tissues. Ndufs4-/- mice have marked Complex I deficiency in all tissues tested and show temporary fur loss, growth retardation, unsteady gait and abnormal body posture when suspended by the tail. BN-PAGE assembly analysis of tissues from Ndufs4-/- mice shows a severe complex I assembly defect, including the presence of a 'crippled' assembly intermediate also seen in tissues from children with NDUFS4 mutations, who suffer from the neurodegenerative condition Leigh syndrome. Treatment of mitochondrial disorders is currently inadequate and we anticipate that these mouse models will be useful to better characterise the pathogenic mechanisms and for treatment trials.

BIOPSYING CHILDREN FOR INVESTIGATION OF SUSPECTED MITOCHONDRIAL DISEASE: MUSCLE, LIVER OR BOTH? (O57)

S. Tregoning, D. M. Kirby and D. R. Thorburn

Mitochondrial and Metabolic Research Group, Murdoch Childrens Research Institute and VCGS Pathology, Royal Children's Hospital, and Department of Paediatrics, University of Melbourne, Parkville, Australia

Mitochondrial respiratory chain defects cause a wide range of neurological and other symptoms. They are caused by mutations in most of the 37 mitochondrial DNA genes and in ~60 known nuclear genes. A small proportion of children with suspected mitochondrial disease are diagnosed by direct mutation testing but most diagnoses rely on first identifying a respiratory chain enzyme defect, in order to guide subsequent mutation analysis. Typically this involves obtaining a skeletal muscle biopsy, a liver biopsy or both. We performed an audit of muscle and liver biopsies received for enzyme diagnosis between January 1, 2004, and December 31, 2006. Exclusions were biopsies that were unsuitable for analysis and all biopsies from Queensland, who only refer liver biopsies to our centre. Biopsies were received from 190 patients. 'Definite' diagnoses of a respiratory chain defect (see criteria of Bernier et al., 2002, *Neurology 59*:1406–1411) were obtained in 26% of 97 patients who had both muscle and liver biopsies, 16% of 82 patients with just muscle biopsy and 0% of 11 patients with just liver biopsy. Using less stringent criteria of 'near certain' improved diagnostic yield to 31%, 18% and 9%, respectively. Different referral centres vary markedly in the proportion of referrals having just muscle biopsy or both muscle and liver biopsy. This decision is influenced by clinical presentation and degree of suspicion so interpretation of our audit is not trivial. Nonetheless, it is worth noting the higher diagnostic yield in children receiving both muscle and liver biopsies.

LIFESTYLE FACTORS AND THE AGE AT ONSET OF HUNTINGTON DISEASE (O105)

K. Trembath,[1] Z. Horton,[1] L. Tippett,[3] V. Hogg,[3] V. Collins,[1,2] A. Churchyard,[4] D. Velakoulis[5] and M. Delatycki[1,2]

[1] *Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia*

[2] *Genetic Health Services Victoria, Royal Children's Hospital, Parkville, Australia*

[3] *Department of Psychology, The University of Auckland, New Zealand*

[4] *Department of Neurology, Monash Medical Centre, Australia*

[5] *Department of Neuropsychiatry, Royal Melbourne Hospital, Australia*

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder due to an expanded CAG repeat in the *IT15* gene. Transgenic HD mouse model studies have shown that raising mice in an enriched environment delays the onset of symptoms, leading us to consider whether premorbid lifestyle affects age-at-onset in humans. Subjects with symptomatic HD were interviewed using a questionnaire to ascertain pre-morbid lifestyle during three life stages (teens, 20s/30s, 40s/50s). Recorded activities were classified as physical, intellectual or passive, and activity scores generated. Surveys were matched with the subject's age-at-onset and CAG repeat length. Preliminary analysis ($n = 92$) showed a mean age-at-onset of 44.9 years (range 21–76), with a strong inverse correlation to CAG repeat length ($r = –0.728$, $p < .001$). Linear regression indicated a negative association between average pre-morbid leisure-time passivity and age-at-onset ($b = –0.744$, $R^2 = 0.109$, $p = .001$) that remained significant when adjusted for CAG repeat length ($b = –0.333$, $R^2 = 0.55$, $p = .048$). This association was most apparent for passivity during the teens and in men. Comparison of the mean age-at-onset in groups below and above the median passivity score showed a difference of 6.0 years (95%CI = 1.2 to 10.7). No significant relationship was demonstrated between average intellectual or average physical leisure-time activity and age-at-onset or CAG repeat length. Data from over 150 interviews in Australia and New Zealand will be presented. Passivity in leisure-time is associated with age-at-onset of HD, and CAG repeat length, suggesting that passivity contributes to earlier onset of symptoms, or is a preclinical manifestation of HD, more apparent in those with larger CAG repeat lengths.

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VANISHING VLCAD? TRANSIENT ABNORMAL ACYL CARNITINE PROFILE IN AN INFANT WITH HYPOGLYCAEMIC ENCEPHALOPATHY AND HYPERAMMONEMIA (P29)

M-U. Trinh,[1] R. Gerace,[1] E.Ranieri,[1] J. R. Harrison,[1] J. M. Fletcher,[1] D. B. Ketteridge[1] and B. Andresen[2]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Aarhus University, Denmark*

Introduction: Fatty acid oxidation defects are well recognised as common causes of hypoglycaemic encephalopathy and the majority of these are diagnosed by tandem mass spectrometry in the newborn period. We present a case where the only acyl carnitine abnormality was present in the sample collected at the time of the clinical episode. *Case:* This infant of first cousin parents, presented at 9 months of age with hypoglycaemia in the context of an unexplained death in a sibling. Plasma glucose was 1.0 mM, ammonium 173 uM (RR 40-80), CK 5418 U/L (RR<200) and the FFA/ßOHB ratio was increased. Cardiac echo was normal. Samples for an acyl carnitine profile and urine organic acids were collected at presentation. She was managed with IV dextrose and graded over to a low fat diet. She remains well on an 'avoidance of prolonged fasting' regime. *Methods:* Acyl carnitine analysis was performed using tandem mass spectrometry with stable isotopes as previously described. Urine organic acids were assayed by GC/MS. *Results:* The acute acyl carnitine profile was consistent with VLCAD deficiency with elevations of C12, 12:1, 14, 14:1, 14:2 carnitine and associated ratios. Organic acid analysis was notable for a relatively modest ketonuria in the context of a marked elevation of medium-chain and 3-hydroxy dicarboxylic acids and normalisation in subsequent samples within 24h. These results were confirmed by another laboratory (Lawrence Greed, Princess Margaret Hospital, Perth). No VLCAD mutations have been found.

NEW CHALLENGES IN CANCER GENETIC COUNSELLING: GENETIC TESTING FOR CLINICAL TRIAL ELIGIBILITY (O12)

J. Tyler and J. Koehler

Hereditary Cancer Clinic, Prince of Wales Hospital, Australia

There is a significant amount of research being done in attempting to translate knowledge of genetic conditions into gene-specific therapies. Bryant et al. (2005) published the first reports of possible targeted therapies for BRCA1/2 carriers. Soon after, clinical trials in patients with metastatic cancer began and results were promising. In 2007, Phase 2 trials of PARP inhibitors were established for BRCA1/2 mutation carriers with metastatic breast/ovarian cancer. Additional trials are now underway and we are receiving an increasing number of referrals for BRCA1/2 testing to determine trial eligibility. Providing genetic counselling in this new setting raises a number of new practical, ethical and psychosocial challenges. We have noted that patient expectations and motivations are quite different compared to those referred for conventional genetic counselling. We will present our experience of genetic counselling and testing in this unique, but potentially expanding, clinical situation.

THREE GENERATIONS OF ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY: TESTING, PRESENTATION AND IMPACT (O5)

H. J. Upton, H. Peters and A. Cozens

Genetic Health Services Victoria, Royal Children's Hospital, Parkville, Australia

A 55-year-old man (B) was referred to our service after his brother had been diagnosed with ornithine transcarbamylase (OTC) deficiency. The brother had collapsed suddenly into a prolonged coma, and is recovering slowly. A specific OTC gene mutation, previously known to cause late onset OTC deficiency had been identified. B came requesting genetic testing, for himself and his family. B has 2 adult daughters, J and A, who are obligate hemizygote carriers for OTC. Following extensive counselling, B, J and A requested DNA testing for themselves, and J for her son Z. B is a successful, articulate man in a senior, but stressful position in public service. He has additional serious health issues. B's eldest daughter, J, struggles with significant mental health issues and poor health. She is a single parent and her son Z, has difficulties with social interaction and learning at school. B's younger daughter, A, is a capable, independent young woman, in excellent health. This family raised a number of important counselling issues:

1. What is late onset or mild OTC deficiency?
2. Anxiety as a result of B's brother's coma.
3. Impact of the condition on the general health and lifestyle of B, daughters A and J, and J's son Z.
4. Clinical variability in females
5. Is this a 'belated' explanation for the health difficulties of J.
6. Is this an explanation for the learning difficulties of Z?

A COST-EFFECTIVE, TIME-SAVING STRATEGY FOR PMS2 GENE TESTING (O47)

C. Vakulin, D. Henry, Z. Rudzki and J. Carroll

Division of Molecular Pathology, Institute of Medical and Veterinary Science, Adelaide, Australia

Hereditary nonpolyposis colorectal carcinoma (HNPCC) is associated with mutations in the mismatch repair (MMR) genes, MLH1, MSH2, MSH6 & PMS2. To date, we have performed PMS2 gene screens for 118 probands of which we have found a pathogenic sequence mutation in 11 and a deletion of one or more exons by MLPA in 9. This represents a mutation pick up rate of 9.3% and 7.6% respectively. Of the 11 pathogenic sequence mutations identified, 1 was a nonsense mutation, 2 were missense mutations and 8 were frameshift mutations. Seven (7) of the frameshift mutations could be attributed to a NM_000535.4 (PMS2):c.736_741del6ins11, NP_000526.1(PMS2):p.P246CfsX3 mutation. Interestingly, this mutation alters the target site for the exon 7 probe in Kit P008 and is therefore detectable by MLPA. Two patients with a whole gene deletion have been identified in our cohort. In addition, we have detected the homozygous deletion of exon 12, the homozygous deletion of exon 7 (not attributable to the indel described above) and the heterozygous deletion of exon 10 on a number of occasions. In all these cases, DNA sequencing was normal. In total, nearly 13% of mutations in the PMS2 gene can be identified (if not characterised) by MLPA. This then raises the question of whether our screening strategy, which currently involves PCR and sequencing followed by MLPA, should be altered. By performing the MLPA first, which is less labour-intensive, we should potentially decrease both the time taken to screen our patients and make better use of available resources.

GENETICS OF LEARNING DISABILITY OF SOUTH AUSTRALIA — GOLD SA (P66)

L. Vandeleur,[1] M. Shaw,[1] S. Rujirabanjerd,[1] Z. Al Raisi,[2] E. Haan[2] and J. Gecz[1,3,4]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *SA Clinical Genetic Service, Australia*

[3] *School of Paediatrics and Reproductive Health, University of Adelaide, Australia*

[4] *Women's and Children's Health Research Institute, Adelaide, Australia*

The Genetics of Learning Disability program of South Australia (GOLD SA) was established in January 2007 with philanthropic funding. It is a younger sibling of the highly successful NSW GOLD Service, established by Prof. Gill Turner in 1986. The main aim of GOLD SA is to characterise the underlying molecular basis of heritable forms of intellectual disability among South Australian families so they can benefit from this knowledge. GOLD SA's first year focussed on identifying and contacting families with X-linked mental retardation. 40 X-linked families were identified and contacted and, following consent, affected and unaffected family members provided biological material. This included one or more of: blood for DNA isolation, blood for the establishment of lymphoblastoid cell lines, saliva samples or buccal swabs. 20 families, selected on the basis of family size and willingness to participate, were studied actively. We systematically performed linkage mapping, X-chromosome array CGH, and in some families, comprehensive resequencing of candidate XLMR genes. While GOLD SA has initially focused on X-linked forms of intellectual disability, we hope to broaden its focus in the future to include families with autosomal forms. Our vision for the future is for Australia to have a government(s) supported, national GOLD program. We would like to thank Mr Denis Harwood for his generous support, which enabled the GOLD SA program to be established.

DIAGNOSIS OF ADENYLOSUCCINATE LYASE DEFICIENCY AND A TRIAL OF S-ADENOSYL-METHIONINE TREATMENT (O15)

M. A. van Werkhoven,[1,2] J. A. Duley,[3] J. L. Freeman[4] and J. J. Pitt[2,5]

[1] *Murdoch Childrens Research Institute, Australia*

[2] *VCGS Pathology, Royal Children's Hospital, Melbourne, Australia*

[3] *Department of Pathology, Mater Hospital, School of Pharmacy, University of Queensland, Australia*

[4] *Department of Neurology, Royal Children's Hospital, Melbourne, Australia*

[5] *Department of Paediatrics, University of Melbourne, Australia*

Adenylosuccinate lyase (ADSL) deficiency is a rare disorder of the purine biosynthesis pathway. We describe a boy with this disorder who presented at 3 months of age with hypotonia and seizures. Urine metabolic screening by tandem mass spectrometry showed elevated levels of succinyladenosine (S-Ado) which raised the suspicion of ADSL deficiency. Purine concentrations were measured by HPLC, which confirmed grossly increased levels of S-Ado and also succinylaminoimidazole carboxamide riboside (SAICAr) in the urine of this patient. The patient was given a trial of S-adenosylmethionine (SAMe) to act as an adenosine donor. However, the levels of S-Ado and SAICAr in 5 following urines taken over the course of a month, showed virtually the same concentrations of S-Ado and SAICAr. Clinically, there was no clear response to SAMe treatment after 9 months although the parents reported poorer head control and visual fixation after discontinuation of the SAMe.

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ARE WE THERE YET? THE GENETIC COUNSELLING PROFESSION IN AUSTRALASIA (O9)

S. Wake

Genetic Health Services Victoria, Melbourne, Australia

This presentation will review the history and development of the genetic counselling profession in Australasia and will include reference to the establishment and work of two important bodies: the Human Genetics Society of Australasia (HGSA) Board of Censors for Genetic Counselling, and the Australasian Society of Genetic Counsellors (ASGC). Information for the presentation will be gathered from various sources including HGSA and ASGC archival material, and the personal reflections of several individuals. The presentation will highlight past achievements, current challenges, and speculate on what the future may hold for the profession of genetic counselling in Australasia.

PRICKLE1 MUTATIONS ARE ASSOCIATED WITH PROGRESSIVE MYOCLONIC EPILEPSY (O124)

R. H. Wallace, A. Bassuk, M. E. Mangelsdorf and S. F. Berkovic

Queensland Brain Institute, University of Queensland, Australia and Department of Pediatrics, Division of Neurology, University of Iowa, United States of America

Progressive myoclonic epilepsy type 1 (EPM1), or Unverricht–Lundborg disease, is an autosomal recessive neurodegenerative disorder that is characterized by progressive, stimuli- sensitive myoclonic jerks and generalized tonic-clonic seizures. In most patients, EPM1 is caused by a dodecamer repeat expansion that prevents transcription of the cystatin B (*CSTB*) gene on chromosome 21. Following exclusion of *CSTB* mutations, we mapped a new gene in one large family with EPM1, to the centromeric region of chromosome 12. A mutation was subsequently identified in exon 3 of the *PRICKLE1* gene. The mutation segregates with all affected individuals in the family, has not been reported in any single nucleotide polymorphism (SNP) database and was not present in control populations. The single nucleotide mutation identified changes an arginine to a glutamine at amino acid residue 104 (R104Q) of the PRICKLE1 protein. The R104 amino acid is conserved in all species that have been sequenced to date and is located within a known protein binding domain (PET domain). PRICKLE1 is a negative regulator of the Wnt signaling pathway; a cellular communication pathway that plays critical roles in development and disease. This is the first direct evidence that altered Wnt signalling has a role in the pathogenesis of human epilepsy.

QUANTITATION AND CHARACTERISATION OF THE O-LINKED GLYCAN ISOFORMS OF HUMAN APO C-III BY IMMUNOCAPTURE AND MALDI-TOF/TOF MASS SPECTROMETRY (O31)

T. Wallis, T. Munce and F. Bowling

Metabolic Diseases Unit, Mater Children's Hospital, Brisbane, Australia

Apolipoprotein C-III (Apo C-III) is a human mucin type I glycoprotein used to identify individuals with defects in O-glycan synthesis. Carbohydrate deficient glycoprotein syndromes have profound implications in metabolism and development. Characterisation of the defects at the molecular level facilitates identification of the inherited defect. Apo C-III represents an attractive target for development of a method for mass spectrometry based O-linked glycosylation analysis by being both relatively small (< 10 kDa), and having a single site for O-linked glycosylation, which greatly reduces the potential complexity of analysis. Apo C-III was immunocaptured from human serum using a biotinylated monoclonal antibody, and the resulting antibody/Apo C-III complex bound with extremely high affinity to microtitre plate wells containing immobilised streptavidin. Following washing to remove unbound proteins, the Apo C-III was eluted from the bound antibody and subjected to digestion with trypsin. Tryptic peptides, including glycopeptide isoforms, were separated from each other using capillary high performance liquid chromatography (HPLC), robotically arrayed onto a target and analysed by matrix assisted laser desorption ionisation time-of-flight/time-of-flight (MALDI-TOF/TOF) mass spectrometry to derive mass and fragmentation information for each peptide. O-linked glycopeptides were identified and characterised by their unique fragmentation spectra, and the relative abundance of each glycoform determined by the intensity of its peptide backbone absorbance at 214nm in the HPLC chromatogram. The results of this approach to characterisation of the O-linked glycosylation of a number of individuals with Apo C-III variants are presented. This method provides a rapid and informative approach to any individual suspected of defects in glycosylation.

ENERGY AND NUTRIENT INTAKE IN UREA CYCLE DISORDERS (O27)

J. Watkins

Metabolic Service, Genetic Health Services Victoria and Department of Nutrition and Dietetics, Royal Children's Hospital, Melbourne, Australia

Background: Low protein diets make meeting some micronutrient requirements a challenge in patients with urea cycle disorders (UCDs). Nutrient requirements are difficult to determine for these patients as they are not considered 'well' or representative of the population. Many patients have protein aversion or feeding disorders. Additionally, the protein intake of patients with UCDs is often met predominantly by low bioavailable (natural) protein. There are no set targets for patients with UCDs though traditionally meeting nutrient recommended daily intake (RDIs) has been the practice. Many patients fail to meet these targets for some micronutrients and signs of nutrient deficiency are evident in some but not all of these cases. *Aim:* To identify those patients with UCDs who consume less micronutrients than the nutrient reference ranges (NRVs) and the consequences of this on their nutritional status. *Method:* Retrospective analysis of dietary histories from clinic visits (when not acutely unwell) and comparison with NRVs.[1] This includes comparison to estimated energy requirements (EERs), estimated average requirements (EAR), RDIs for energy, protein, iron and calcium. Branch chain amino acids (BCAAs), haemoglobin, iron studies and calcium were also recorded. *Results:* Of the 8 patients analysed with UCDs (5 OTC, 3 CPS, 5 boys, 3 girls, aged 11 months to 12 years) all 8 patients consumed less than the EER (40-97%EER, mean 71%); 2 patients (OTC deficiency) consumed less than the RDI for of RDI for protein (~75%) and consequently had low BCAAs however another 5 patients also had low BCAAs despite meeting the RDI for protein (150–180%). 4 patients had an iron intake of less than both EAR & RDI and all showed low iron studies (30-90%). Additionally another 2 showed low iron, saturation or Hb despite meeting the RDI (175–190%). 6 had calcium intake at less than the EAR and RDI. *Conclusions:* Low protein diets for UCDs may fail to meet NRVs for energy, protein, iron and calcium. Our results suggest that targets for many nutrients should be above the RDI. Quantitative nutrient intake should be assessed in conjunction with clinical, biochemical and radiological markers when determining nutrient adequacy in this group of patients.

1 NHMRC Nutrient Reference Values for Australia and New Zealand, September 2005.

ANALYSIS OF A 3-DAY FOOD RECORD USING THE NRVS FOR A TODDLER WITH PKU (P26)

P. Watson

Department Nutrition and Dietetics, The Children's Hospital at Westmead, Sydney, Australia

The Nutrient Reference Values (NRVs) for Australia and New Zealand (including recommended dietary intakes) were published in 2005. The purpose of this analysis is to review the usual intake of a healthy toddler with phenylketonuria (PKU) against the new NRVs using the Recommended Dietary Intake (RDI) or the Adequate Intake (AI) for infants and young children 1–3 years. Master J (DOB: 29/08/06 at 39 weeks) is 18 months and was diagnosed with PKU by Newborn Screening. Blood phenylalanine levels have been well controlled with growth and development appropriate for age. J has tracked along the 50th %ile (CDC) for length since infancy. A 3 day weighed food record was analysed using FoodWorks (v5). J takes 90g XP Maxamaid daily providing ~1206kJ/d of energy (30% RDI) and 23g/d protein (164% RDI). Additional dietary protein of 8g/day provides a total intake of 31g/d (2.7g/kg) equating to 221% RDI. His supplement alone meets all requirements for most nutrients except for five micronutrients while zinc and copper both exceed the Upper Limit (UL) (+4.1mg/d and +0.6mg/d respectively). One micronutient (biotin) provides 1380% of the RDI. Fibre intake is 50% of AI. Both calcium and niacin intake, sourced predominantly from the supplement, exceed the RDI (154% & 394% respectively). Total iron intake is 154% of RDI however, if the PKU diet is considered a vegetarian diet, the RDI increases resulting in current intake being only 86% of RDI. This analysis raises questions about current supplement prescribing protocols — are we over prescribing for this age group?

MEETING NUTRITIONAL REQUIREMENTS ON A LOW PROTEIN DIET: A CASE STUDY OF A WOMAN WITH ARGININOSUCCINATE LYASE DEFICIENCY (O26)

M. Westbrook

Adult Metabolic Service, Westmead Hospital, Sydney, Australia

A case study is presented of a 53-year-old woman with argininosuccinate lyase deficiency who was admitted to Westmead Hospital in June 2005 with severe pneumonia, encephalopathy and an ammonia level of 181 umol/L. After treatment and recovery she was discharged on a protein

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restricted diet of 40 gram protein with 10g essential amino acids, a multivitamin and mineral supplement and an iron supplement. Later, based on pathology results, Caltrate with vitamin D and vitamin B12 injections were added. Prior to hospital admission the woman was living independently and eating mainly chocolate and chips. Dietary education in hospital encouraged a healthy low protein diet. When she returned home she initially chose foods that required little preparation, including mainly bread and high-fat foods like mini meat pies, sausage rolls and devon. She has gradually introduced more fruit, vegetables and leaner meats and started counting grams of fat as well as protein intake. She initially lost weight after leaving hospital but now has regained this weight and has been diagnosed with high cholesterol and glucose intolerance. She has been investigated for gastrointestinal bleeding as a possible cause of her iron deficiency. Her current dietary history will be presented and an analysis of her nutrient intake from food and supplements will be compared with the new nutrient reference values to determine if her diet is meeting them and if the supplements she is taking are appropriate.

ELEVATED PLASMA CHITOTRIOSIDASE ACTIVITY IN NIEMANN-PICK DISEASE TYPE C PATIENTS (P76)

K. L. Whenan, K. Nelson, J. M. Fletcher and M. J. Fietz

Department of Genetic Medicine, Child, Youth and Women's Health Services, Adelaide, Australia

Background: Chitotriosidase is a glucosylhydrolase secreted by activated human macrophages in response to a number of lysosomal storage disorders (LSD). Its analysis has been used to assist with the diagnosis and monitoring of Gaucher disease. It is also reported to be partially elevated in Niemann-Pick disease type C (NPC), which is an autosomal-recessive LSD. Definitive diagnosis of NPC requires skin fibroblast studies. *Aim:* To assess the suitability of chitotriosidase as an initial screen for NPC by performing retrospective and prospective analysis of patients referred to the National Referral Laboratory (NRL) for lysosomal enzyme studies or NPC analysis. *Method:* Chitotriosidase analysis was performed on 5 patients previously diagnosed with NPC. In addition, analysis has also been performed on 108 samples referred for lysosomal enzyme studies. *Results:* 4 of the 5 previously diagnosed cases showed levels of chitotriosidase activity significantly above our reported normal range (89-410 nmol/h/mL, NR 3.6-78). Studies are being performed to determine if the normal activity in the fifth patient is due to the presence of the common duplication in the gene encoding chitotriosidase. Prospective analysis has shown that 4/108 samples yielded elevated levels of chitotriosidase activity (92–100 nmol/h/mL). Two of these have been diagnosed subsequently with NPC. Conclusion: These studies indicate that a significant proportion of NPC patients have elevated chitotriosidase levels, indicating that it may be a useful biochemical marker in the diagnosis of NPC. However, it is also evident that, used alone, chitotriosidase analysis will not detect all patients affected by NPC.

CREATINE TRANSPORTER DEFECT: RESULTS OF 6 MONTHS' TREATMENT (O17)

B. Wilcken, E. Fagan, K. Sim and K. Carpenter

The Children's Hospital at Westmead University of Sydney, Australia

Creatine transporter deficiency is one of the three described cerebral creatine deficiencies. It is caused by mutations in the SLC6A8 gene, is X-linked, and associated with mental retardation, speech and language delay, and seizures. Creatine medication has been somewhat successful in treating the creatine synthesis defects, but so far no effective treatment has been described for the transporter defect. A 6-month-old boy presented with global delay, hypotonia, and constipation. An MRI/MRS at 9 months showed virtual absence of a creatine peak. Plasma creatine and guanidinoacetate levels were normal, but the urinary creatine:creatinine ratio was significantly elevated, with a normal guanidinoacetate:creatinine ratio. At 1 year he had global delay, gross language delay and hand hyperkinesias. Treatment was started with oral creatine, arginine and glycine, the latter being precursors of creatine. Clinically he progressed well, sitting unsupported by 16 months, attempting a pull-to-stand by 19 months. Hand hyperkinesias had disappeared. Language was not improved. A repeat MRI/MRS at 20m showed an increased creatine peak. The N-acetylaspartate:creatine ratio had decreased by 20% and the choline:creatine ratio decrease was 28%. While there seems no doubt that the brain creatine level had increased in the basal ganglia (where measurements were made) it is not clear how much his developmental progress is related to this.

NONDERIVATISED SAMPLE PREPARATION FOR TANDEM MASS SPECTROMETRY USED IN NEWBORN SCREENING IN NEW SOUTH WALES (O21)

V. Wiley,[1,3] K. Carpenter[2,3] and B. Wilcken[1,2,3]

[1] *NSW Newborn Screening Programme, The Children's Hospital at Westmead, Australia*

[2] *NSW Biochemical Genetics Service, The Children's Hospital at Westmead, Australia*

[3] *Disciplines of Genetic Medicine and Paediatrics and Child Health, University of Sydney, Australia*

Since incorporating the use of electrospray tandem mass spectrometry to expand the number of disorders included in the routine newborn screening protocol from 5 to over 30, 10 years ago, nearly 1 million babies have been tested. The method used to prepare the dried blood spot samples for analysis for most of these babies included chemical derivatisation of the amino acids and acyl carnitines with a strongly corrosive chemical, butanolic HCl, to enhance analytical sensitivity and required 2 hours of person time (6 hours actual time) for the average 5 × 96 well microtitre plates per day. Engineering improvements for current models of the mass spectrometer have increased sensitivity allowing the elimination of the derivatisation step from the procedure. No change of the analytical parameters was required apart from the simple modification of the ion pairs used previously. Precursors are 56Da less per butanolic moiety and products are detected by a constant neutral loss of 46Da for most amino acids whilst detection for acyl carnitines remains an 85Da fragment. Over 100,000 babies have been prospectively screened with the simplified sample preparation leading to detection of 35 babies: 10 babies with elevated phenylalanine (7PKU, 4 hyperphenylalaninaemia); 5 with a disorder of the urea cycle; 5 with other aminoacidopathies; 11 with MCAD; 4 with GAI; plus 4 mothers identified with 3MCCC. Eliminating the derivatisation step of the sample preparation procedure reduced the person time and actual time requirements as well as improved occupational health and safety without apparent loss of detection of disorders.

RAPID PRENATAL DIAGNOSIS OF CHROMOSOME ANEUPLOIDY BY QF-PCR (P11)

K. Woodward, L. Gray, M. Fenn, C. Lucas, K. Patton, T. Grumball and N. Hadlow

Cytogenetics, Western Diagnostic Pathology, Myaree, Australia

Quantitative fluorescence-PCR (QF-PCR) is a reliable, inexpensive and rapid method for prenatal diagnosis of common chromosome abnormalities in high risk pregnancies. We present our experience of QF-PCR over a 23 month period. A total of 1039 samples were analysed, 922 amniotic fluid (AF) samples and 117 CVS samples. A two tube test for aneuploidy of chromosomes 13,18,21, X and Y was used. Mean time for processing samples during the working week was 1.25 days. Results were compared to chromosome analysis obtained on average 10.6 days later. The QF-PCR abnormality rate was 3.9% for AF and 20.5% for CVS samples. In the whole cohort there were 60 aneuploidies, all detected by QF-PCR and confirmed by karyotyping. Karyotyping identified a further 20 abnormalities involving chromosomes not tested by QF-PCR. If abnormalities with low risk of a clinically significant outcome were classified as normal (inherited balanced translocations, inversions and markers) then the number of undetected high risk abnormalities would be 14. Blood-staining in 353 AF samples (37.6%) resulted in 20 patients (2%) not receiving a QF-PCR report due to maternal cell contamination. QF-PCR was concordant with the karyotyping for 100% of cases with normal karyotypes and 81% (60/74) of cases with abnormal karyotypes. We conclude that QF-PCR is a valuable technique for aneuploidy screening. Advantages compared to FISH include low cost, speed, automation and ability to detect maternal cell contamination. However, karyotyping still remains the gold standard for detection of numerical and structural abnormalities with QF-PCR providing a fast and reliable interim result.

PREGNANCIES CONCEIVED USING ASSISTED REPRODUCTIVE TECHNOLOGIES HAVE A LOW SERUM PAPP-A RESULTING IN A HIGH FALSE POSITIVE RATE AT FIRST TRIMESTER SCREENING (O111)

J. Xu, A. Jacques, J. Halliday, I. Francis, D. Healey, G. Baker and D. Amor

Murdoch Childrens Research Institute

Aim: To examine the relationship between the use of Assisted Reproductive Technologies (ART: IVF, ICSI and GIFT) and the likelihood of obtaining a false positive result at first trimester combined screening. *Methods:* A population-based retrospective cohort study was conducted comparing the levels of fβ-hCG, PAPP-A, NT and false positive rate in 1,739 ART-conceived singleton pregnancies and 50,253 naturally conceived singleton pregnancies (controls). Data were obtained from the

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Victorian Perinatal Data Collection Unit, VCGS Pathology and the Victorian ART providers. *Results:* After controlling for gravidity and maternal age, singleton pregnancies conceived by ART were 62% more likely than naturally conceived pregnancies to receive a false positive result in the first trimester combined screen (OR 1.62, 99% CI 1.29–2.03). This increased false positive rate was due to a significantly lower PAPP-A being detected in the ART pregnancies (0.83 MoM) compared to the controls (1.00 MoM). No significant differences in fβ-hCG and NT were observed between the ART pregnancies and controls. A significantly decreased PAPP-A was observed for all forms of ART (IVF, ICSI and GIFT), and for fresh and frozen embryo transfers. The decreased PAPP-A was not associated with adverse perinatal outcomes or obstetric complications. *Conclusion:* Couples who conceive using ART are significantly more likely to receive a false positive result at first trimester screening because of a reduced PAPP-A level. The mechanism underlying the reduced PAPP-A in ART pregnancies is not known.

OUTCOME OF ENZYME REPLACEMENT THERAPY (ERT): FIRST AUSTRALIAN MPS II PATIENT (O16)

J.Yaplito-Lee, M. Delatycki and H.Peters

Genetic Health Services Victoria, Royal Children's Hospital, Melbourne, Australia

Mucopolysaccharidosis (MPS) II is a rare X-linked condition due to a deficiency of a lysosomal enzyme, iduronate-2-sulfatase. Affected patients present with multisystem involvement that has a varying age of onset and varying range of severity. We report the first MPS patient to be treated with Elaprase (Idursulfase) in Australia. The patient is 12 years of age with a normal intelligence. Main problems include: optic nerve compression due to scleral thickening, hepatosplenomegaly, multiple joint contractures, recurrent ear infections, nasal polyposis, thickened mitral and aortic valves. A year of weekly enzyme infusion has been completed with no infusion associated adverse reactions. Marked improvement was observed in height, weight, 6 minute walk test, facial coarse features, skin nodular lesions, urinary glycosaminoglycans level and general well being. There was also reduction of hepatosplenomegaly and improvement in the mobility of certain joints such as hip, shoulder and elbow. Other parameters such as optic nerve swelling, skeletal problems and narrowing of cervical canal showed no improvement. Our patient demonstrates some of the beneficial effects of ERT. However, further evaluation is needed after a longer period of enzyme infusion.

MANAGEMENT OF FAMILIES WITH SUDDEN CARDIAC DEATH: A MULTIDISCIPLINARY APPROACH (O109)

L.Yeates,[1] J. Ingles[1] and C. Semsarian[1,2,3]

[1] *Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney*

[2] *Central Clinical School, Faculty of Medicine, University of Sydney, Sydney*

[3] *Department of Cardiology, Royal Prince Alfred Hospital (RPAH), Sydney*

Background: Sudden cardiac death (SCD) in the young is a tragic event, and is commonly caused by an underlying genetic heart disorder. A number of management issues arise in families with SCD, including clinical, genetic, and psychosocial concerns. The Genetic Heart Disease Clinic at RPAH, Sydney was established in 2003. This clinic provides clinical cardiology screening, genetic counselling, opportunities to participate in research studies, and links to other medical professionals/services (e.g., clinical geneticist, patient support groups). *Methods:* We reviewed the progress of the Genetic Heart Disease Clinic from 2003-2007, with an emphasis on families with SCD. *Results:* The Genetic Heart Disease Clinic has seen 240 families (total 574 patients), including 44 families with a history of SCD. Of these 44 families, a diagnosis has been established in 13 (30%) families. Clinical screening of over 90 first-degree relatives has identified causes of death as: hypertrophic cardiomyopathy (21%), arrhythmogenic right ventricular cardiomyopathy (2%), and coronary artery disease (7%). In the remaining 30 families, SCD is likely due to an inherited arrythmogenic disorder such as long QT syndrome. Clinical screening has lead to early diagnosis in relatives, opportunities for genetic counselling and genetic testing, and initiation of treatment/prevention strategies to prevent further SCD in families. *Conclusions:* SCD is a complication of a number of genetic heart disorders. The clinical, genetic, and psychosocial complexities seen in families with SCD highlight the need for a multidisciplinary team, including a cardiologist, genetic counsellor, clinical geneticist and forensic pathologist, with the ultimate goal to reduce SCD in our community.

PALLISTER-KILLIAN SYNDROME CAUSED BY MOSAICISM FOR A SUPERNUMERARY RING CHROMOSOME 12P (P42)

A.Yeung,[1,2] D. Francis,[2] O. Giouzzepos[2] and D.Amor[1,2,3]

[1] *Genetic Health Services Victoria, Royal Children's Hospital, Melbourne, Australia*

[2] *Murdoch Children's Research Institute, Australia*

[3] *Department of Paediatrics University of Melbourne, Australia*

Pallister-Killian syndrome (PKS) is a rare sporadic disorder distinguished by mental retardation and characteristic facial features. Major structural anomalies are occasionally observed including diaphragmatic defects, anal anomalies, genital malformations and cardiac abnormalities. The characteristic cytogenetic abnormality found in PKS is an additional linear isochromosome 12p conferring mosaic tetrasomy. We describe a unique case of PKS caused by a supernumerary ring chromosome 12p, a novel finding that has not been documented in the literature to date. Our case demonstrated the typical dysmorphic features of PKS including frontal bossing, frontotemporal alopecia, shallow supraorbital ridges, cleft palate, long philtrum and small, dysplastic ears. Bilateral accessory nipples were noted as well as hypoplasia of the labia and a common anal and vaginal opening. The unusual finding in our case was a relatively rapid rate of developmental progress with the child walking and vocalising at 16 months of age. Most reported adult cases of PKS are nonverbal and few manage to walk. Initial interphase FISH analysis was performed on a buccal swab and the result was confirmed on a fibroblast sample. We discuss the characteristics inherent to ring chromosomes and suggest a number of mechanisms for the milder phenotype in this patient.

RARE GENOMIC IMBALANCES IDENTIFIED BY USING MLPA, ARRAY CGH AND FISH (P82)

S.Yu,[1] S. Brown,[1] A. Correll,[1] S. Bain,[1] D. Bratkovic,[2] L. McGregor,[1] J. Liebelt[1] and J. Nicholl[1]

[1] *Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia*

[2] *Department of Paediatrics and Child Health, Flinders University, Australia*

The combination of MLPA, array CGH and FISH provides a powerful tool to detect and size genomic imbalances, which account for a significant proportion of cases with developmental delay (DD) and intellectual disability (ID). Documentation of rare genomic imbalances facilitates phenotype and genotype comparison. Case 1 is a 2-year-old boy with short stature (<1st percentile), DD and facial dysmorphism. MLPA and Array CGH identified a 15q deletion (~4.5 Mb) including the insulin like growth factor 1 receptor (IGF1R) gene. The only other published 15qter deletion case had similar clinical features to case 1. Case 2 is a 12-year-old boy with mild ID. MLPA identified a 2pter deletion (~0.8Mb). The only other reported case of a 2pter deletion (3.3 Mb) had generalized obesity, proportionate tall stature, large hands and feet, ID and dysmorphism. Case 3 is a 5-year-old girl with hemifacial microsomia, pre-auricular tag and branchial remnant. MLPA identified a SHOX gene duplication at Xpter. Her mother and maternal grandmother carry the duplication and both have a normal phenotype. SHOX deletions are associated with Leri-Weill dyschondrosteosis. However, SHOX duplications are rarely reported and are of uncertain clinical significance. In this family, the SHOX duplication is familial, and thus likely to be a polymorphism in female carriers. The effect, if any, on males carrying the duplication remains to be elucidated. Routine use of MLPA and array CGH will reveal more rare genomic imbalances in patients with DD/ ID and should facilitate genotype/phenotype correlation.

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