Velo-cardio-facial syndrome: a model for understanding the genetics and pathogenesis of schizophrenia

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Background Individuals with velo-cardio-facial syndrome (VCFS), a genetic disorder associated with microdeletions of chromosome 22q11, are reported to have high rates of psychiatric disorder, particularly schizophrenia.

Aims To review the evidence for an association between VCFS and schizophrenia: to outline recent neuropsychological, neuroanatomical and genetic studies of individuals with VCFS; and to make recommendations for future work.

Method A selective literature review was undertaken.

Results Individuals with VCFS have high rates of psychotic disorders, particularly schizophrenia. In addition, specific neuropsychological and neuroanatomical abnormalities have been reported although it is unclear whether such abnormalities relate to the presence of psychiatric disorder in affected individuals.

Conclusions Deletion of chromosome 22q11 represents one of the highest known risk factors for the development of schizophrenia. It is likely that haploinsufficiency (reduced gene dosage) of a neurodevelopmental gene or genes mapping to chromosome 22q11, leading to disturbed neuronal migration, underlies susceptibility to psychosis in VCFS.

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Velo-cardio-facial syndrome (VCFS), a syndrome characterised by distinctive dysmorphology, congenital heart disease and learning disabilities, is associated with small interstitial deletions of chromosome 22q11. Previously, we have reported an apparent association between VCFS and major psychiatric disorder, particularly schizophrenia, and suggested that the presence of a cleft lip and/or palate, characteristic dysmorphology, learning disability, congenital heart disease or hypocalcaemia in individuals with schizophrenia or schizoaffective disorder should raise the suspicion of a chromosome 22q11 deletion (Murphy & Owen, 1996*a*). In the 5 years since publication, increasing numbers of previously undetected individuals with VCFS have been identified. In addition, considerable excitement has been generated by the emergence of increased evidence for an association between VCFS and psychosis. The purpose of this article is to: (a) review this evidence; (b) outline recent neuropsychological, neuroanatomical and genetic studies of individuals with VCFS; and (c) make recommendations for future work.

ELEVATED RATES OF PSYCHIATRIC DISORDER IN VCFS

Table 1 summarises the principal studies of the psychiatric phenotype in individuals with VCFS. As the first recognised cohort of children and adolescents with VCFS was followed up into adulthood, high rates of major psychiatric disorder were observed. Shprintzen *et al* (1992) suggested that more than 10% had developed psychiatric disorders that mostly resembled chronic schizophrenia with paranoid delusions, although operational criteria were not used. Subsequently, in a small study of VCFS adults (n=14), 11 (79%) were found to have a psychiatric diagnosis of whom four (29%) had DSM–III–R (American Psychiatric Association, 1987) schizophrenia or schizoaffective disorder (Pulver *et al*, 1994*a*). In a further study of a group of children and adults with VCFS (n=25), Papolos *et al* (1996) reported that four (16%) had psychotic symptoms while 16 (64%) met DSM–III–R criteria for a spectrum of bipolar affective disorders. Interestingly, although no individual had schizophrenia, the two oldest members of this cohort (aged 29 and 34 years) both had schizoaffective disorder.

In the largest study of its kind yet performed, Murphy *et al* (1999) found that 18 (42%) of a sample of 50 adults with VCFS had a major psychiatric disorder; 15 (30%) had a psychotic disorder, with 12 (24%) fulfilling DSM–IV criteria for schizophrenia while a further six (12%) had major depression without psychotic features. The individuals with schizophrenia had fewer negative symptoms and a relatively later age of onset (mean age=26 years) compared to non-deletion controls. Using different ascertainment strategies however, Bassett *et al* (1998) reported a relatively early age of onset (mean age=19 years) in their sample of 10 individuals with VCFS and schizophrenia. This discrepancy is likely to be the result of small sample sizes and differences in ascertainment between these studies. Future work will be required in extended samples to determine whether a clinical subtype of schizophrenia occurs in VCFS and if so, whether such a clinical phenotype is associated with linkage to chromosome 22q11 in individuals with schizophrenia in the wider population.

Numerous studies of individuals with VCFS have reported an association between VCFS and schizophrenia (Karayiorgou *et al*, 1995; Gothelf *et al*, 1997; Bassett *et al*, 1998; Murphy *et al*, 1999; Usiskin *et al*, 1999). However, although replication is required by other groups, Papolos *et al* (1996) suggested that, in addition to increased rates of attention-deficit disorder, the spectrum of severe psychiatric disorder seen in children with VCFS might also extend to include affective disorders such as bipolar disorder. Although longitudinal studies are required to test this hypothesis, it has been suggested that the psychiatric or behavioural phenotype observed in children and adolescents with VCFS might in some cases evolve into schizophrenia or schizoaffective disorder as the children get older (Murphy *et al*, 1999). Alternatively, the high rates of bipolar disorder reported

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Table I Rates of psychiatric disorder in studies of individuals with velo-cardio-facial syndrome (VCFS)

	Individuals with VCFS (*n*)	Age of sample (years)	Psychiatric disorder
Shprintzen *et al* (1992)	>90 children/adults	Unspecified	Chronic paranoid schizophrenia (~10%) (not operationally defined)
Pulver *et al* (1994*a*)	14 adults	17–41	Schizophrenia or schizoaffective disorder (29%)
Papolos *et al* (1996)	15 children/adolescents	5–16	Bipolar II disorder (47%), attention-deficit hyperactivity disorder (27%), attention-deficit disorder without hyperactivity (13%)
	10 adults	17–34	Psychosis (40%), schizoaffective disorder (20%), bipolar type I disorder (30%), bipolar type II disorder (30%)
Murphy *et al* (1999)	50 adults	17–52	Psychosis (30%), schizophrenia or schizoaffective disorder (26%), bipolar disorder (2%), psychosis not otherwise specified (2%), major depressive disorder (12%)

in children with VCFS may suggest that a more specific association exists between bipolar disorder and VCFS – and this has received some support from recent genetic evidence reviewed below.

Learning disability is a recognised, but by no means invariable, component of the VCFS phenotype. In addition, in a large series of individuals with learning disability, Murphy *et al* (1998) reported that 12% of people with mild learning disability were found to have a chromosome 22q11 deletion. This raises the question of whether the high prevalence of schizophrenia in VCFS simply reflects a non-specific association with learning disability. This appears unlikely as it is generally estimated that the prevalence of schizophrenia in people with learning disability is only 3% (Fraser & Nolan, 1994) compared with a prevalence of 24% reported in VCFS (Murphy *et al*, 1999). In addition, Murphy *et al* found no correlation between the presence of psychosis and the degree of intellectual impairment; the mean IQ of individuals with VCFS and schizophrenia was in the non-learning-disability range (Murphy *et al*, 1999). Moreover, genetic evidence reviewed below implicating 22q11 in psychosis in individuals without VCFS also suggests a more specific relationship.

What is the true prevalence of schizophrenia in VCFS? Although we have reported that 12 (24%) out of 50 adults with VCFS fulfilled DSM–IV criteria for schizophrenia, 80% were younger than 40 years of age and are therefore still within the age of risk (Murphy *et al*, 1999). In addition, there is an ascertainment bias implicit in any study of adults with VCFS, as they will have been selected for a less severe phenotype because they have survived into adulthood. If this is so, the true lifetime prevalence of schizophrenia in VCFS may be considerably higher than the 24% reported in this study. Consequently, longitudinal studies of children with VCFS are required to determine the true lifetime prevalence of schizophrenia in individuals with VCFS.

A major goal of schizophrenia research over the past three decades has been the identification of precursor symptoms and areas of dysfunction in children and adolescents which precede the later development of schizophrenia. The high-risk method was developed to assess early social, psychological and biological characteristics in individuals with higher than average risk of psychiatric disorders such as schizophrenia before the onset of psychopathology, using a prospective, longitudinal research design. Several high-risk studies of children and adolescents have been performed and the majority selected children who are the offspring of parents with schizophrenia as their patient cohort (Erlenmeyer-Kimling *et al*, 1991; Cannon & Mednick, 1993). Children with VCFS offer a unique opportunity to perform a novel high-risk study of schizophrenia susceptibility. In view of this, longitudinal studies of children with VCFS are also required to identify precursor symptoms and areas of dysfunction which precede the later development of schizophrenia in individuals with VCFS. Identification of such prodromal features in VCFS may have enormous implications for the clinical management of individuals with schizophrenia, with or without VCFS.

NEUROPSYCHOLOGICAL ABNORMALITIES IN VCFS

Early reports of children with VCFS described language abnormalities, including immature language usage, poor development of numeric skills and significant impairments in reading and spelling (Golding-Kushner *et al*, 1985; Goldberg *et al*, 1993). In a study of 37 children with VCFS, Swillen *et al* (1997) reported a wide variability in IQ, ranging from moderate learning disability to average IQ with a mean full-scale IQ (FSIQ) of approximately 70. Forty-five per cent of individuals (n=17) had a learning disability, in the majority (82%) of whom it was mild. Similarly, Moss *et al* (1999) reported that the mean FSIQ of their sample of 33 children and adults was 71, with 17 (52%) of their sample demonstrating learning disability. There were no differences in mean FSIQ measures between children with congenital heart disease or palate anomalies compared to those without. However, VCFS individuals with a familial deletion were found to have a lower mean FSIQ than individuals with a *de novo* deletion (Swillen *et al*, 1997; Gerdes *et al*, 1999).

A specific neuropsychological profile has also been described in children with VCFS with verbal IQ exceeding performance IQ on tests of general intellectual functioning (Moss *et al*, 1995, 1999; Swillen *et al*, 1997, 2000). This discrepancy may relate to difficulties in planning ability, visuospatial ability and non-verbal reasoning in addition to deficits in novel reasoning and concept formation (Moss *et al*, 1999). Unfortunately, these studies have been limited by small sample size and the absence of appropriately matched control groups. Consequently, it is unclear whether these findings are specific to VCFS or whether they simply reflect deficits associated with lower levels of intellectual ability. In addition, it is unclear whether such findings are specific to VCFS children or whether they persist into adulthood. Future

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work with VCFS children and adults using appropriately matched controls will be required to address these questions.

While studies which have examined neuropsychological impairments in individuals with schizophrenia have generally reported a lack of specificity (Blanchard & Neale, 1994), impairments of language, attention, memory and executive function have repeatedly been described (Hoff *et al*, 1992; Jones *et al*, 1994; Elliott & Sahakian, 1995; Elliott *et al*, 1995; Bilder, 1996; Heinrichs & Zakzanis, 1998). Similar neuropsychological impairments have also been reported in the relatives of individuals with schizophrenia (Faraone *et al*, 1995; Byrne *et al*, 1999). It is unclear whether similar neuropsychological deficits are observed in VCFS or whether they are associated with or predict the later development of schizophrenia or other major psychiatric disorder in these individuals, and future work will need to address these issues.

Sensorimotor gating abnormalities, including defects in prepulse inhibition, have also been described in individuals with schizophrenia (Ellenbroek & Cools, 1990). Such objectively measured abnormalities hold great promise as they can be measured in both humans and animals. A mouse model deleted for the syntenic region of mouse chromosome 16 that corresponds to human chromosome 22q11 has now been produced with congenital cardiac abnormalities similar to those observed in VCFS (Lindsay *et al*, 1999). Such animals should be investigated closely for neuroanatomical and behavioural phenotypes of possible relevance to schizophrenia. Recently, a mutation of the proline dehydrogenase gene, which maps to the syntenic region of mouse chromosome 16 and is a candidate gene for schizophrenia, resulted in sensorimotor gating deficits in mice (Gogos *et al*, 1999).

BRAIN STRUCTURAL ABNORMALITIES IN VCFS

Although it is now widely recognised that individuals with VCFS have severe neuropsychological deficits with high rates of major psychiatric disorder, until recently, little was known about the neurobiology underlying these abnormalities. Most structural neuroimaging studies of VCFS individuals have been qualitative and report the presence of a small cerebellum (36%), white matter hyperintensities (27–90%) and developmental midline anomalies such as cavum septum pellucidum/vergae (40–45%) (Mitnick *et al*, 1994; Chow *et al*, 1999; van Amelsvoort *et al*, 2001). The few quantitative neuroimaging studies that have been performed report relatively reduced volumes of total brain, left parietal lobe grey matter and right cerebellar white matter but increased volumes of both frontal lobes and mid-sagittal corpus callosum areas and enlarged Sylvian fissures (Bingham *et al*, 1997; Usiskin *et al*, 1999; Eliez *et al*, 2000). Unfortunately, these studies have been limited by small sample sizes, the absence of appropriately IQ-matched control groups and their inclusion only of children with VCFS. Recently, however, in a quantitative neuroimaging study of adults with VCFS, van Amelsvoort *et al* (2001) reported that, compared with an age- and IQ-matched control group, adults with VCFS exhibited widespread differences in white matter bilaterally and regional specific differences in grey matter in the left cerebellum, insula, frontal and right temporal lobes.

Numerous structural neuroimaging studies of individuals with schizophrenia have reported enlarged ventricles, reduced total brain volume (particularly grey matter reduction) and midline brain abnormalities, including cavum septum pellucidum and a hypoplastic vermis (Lewis & Mezey, 1985; Martin & Albers, 1995; Ward *et al*, 1996; Lawrie & Abukmeil, 1998), abnormalities which are also present in individuals with VCFS (Mitnick *et al*, 1994; Lynch *et al*, 1995; Vataja & Elomaa, 1998; Chow *et al*, 1999; van Amelsvoort *et al*, 2001). However, it remains unclear whether these brain structural abnormalities reported in individuals with VCFS relate to the neuropsychological deficits or major psychiatric disorder observed in such individuals, and future studies will need to address this.

CHROMOSOME 22 AND PSYCHOSIS

Evidence from family, twin and adoption studies demonstrates a major genetic contribution to the aetiology of psychotic disorders such as schizophrenia (McGuffin *et al*, 1994). The high rates of psychosis (especially schizophrenia) in VCFS suggest that, with the exception of being the offspring of a dual mating or the monozygotic co-twin of an affected individual, deletion of chromosome 22q11 represents the highest known risk factor for the development of schizophrenia identified to date.

There are also several other lines of evidence to suggest that a locus conferring susceptibility to schizophrenia resides on chromosome 22q. Karayiorgou *et al* (1995) have reported that two of 100 individuals with schizophrenia recruited from a large-scale epidemiological sample were found to have a previously undetected 22q11 deletion. In addition, when individuals with schizophrenia have been selected for the presence of clinical features consistent with VCFS, 22q11 deletions have been identified in 20–59% of cases (Gothelf *et al*, 1997; Bassett *et al*, 1998). Furthermore, results from linkage studies of individuals with schizophrenia provide supportive evidence for a susceptibility locus on 22q although, in common with other chromosomal regions suggestive of linkage, replication has been inconsistent. While markers telomeric to the VCFS region have been implicated in some of these studies (Pulver *et al*, 1994*b*; Schizophrenia Collaborative Linkage Group, 1996), several groups have also reported evidence for linkage to markers close to the VCFS region both for schizophrenia itself (Lasseter *et al*, 1995; Blouin *et al*, 1998; Shaw *et al*, 1998) and for an inhibitory neurophysiological phenotype associated with schizophrenia (Myles Worsley *et al*, 1999).

Linkage studies of individuals with bipolar disorder have also provided supportive evidence for a susceptibility locus on 22q. Although markers telomeric to the VCFS region have been implicated (Kelsoe *et al*, 1998), the same region where most of the positive results in schizophrenia were reported, Kelsoe *et al* (1999) have also reported evidence for linkage to the VCFS region. Such findings suggest that: (a) a susceptibility locus on 22q11 might predispose to both schizophrenia and bipolar disorder; or (b) two susceptibility loci might map to chromosome 22q11, one predisposing to schizophrenia and the other predisposing to bipolar disorder.

The strong association between schizophrenia and VCFS suggests that a gene or genes mapping to chromosome 22q11 may play a role in the aetiology of both disorders. If this is so, what is the common pathogenetic mechanism? There is compelling evidence that a defect in early embryonic development is the cause of many of the abnormalities present in individuals with

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VCFS. The importance of cephalic neural-crest-derived cells in the development of the conotruncal region of the heart, the thymus, the parathyroid glands and the palate, all structures that are affected in VCFS, has been demonstrated by micro-ablation and transplantation studies in avian embryos (Le Dourain *et al*, 1993). On the basis of these observations, it is therefore reasonable to hypothesise that a gene or gene located within the 22q11 deleted region is involved in the process of neuronal migration or differentiation in the pharyngeal arches and that haplo-insufficiency (reduced gene dosage) of such a gene or genes disrupts proper development of these systems, leading to multiple organ and tissue abnormalities.

SCHIZOPHRENIA IN VCFS – NEURODEVELOPMENTAL OR NEUROCHEMICAL?

What is the evidence that schizophrenia *per se* is associated with abnormal early brain development? First, as discussed earlier, neuroimaging studies of people with schizophrenia have repeatedly demonstrated ventricular enlargement with decreased cerebral (particularly cortical and hippocampal) volume (Lawrie & Abukmeil, 1998; Harrison, 1999). Second, post-mortem studies report a relative absence of gliosis, suggesting that schizophrenia may be neurodevelopmental rather than neurodegenerative in origin (Harrison, 1997, 1999). Third, cytoarchitectural abnormalities such as neuronal disarray, heterotopias and malpositioning are suggestive of aberrant neuronal migration (Kovelman & Scheibel, 1984; Jakob & Beckmann, 1986; Arnold *et al*, 1991; Akbarian *et al*, 1993) although none of these cytoarchitectural abnormalities has been unequivocally established to be a feature of schizophrenia (Harrison, 1999). Fourth, several studies have indicated that 'minor physical anomalies' (MPAs) occur in excess in people with schizophrenia. MPAs are slight anatomical defects of the head, hair, eyes and mouth and are usually attributed to disturbed neurodevelopment during the first or second trimester of foetal life. While a high arched palate is one of the most consistent findings (Clouston, 1891; Green *et al*, 1989; Lane *et al*, 1996), until recently the topography of MPAs in schizophrenia was poorly understood (Murphy & Owen, 1996*b*). Using an anthropometric approach, several more recent studies have reported multiple quantitative and qualitative abnormalities of craniofacial and other structures in individuals with schizophrenia. Lane *et al* (1997) reported a core topography of dysmorphology characterised primarily by an overall narrowing and elongation of the mid and lower anterior facial region, in terms of heightening of the palate and reduced mouth width, with widening of the skull base and extensive abnormalities of the mouth, ears and eyes. In addition, Deutsch *et al* (1997) identified a similar topography of frontonasal dysmorphology in schizophrenia. It is interesting to observe that these abnormalities are reminiscent of the craniofacial abnormalities characterising individuals with VCFS. This observation leads to two further hypotheses: (a) the increased rates of MPAs reported in studies of people with schizophrenia may reflect in part the contribution of undetected VCFS; and (b) VCFS and schizophrenia may both be associated with similar mechanisms disrupting neuronal migration.

Although schizophrenia is increasingly seen as a neurodevelopmental disorder, disturbances in catecholamine neurotransmission have also long been postulated to play a key aetiological role. Consequently, the gene coding for catechol-*O*-methyltransferase (COMT), an enzyme catalysing the *O*-methylation of catecholamine neurotransmitters (dopamine, adrenaline and noradrenaline), has been considered a candidate gene for the aetiology of schizophrenia. The gene coding for COMT maps to the region of chromosome 22q11 frequently deleted in VCFS and is therefore an outstanding candidate gene for the high rates of schizophrenia seen in VCFS individuals. As an amino acid polymorphism (Val-108-Met) of this gene determines high and low activity of COMT, Dunham *et al* (1992) postulated that individuals hemizygous for COMT and carrying a low-activity allele on their non-deleted chromosome may be predisposed to the development of schizophrenia by a resulting increase in brain dopamine levels. However, we found no evidence that possession of the low-activity COMT allele was associated with the presence of schizophrenia in a series of VCFS individuals (Murphy *et al*, 1999). Consequently, although a minor effect for genetic variation in COMT cannot be excluded, it does not appear that the COMT gene exerts a major effect in the development of schizophrenia in individuals with VCFS.

Thus, a review of the current evidence provides support for a neurodevelopmental model of schizophrenia in VCFS. In view of this, it is likely that haploinsufficiency of a neurodevelopmental gene or genes mapping to chromosome 22q11, leading to disturbed neuronal migration, underlies susceptibility to the high rates of schizophrenia reported in VCFS. However, it is also possible that the COMT gene or other genes mapping to chromosome 22q11 (or elsewhere) may act as modifiers in the production of the psychotic phenotype seen in VCFS. As increasing numbers of neurodevelopmental and other candidate genes mapping to chromosome 22q11 are identified (Gogos *et al*, 1999; Yamagishi *et al*, 1999), future work is required to determine the possible relevance of such genes to the development of schizophrenia in VCFS individuals.

IMPLICATIONS FOR THE AETIOLOGY OF SCHIZOPHRENIA IN THE WIDER POPULATION

While deletion of chromosome 22q11 may account for only a small proportion of risk for the development of schizophrenia in the general population, non-deletion mutations or polymorphisms of genes within the VCFS region may make a more general and widespread contribution to susceptibility to schizophrenia in the wider population. Experience with other complex diseases (e.g. Alzheimer's disease, diabetes and breast cancer) suggests that understanding the molecular basis for uncommon subtypes with high penetrance has been shown to be the most successful approach to understanding the genetics and underlying pathophysiology of complex diseases. As the entire sequence of chromosome 22 has now been determined, the future identification of the genetic determinants of the psychiatric, neuropsychological and neuroanatomical phenotypes in individuals with VCFS will have profound implications for our understanding of the molecular genetics and pathogenesis of psychosis in the wider population.

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CLINICAL IMPLICATIONS

- Velo-cardio-facial syndrome (VCFS) provides a useful model for understanding the genetics and pathogenesis of schizophrenia.
- Identification of the genetic determinants underlying the high rates of psychotic disorders in individuals with VCFS may have important implications for the classification and treatment of psychotic disorders in the general population.
- Chromosome 22q11 studies should be requested in individuals with psychotic disorder or learning disability who present with a history of cleft palate/lip, characteristic dysmorphology, congenital heart disease or hypocalcaemia.

LIMITATIONS

- There is only a relatively small number of published studies about VCFS.
- Deletion of chromosome 22q11 may account for only a small proportion of risk for the development of schizophrenia in the general population.
- It remains unclear whether the neuropsychological or neuroanatomical abnormalities reported in VCFS relate to the presence of psychiatric disorder in affected individuals.

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