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REVIEW ARTICLE

The current state of play on the molecular genetics of depression

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Background. It has been well established that both genes and non-shared environment contribute substantially to the underlying aetiology of major depressive disorder (MDD). A comprehensive overview of genetic research in MDD is presented.

Method. Papers were retrieved from PubMed up to December 2011, using many keywords including: depression, major depressive disorder, genetics, rare variants, gene–environment, whole genome, epigenetics, and specific candidate genes and variants. These were combined in a variety of permutations.

Results. Linkage studies have yielded some promising chromosomal regions in MDD. However, there is a continued lack of consistency in association studies, in both candidate gene and genome-wide association studies (GWAS). Numerous factors may account for variable results including the use of different diagnostic approaches, small samples in early studies, population stratification, epigenetic phenomena, copy number variation (CNV), rare variation, and phenotypic and allelic heterogeneity. The conflicting results are also probably, in part, a consequence of environmental factors not being considered or controlled for.

Conclusions. Each research group has to identify what issues their sample may best address. We suggest that, where possible, more emphasis should be placed on the environment in molecular behavioural genetics to identify individuals at environmental high risk in addition to genetic high risk. Sequencing should be used to identify rare and alternative variation that may act as a risk factor, and a systems biology approach including gene–gene interactions and pathway analyses would be advantageous. GWAS may require even larger samples with reliably defined (sub)phenotypes.

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Introduction

The prevalence of mental disorders in the general population is remarkably high (Kessler *et al*. 1994). Data collected by the World Health Organization (WHO) suggest that, as a leading cause of disability in adults, major depressive disorder (MDD) closely follows cardiovascular disease (Murray & Lopez, 1997) and is predicted to top the list by 2030. It is unfortunate, therefore, that the aetiology of affective disorders is not yet well understood, and risk genes for MDD not yet convincingly identified. This review describes heritability, the current state of play of molecular genetics in MDD, and how as a community we may go forward with our research aiming to improve molecular knowledge of the disorder.

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Are genetics important in depression?

Twin studies indicate a substantial contribution of genetic and unique environmental factors to the variance observed in depression, with little or no shared environmental contribution. A meta-analysis of five twin studies, four of which were population based, suggests that genetic factors explain 37% of the variance, with unique environment accounting for 63%, and no shared environmental effects (Sullivan *et al*. 2000). However, heritability estimates are higher, at around 70%, in studies that either take into account diagnostic unreliability, because measurement error inflates the unique environment estimation (Kendler *et al*. 1993), or focus on clinically ascertained twins (McGuffin *et al*. 1996). These heritability estimates provide good reasoning for the attempt to identify genes that may influence susceptibility to depression, with non-shared environmental effects remaining substantial and important.

Although it has been suggested that earlier age of onset presents increased familial loading (Puig-Antich

et al. 1989; Weissman *et al*. 1992), this is not supported by a more recent meta-analysis by Sullivan *et al*. (2000) or by a later clinical twin study (McGuffin *et al*. 2003). Moreover, some studies suggest that prepubertal onset depression is largely dependent on environmental factors whereas post-pubertal onset is more genetically influenced (Weissman *et al*. 1987; Harrington *et al*. 1997). This is supported by twin (Thapar & McGuffin, 1994) and adoption studies (Eley *et al*. 1998).

Finding genes involved in depression

Linkage and association studies are complementary methods of locating susceptibility genes for MDD. Linkage can be detected over comparatively large distances but power is problematic when searching in genome-wide scans for quantitative trait loci (QTLs) with small effect sizes. By contrast, traditional association studies can detect small effects but only over very short distances. More recently, genome-wide association studies (GWAS) have become feasible, using the huge numbers of markers now available. This method combines the advantage of the breadth of linkage with the power of association, although this may be compromised by allelic heterogeneity, as discussed later.

Linkage studies in MDD

Despite inconsistent linkage results in MDD in earlier, mainly smaller studies (e.g. Nurnberger *et al*. 2001; Zubenko *et al*. 2002; Abkevich *et al*. 2003), some consistencies have started to emerge in studies using several hundreds of affected sib pairs (ASPs) (Holmans *et al*. 2004; McGuffin *et al*. 2005; Holmans *et al*. 2007). In the first wave of the Genetics of Recurrent Early-Onset Major Depression (GenRED) study, consisting of 415 ASPs, significant genome-wide linkage to chromosome 15q with no sex effects was reported, together with suggestive evidence for sex-specific linkage on chromosomes 6q, 8p and 17p in males (Holmans *et al*. 2004). It is worth noting, however, that the latter sex-specific findings may be spurious given the small male–male sample size. Two independent large-scale studies, the European–US Depression Network (DeNt) study (McGuffin *et al*. 2005) and a study from Utah (Camp *et al*. 2005), provided support for linkage in the 15q region although this was male specific in the Utah study. Similar phenotypic definitions of MDD were applied in these three studies, all investigating recurrent depression, with the GenRED and Utah studies specifically investigating early onset. The results of the final stage of a whole-genome linkage scan of 656 families in the GenRED study included fine mapping of the 15q linkage region (Holmans *et al*. 2007; Levinson *et al*. 2007; Verma *et al*. 2008). The findings are promising, providing what may be the first example of a genome scanning approach giving insight into the aetiology of MDD (McGuffin *et al*. 2007).

A second region has recently been identified that presents evidence for linkage in the combined first and second waves of the DeNt study and an independent MDD sample in the 3p24.9-26 region (Breen *et al*. 2011; Pergadia *et al*. 2011). The samples differed slightly in that DeNt was a recurrent depressive family sample with analyses restricted on impairment severity (Breen *et al*. 2011), and the second a depression family sample originally ascertained to explore the genetics of smoking (Pergadia *et al*. 2011). Although case-control association analyses in this region have not so far helped in identifying specific genes (Breen *et al*. 2011), the region remains of interest and the next stage for both 15q and 3p linkage regions should involve a meta-analysis, or ideally mega (combined) analyses of raw data from all available sources. It is also possible that variants contributing to the linkage peaks may be rare variants that are not detected individually by whole-genome analysis methods, and so sequencing of the candidate regions should also be carried out.

Genetic association studies

We are currently in an era of GWAS. However, these have only been feasible in the past few years and the majority of association studies in MDD have focused on candidate genes. In trying to establish where we need to go in the future, it is important to be aware of what has been found in the past. GWAS do not make candidate gene studies redundant because a vast majority of these studies were based on only a few single nucleotide polymorphisms (SNPs) within each candidate gene, thus not giving full coverage.

Monoamines

Based on what is assumed to be the mode of action of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), obvious candidate genes for association studies in depression are those relevant to monoamine synthesis and transport together with monoamine receptors and associated G proteins.

Monoamine oxidase

Monoamine oxidase type A (MAOA) is a mitochondrial enzyme that has an important role in the

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degradation of biological amines including 5-hydroxytryptamine (5-HT), noradrenaline and dopamine (Syagailo *et al*. 2001; Youdim *et al*. 2006). The *MAOA* gene is located on chromosome Xp11.23-p11.4 (Ozelius *et al*. 1988; Levy *et al*. 1989) and several polymorphisms have been identified. Two functional markers have been studied in relationship to depression; the T941G polymorphism (rs6323) does not seem to be associated with MDD (Sasaki *et al*. 1998; Tadic *et al*. 2003; Zhang *et al*. 2010). Many studies indicate no association with a second functional polymorphism, a variable number tandem repeat (VNTR), and affective disorder or specifically depression (e.g. Kunugi *et al*. 1999; Christiansen *et al*. 2007). However, positive reports include allele and homozygous genotype association of the high-activity variants with MDD, particularly in females (Schulze *et al*. 2000; Yu *et al*. 2003; Rivera *et al*. 2009), and association with subtypes of MDD (Gutierrez *et al*. 2004). There has also been a conflicting report associating the low-activity allele with depressive symptoms (Brummett *et al*. 2007).

Serotonin

The serotonin transporter

The serotonin transporter (*5HTT*) gene located at 17q11.1-q12 has been studied extensively, with two well-characterized polymorphisms the focus of much depression-related genetic research. At the 5′ flanking regulatory region of the human *5HTT* gene there is a functional 44-base-pair (bp) insertion/deletion polymorphism, known as the serotonin-transporter-linked polymorphic region, *5HTTLPR* (Heils *et al*. 1996), conferring long and short alleles associated with differential *5HTT* expression and 5-HT reuptake in lymphoblastoid cell lines (Lesch *et al*. 1996).

Despite its strong candidacy, the numerous association studies investigating the *5HTTLPR* and depression have reported equivocal results (e.g. Collier *et al*. 1996; Furlong *et al*. 1998*b*; Minov *et al*. 2001; Hauser *et al*. 2003). This could be a consequence of small sample sizes and several meta-analyses have been conducted in an attempt to circumvent this problem. The first included a total of 275 depressed patients and 739 controls of Caucasian origin, and demonstrated an association with the short allele and depression (Furlong *et al*. 1998*b*). This has since been supported by two further meta-analyses (Lotrich & Pollock, 2004; López-León *et al*. 2008); however, two other meta-analyses present no evidence for association (Anguelova *et al*. 2003; Willis-Owen *et al*. 2005). This may be explained by the heterogeneity of inclusion criteria for the analyses.

Although the *5HTTLPR* has been reported to affect transcriptional activity alone, other studies indicate a more complex situation (e.g. Nakamura *et al*. 2000). An SNP, rs25531 (A/G), has been described that influences transcriptional activity as part of a haplotype with the *5HTTLPR* (Nakamura *et al*. 2000; Wendland *et al*. 2006). This G substitution in combination with the long allele (L_G) seems to reduce the expression to the same level as the short allele, thereby creating two functional haplotype groups: L_A *versus* L_G, S_A and S_G. Relatively little research incorporating this SNP has been published to date. One study reports a female-specific association with melancholic depression specific to L_A as the risk haplotype (Baune *et al*. 2008) whereas another study reports a protective effect of this haplotype on treatment-resistant depression (Bonvicini *et al*. 2010). The situation may be further complicated by the apparent functional impact of additional proximate SNPs (Martin *et al*. 2007).

A 16/17-bp VNTR (Cowen & Charig, 1987; Kaiser *et al*. 2001) in the second intron of the *5HTT* gene (STin2) has also been investigated in association with MDD. Again, association studies have been equivocal; the most promising association is with the 9-repeat (e.g. Battersby *et al*. 1996; Ogilvie *et al*. 1996; Bozina *et al*. 2006), although several studies suggest this is not the case (e.g. Kunugi *et al*. 1997; Furlong *et al*. 1998*b*). Three meta-analyses suggest that no significant association exists between the VNTR alleles and/or genotypes and depression (Furlong *et al*. 1998*b*; Anguelova *et al*. 2003; López-León *et al*. 2008), but samples analysed to date have had low numbers.

The serotonin receptors

The serotonin receptor 1A is encoded by an intronless gene (*HTR1A*) located at 5q11.2-q13 (Melmer *et al*. 1991). Most studies indicate little evidence for association of this locus as confirmed by a meta-analysis of the marker SNP rs6295 (López-León *et al*. 2008). The serotonin receptor 1B gene (*HTR1B*) maps to human chromosome 6q13, a region for which sex-specific (male) linkage to depression and/or anxiety has been reported (Holmans *et al*. 2004; Nash *et al*. 2004). The variant G861C (rs6296) is a functional polymorphism (Maura *et al*. 1993); however, no significant association has been found directly with MDD although it has been suggested that rs6296 may only be associated with a more severe (i.e. recurrent) form of depression (Huang *et al*. 2003).

Studies investigating the serotonin receptor 2A gene (*HTR2A*) at 13q14-q21 have also been inconclusive. Two meta-analyses indicate no association with depression (Anguelova *et al*. 2003; López-León *et al*. 2008). The serotonin receptor 2C gene (*HTR2C*) is

situated on chromosome Xq24, with a functional polymorphism (rs6318, a Cys23Ser substitution) in the hydrophobic region of the receptor (Lappalainen *et al*. 1995; Quested *et al*. 1999). Although no convincing evidence for association exists (Lerer *et al*. 2001; Koks *et al*. 2006), given the sex imbalance observed in depression, further research investigating this X-linked gene is merited.

Other serotonin receptor genes studied include *HTR3A* and *HTR3B*, which are tandemly positioned at 11q23 (Miyake *et al*. 1995; Davies *et al*. 1999). Little evidence for association is observed, although three-marker haplotypes spanning a seven-marker region in the *HTR3B* gene are reported to be associated in the Japanese female population (Yamada *et al*. 2006) (see online Supplementary Table 1). Other receptor genes have also been examined, including *HTR5A* (7q36.1) and *HTR6* (1p35-36), but no strong evidence for association has emerged.

Tryptophan hydroxylase (*TPH*)

TPH is rate limiting in the biosynthesis of 5-HT (Priestley & Cuello, 1982). The *TPH1* gene has been mapped to human chromosome 11p15.3-p14 (Craig *et al*. 1991). An association with the C/C genotype of the A218C (rs1800532) SNP and depression has been reported (Tan *et al*. 2003), particularly with severe depression (Viikki *et al*. 2010); however, an increase in the frequency of the A allele in depressed patients has also been observed (Tsai *et al*. 1999; Wang *et al*. 2011). Population stratification could account for this as the former two studies used Singaporean and Finnish subjects, and the latter Chinese and Taiwanese. However, multiple negative studies have also been published (e.g. Frisch *et al*. 1999; Gizatullin *et al*. 2006). A meta-analysis including both the positive and negative studies suggests that the A128C SNP is not associated with MDD (López-León *et al*. 2008). A second SNP in intron 7, C779A (rs1799913), has been associated with depression (Gizatullin *et al*. 2006), although this has not been replicated (Koks *et al*. 2006).

A second TPH isoform was first identified in the mouse (*Tph2*) and shares 72% sequence homology with the *TPH1* gene (Walther & Bader, 2003). In humans, *TPH2* at 12q21 falls within a previously reported MDD linkage region (Abkevich *et al*. 2003). There was considerable excitement when a loss-of-function mutation, *R441H*, was described and reported to be highly associated with MDD (Zhang *et al*. 2005); however, this variant seems to be extremely rare and has not been observed in multiple independent studies since the initial report (e.g. Glatt *et al*. 2005).

Noradrenaline

The noradrenaline transporter

Serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressant medication is known to act on the noradrenaline transporter (SLC6A2) and a reduction in its density in the locus coeruleus has been reported in depressed patients (Klimek *et al*. 1997). The *SLC6A2* gene maps to chromosome 16q12.2 (Porzgen *et al*. 1995). Many studies investigating different populations have failed to detect an association using a promoter polymorphism, T-182C (rs2242446), the synonymous variant G1287A (rs5569) and/or the non-synonymous exonic variant C296T/Thr99Ile and depression (e.g. Owen *et al*. 1999; Inoue *et al*. 2007), whereas two studies on –182T/C report an association but with different genotypes (Inoue *et al*. 2004; Ryu *et al*. 2004).

Unsurprisingly, a meta-analysis of the –182T/C locus presents no evidence for association with MDD (López-León *et al*. 2008). However, a study that sequenced the exons to identify all SNP variations does report evidence for association in a Mexican-American population, highlighting the importance of a comprehensive approach (Dong *et al*. 2009).

The adrenaline and noradrenaline receptors

The α_{2A}- and α_{2C}-adrenergic receptors, unlike α_{2B}, are both expressed in brain and have been implicated in stress (e.g. Fuchs & Flugge, 2003) and MDD (e.g. Ordway *et al*. 2003). Nevertheless, no association is reported with either the *ADRA2A* –1291C/G polymorphism or the Gly389Arg *ADRB1* polymorphism, and MDD or mood disorder (Ohara *et al*. 1998; Zill *et al*. 2003). A comprehensive survey of 24 markers in nine adrenergic receptor genes, including three that fall within linkage regions for recurrent MDD [*ADRAB1* (5q23-q33.3), *ADRB3* (8p12-p11.2) and *ADRB1* (10q24-q26)] (Zubenko *et al*. 2003), undertaken in a Hungarian cohort of early-onset depression (before the age of 15 years) failed to find strong evidence for association (Burcescu *et al*. 2006).

Dopamine

The dopamine receptors and transporter

Only two published studies have investigated the dopamine D_1 receptor (*DRD1*) gene, located at 5q35.1, in association with MDD. One reported on 10 SNPs (Koks *et al*. 2006) and the other on four (Garriock *et al*. 2006); three were investigated by both groups (–1251G/C, –800T/C, –48G/A). Neither study finds significant association. Similarly, no positive association has been reported for the functional Ser311Cys

substitution (rs1801028) in the *DRD2* gene (11q22.3-q23) and MDD (e.g. Manki *et al*. 1996; Koks *et al*. 2006), or the –141C insertion/deletion in a relatively small study ($n=128$ patients and 262 controls) (Furlong *et al*. 1998*a*). Investigation of nine additional SNPs in the *DRD2* gene further indicate no role of this gene in MDD susceptibility (Koks *et al*. 2006). A *Bal*I polymorphism and a Ser9Gly substitution (rs6280) in the first exon in *DRD3* have been investigated; one study presented significant association with the Gly9 allele and homozygote genotype (Dikeos *et al*. 1999) but this has not been replicated in larger studies (e.g. Manki *et al*. 1996; Garriock *et al*. 2006). A meta-analysis also suggests that there is no association (López-León *et al*. 2008). A 48-bp VNTR has been described in exon 3 of the *DRD4* gene (11p15.5), which has been significantly associated with depression (Manki *et al*. 1996), although again this has not been replicated in other studies (e.g. Oruc *et al*. 1997; Frisch *et al*. 1999).

The dopamine transporter gene (*DAT1* or *SLC6A3*), located on 5p15.33, has also been investigated in MDD. Although studies investigating a 40-bp VNTR in the three prime untranslated region (3′UTR) report no evidence for association (Manki *et al*. 1996; Frisch *et al*. 1999), a meta-analysis comparing the 9/10 genotype with the 10/10 genotype suggests the former to be associated with MDD (López-León *et al*. 2008).

Beyond the monoamine hypothesis

The hypothalamic–pituitary–adrenal (HPA) axis and depression

Given the close relationship between stress and depression (Charney & Manji, 2004), genes associated with the HPA axis are attractive candidates. MDD has been associated with HPA axis hyperactivity (Plotsky *et al*. 1998) and research demonstrates that HPA axis dysfunction is genetic and increases the risk of depression (e.g. Modell *et al*. 1998). Genetic research to date investigating candidate genes in this system are summarized in the online Supplementary Table 2. Although it is clear that no consistent association is observed, studies are few and limited variously by heterogeneous genetic variation, small sample sizes and/or imprecise phenotypes.

Brain-derived neurotrophic factor (BDNF)

Chronic stress has also been associated with hippocampal neuronal atrophy in animal studies (Sapolsky *et al*. 1990) and found to reduce BDNF expression in hippocampal neurons (Smith *et al*. 1995). Antidepressants and electroconvulsive therapy (ECT) have been found to inhibit this stress-induced response (e.g. Duman, 1999). The *BDNF* gene is mapped at 11p13/11p14 (Hanson *et al*. 1992). Depression research has concentrated on one functional polymorphism (rs6265), sometimes coupled with a GT_n microsatellite polymorphism and a range of other SNPs (see online Supplementary Table 3). Although reports have been conflicting, the largest case-control study published to date, while failing to find convincing single-marker association, reports a haplotype association with three markers (rs6265-GT_n repeat-rs988748) that is also observed in a second sample (Schumacher *et al*. 2005). This has not been replicated in a larger case-control sample ($n=1450$ cases and 850 controls; Cohen-Woods, unpublished observations). The involvement of the *BDNF* gene in depression remains controversial, with meta-analyses mirroring the landscape of the inconsistent individual studies (see online Supplementary Table 3), presenting different findings depending on the studies included and whether gender and/or ethnicity is considered (Gratacos *et al*. 2007; Verhagen *et al*. 2010).

GWAS

GWAS using micro-arrays enable the order of one million SNPs to be genotyped simultaneously for each individual. These studies have the potential to identify candidates in underexplored pathways relating to depression. It remains to be seen if the success achieved with other common traits and disorders such as type 2 diabetes (Zeggini *et al*. 2007) and rheumatoid arthritis (Thomson *et al*. 2007), where GWAS have led to the discovery of novel susceptibility genes, can be replicated. In the first report of this kind, the candidature of a gene implicated in monoaminergic transmission (piccolo, *PCLO*) emerged after re-examination of the original cohorts concentrating on samples of greatest similarity (Sullivan *et al*. 2009). A p value of 6.4×10^{-8} was achieved for a non-synonymous SNP near a calcium-binding domain. However, although replication was lacking within the study, a more recent population-based study does replicate an association with the *PCLO* gene and depressive disorders, although it was not a whole-genome association study (Hek *et al*. 2010). Another genome-wide study implicates a novel locus, *BICC1*, but this failed to be confirmed in independent replication samples (Lewis *et al*. 2010). Further whole-genome studies investigating MDD fail to identify any loci or replicable loci (Muglia *et al*. 2010; Rietschel *et al*. 2010; Terracciano *et al*. 2010; Shi *et al*. 2011; Wray *et al*. 2012). A recent meta-analysis has included data from three of these studies (Sullivan *et al*. 2009; Muglia *et al*. 2010; Shi *et al*. 2011) and reported three intronic SNPs in *ATP6V1B2*, *SP4* and *GRM7* as most associated, but

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with p values just short of genome-wide significance (Shyn *et al*. 2011). In addition to meta-analysis it is possible to perform a 'mega-analysis' that pools samples together: this is the approach undertaken by the Psychiatric GWAS Consortium (PGC). In their discovery sample 9240 affected MDD individuals and 9519 controls were included, with independent replication samples totalling 6783 affected MDD individuals and 50 695 controls. In total, more than 1.2 million SNPs were analysed, with none reaching significance in the MDD groups (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2012).

Why has there been so little replication?

Despite significant heritability, failure of replication is a persisting feature and can be attributed to a variety of plausible explanations including sample size, heterogeneity, publication bias, multiple-testing issues, and insufficient quality control. These are discussed briefly in the following sections.

Size of our samples

MDD is a complex multifactorial disease, where it is probable that variants of multiple genes of small effect are being sought. This means that samples must be very large to detect any association, a criterion that has rarely been achieved and that frequently results in false positives, excluding the possibility of replication, thereby creating an unfortunate non-self-fulfilling prophesy. With the advent of whole-genome studies, the issue of power and sample size becomes ever more significant, as larger numbers are required to provide sufficient power to detect association because of the impact of multiple testing in addition to the small effect sizes of risk loci. GWAS had greater numbers than those studies often used in earlier candidate gene studies, but still the numbers do not seem to be sufficient to identify consistently associated loci. The PGC has tried to address this issue with the mega-analysis described earlier, but even with such large numbers little of significance has been identified. Nonetheless, there is a strong argument that we must not give up on GWAS because, although numbers are greater then previously studied, much greater numbers are probably required to detect common variation of small effect in psychiatric disease (Sullivan, 2012). Specifically, in depression GWAS it is proposed that samples need to be 1.8–2.4 times larger than used those successfully in schizophrenia GWAS research (Wray *et al*. 2012).

Population stratification

The frequencies of many markers are sensitive to population differences and ethnic stratification of samples can confound data considerably. Even a small admixture can confound results, particularly in haplotypic analyses when considering multiple markers in combination, and although some studies check for stratification, this is not always reported. It has been reported that homogeneous control Caucasian populations with comparable allelic frequencies can demonstrate different underlying linkage disequilibrium (LD) and haplotype structures within Europe (Mueller *et al*. 2005). This may create difficulty in the replication of specific haplotype associations or even single-marker associations, where the true associated locus is in fact in LD with the single marker and so not detected across populations because of differing population structures.

Multiple testing

A consequence of genome-wide capabilities is the necessity to run hundreds of thousands of statistical tests simultaneously. Although genome-wide significance thresholds have been established in the literature, there is the real risk of false negatives (Panagiotou *et al*. 2012). Thus, sufficiently powered candidate gene studies still have their role within the literature, but authors should attempt to locate multiple samples within which to replicate findings. Similarly, targeted replication can be used to support evidence for a genome-wide associated locus from one study in independent samples. This reduces the multiple testing burden in the replication sample(s). A method that attempts to circumvent, or at least reduce, the problem with multiple testing and assuming independence is by taking a systems biology approach in pathway analysis. To our knowledge there is only one study to date applying this approach in the literature. Although producing interesting results, with pathways including neurotransmitter, immune and inflammatory responses identified, there were in total 17 significantly enriched pathways in MDD; rather too many for specific studies (Kao *et al*. 2012). Therefore, the key findings require replication. The PGC is also working on a huge collaborative pathway analysis effort, despite the lack of individual studies published.

Heterogeneity

Problems with replication may also be a consequence of phenotypic and genetic heterogeneity. Whereas the former is self-explanatory, genetic heterogeneity can take two forms: locus and allelic heterogeneity. Locus

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heterogeneity occurs when different genes (or combinations of genes) influence disease risk between individuals. By contrast, allelic heterogeneity refers to different variants within the same gene influencing disease risk. Allelic heterogeneity has often been cited as a reason for the lack of specific SNP replication across studies in which different alleles of one gene track the disorder. The existence of multiple rare alleles of high impact is a plausible explanation in such cases. Methods to address phenotypic heterogeneity can include using sub- (or endo)phenotypes, such as specific types of depression (e.g. post-natal, melancholic). Deep sequencing enables us to address allelic heterogeneity, targeting genetic regions implicated by either linkage or association studies that may harbour rare or common variations predisposing to MDD. Sequencing would capture variation not genotyped by these studies but linked to the associated locus/region.

Type of variation studied

The discrepancy between results may, however, go beyond basic statistical and methodological issues. The type of variation being studied, genetic and non-genetic, also has the potential to explain in part the problems with replication. This includes environmental factors, epigenetics, copy number variation (CNV) and rare variants, all discussed in brief here.

Further to establishing strong genetic influence in depression, quantitative genetic studies have found substantial influence of an individual's unique environment (Kendler, 1996). Consideration of environmental factors is often ignored in psychiatric genetics and, in such circumstances, it might be unsurprising that consistent results are not achieved. In addition to simply co-acting in an additive fashion, genetic and environmental factors affecting the aetiology of MDD may covary and interact with one another. It has been postulated that one-third of the variance observed between stressful life events and depression is attributable to gene–environment (G–E) correlation (Kendler *et al*. 1999). Evidence of G–E interaction in depression was first demonstrated in a study by Caspi *et al*. (2003), in which the *5HTTLPR* s allele only conferred susceptibility to depression if the carrier had been exposed to stressful life events. This has since been replicated (e.g. Eley *et al*. 2004; Willhelm *et al*. 2006), but not consistently (e.g. Fisher *et al*. 2012). Two meta-analyses failed to support evidence for the G–E interaction, including nine and 14 of the 54 G–E *5HTTLPR* studies published to date respectively (Munafò *et al*. 2009; Risch *et al*. 2009). By contrast, the most recent meta-analysis, which included all but one study, shows that, depending on the type of variation studied (i.e. if limited to childhood maltreatment or physical illness), there is strong evidence for G–E interaction. Consideration of adult life events, or brief life events, did not support G–E interaction, showing the importance of the variables considered (Karg *et al*. 2011). The type of measurement (i.e. subjective *versus* objective) has also been reported to have a potentially significant impact (Uher, 2011). This is exemplified by our own depression study, which found no evidence for G–E interaction when investigating adult life events (Fisher *et al*. 2012) but strong evidence with childhood maltreatment factors (Fisher *et al*., in press). However, a recent study aimed directly at replicating the original *5HTTLPR* interaction with life stress reported by Caspi *et al*. (2003) failed to find any evidence for interaction using a variety of stress and outcome measures, including childhood maltreatment (Fergusson *et al*. 2012). Although this paper has not been included in any meta-analysis to date, there is an ongoing international effort to perform coordinated reanalysis of primary data from this and many other published and unpublished datasets to address the complex question of heterogeneous environmental and outcome measures in G–E *5HTTLPR* studies. This highlights that, although there is some optimism in this field of research, some caution is also necessary (Brown, 2012). Nonetheless, as many candidate gene effects may be influenced by stress, the inclusion of measures of stress-related variables and other environmental factors in research designs is recommended and may soon become the norm; however, the type of variable collected is important in consideration of research designs.

Epigenetic factors have also not been widely investigated in depression, and it has been suggested that a traditional DNA sequence-based approach may not fit many common aetiological characteristics seen in complex disorders (Petronis, 2001). These include the relatively high incidence of discordance among monozygotic twins, the comparatively delayed onset, the frequently reported sex effects, and parent-of-origin effects (Petronis, 2001). Further to this, epigenetics provides a mechanism by which the environment may interact with an individual's genetic vulnerability to precipitate MDD, although epigenetics may be an important factor independent of environmental influence. It seems that no study has yet investigated whether depression exhibits parent-of-origin effects, which, if they exist, would increase the rationale for epigenetic investigation. There is some debate regarding the utility of epigenetic study when we are unable to access the tissue of interest (i.e. brain) in living patients. However, establishing whether epigenetic biomarkers exist in peripheral tissues is important; herein lies the potential to identify

individuals at risk of developing MDD and/or identifying new molecular pathways for improved pharmacotherapeutics.

A further avenue that looks promising is research into CNVs in the human genome. In schizophrenia there seems to be an increased burden of deletions (International Schizophrenia Consortium, 2008), which is also observed in autism (Walsh *et al*. 2008) and in bipolar disorder (Zhang *et al*. 2009). In bipolar disorder, however, the findings have been less consistent, with other studies failing to report such evidence for association with CNVs (McQuillin *et al*. 2011). In depression, only one study has investigated CNVs on a genome-wide level and reported evidence for an increase in burden in the MDD cases (Rucker *et al*. 2011). Of particular interest, two control groups were investigated: one psychiatrically screened control group and the other sourced from the general population (the Wellcome Trust Case Control Consortium 2, WTCCC2). The CNV burden was found to be intermediate between the MDD and the psychiatrically screened control group in the general population controls, indicating that less deletions could in fact be an indicator for well-being; however, this requires independent replication. Another genome-wide CNV study supported the implication of CNVs in MDD but did not analyse the data in the same manner as a majority of studies to date that have focused on burden rather then specific CNV association (Glessner *et al*. 2010).

Finally, in all of the SNP studies and the recent GWAS being published, microsatellites have been generally neglected. These markers are valuable in genetic analysis, having a wide range of population ancestries and in some cases a greater reach of LD. Their impact on the genome may present important structural and functional implications beyond those observed for SNPs. Furthermore, studies have focused on common variation, following the common-disorder common-variant hypothesis; it is possible that the levels of variation implicated in MDD might be rarer than originally anticipated and so have been missed by our candidate and GWAS methods. Sequencing has the potential to address both issues of detecting non-SNP variation, and more rare variants.

Conclusions

In summary, large sample sizes (between 2000 and 10 000) and precise phenotypic definitions may be necessary to detect variants with small effect sizes. This issue is being addressed by the work of the PGC, and the results in MDD will soon be published. Data already collected from GWAS can be applied to other approaches that apply more of a systems biology approach, such as gene–gene interactions and pathway analyses. Regions that have been identified either by linkage studies or by GWAS would benefit from targeted deep sequencing to determine whether there is a rare variation that might contribute to MDD risk. The variation identified should then be genotyped again in independent samples that may have a different underlying LD structure, and so may not have initially presented evidence on the basis of the GWAS data. Subphenotyping to reduce heterogeneity within samples also has the potential to yield loci for more specific aspects, or subgroups, of MDD. Environmental measures should be included in future research designs. Greater emphasis should be placed on the precise nature of environmental measures in molecular behavioural genetics, where possible (including their potential epigenetic consequences), to allow the identification of individuals at high environmental risk in addition to high genetic risk. We accept that not every study is able to address every issue, and each research group should identify what it is their samples might best address; some samples are well disposed to gene–environmental study whereas others are better suited to subphenotyping, epigenetic study and/or sequencing. A combination of all these considerations should lead to more holistic, reliable and perhaps replicable data, reflecting the genetic underpinning of depression and informing the design of future sample ascertainments.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291712001286.

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