High Rates of Schizophrenia in Adults With Velo-Cardio-Facial Syndrome

Kieran C. Murphy, MB, MRCPsych; Lisa A. Jones, PhD; Michael J. Owen, MB, PhD, FRCPsych

**Background:** Velo-cardio-facial syndrome (VCFS), a syndrome characterized by an increased frequency of schizophrenia and bipolar disorder, is associated with small interstitial deletions of chromosome 22q11.

**Methods:** We evaluated 50 adults with VCFS using a structured clinical interview (Schedules for Clinical Assessment in Neuropsychiatry or Psychiatric Assessment Schedule for Adults With Developmental Disability if IQ <50) to establish a DSM-IV diagnosis. The schizophrenia phenotype in individuals with VCFS and schizophrenia was compared with a matched series of individuals with schizophrenia and without VCFS (n = 12). The King’s Schizotypy Questionnaire was administered to individuals with VCFS (n = 41), their first-degree relatives (n = 68), and a series of unrelated normal controls (n = 316). All individuals with VCFS deleted for the N25 probe (n = 48) were genotyped for a genetic polymorphism in the COMT gene that results in variations in enzymatic activity.

**Results:** Fifteen individuals with VCFS (30%) had a psychotic disorder, with 24% (n = 12) fulfilling DSM-IV criteria for schizophrenia. In addition, 6 (12%) had major depression without psychotic features. The individuals with schizophrenia had fewer negative symptoms and a relatively later age of onset compared with those with schizophrenia and without VCFS. We found no evidence that possession of the low-activity COMT allele was associated with schizophrenia in our sample of individuals with VCFS.

**Conclusions:** The high prevalence of schizophrenia in this group suggests that chromosome 22q11 might harbor a gene or genes relevant to the etiology of schizophrenia in the wider population.

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**Velo-cardio-facial syndrome (VCFS),** also known as DiGeorge or Shprintzen syndrome, is associated with small interstitial deletions of chromosome 22q11 in 80% to 85% of individuals. It was first described by Shprintzen et al and has an estimated prevalence of 1 in 4000 births. The syndrome is characterized by distinctive dysmorphology, congenital heart disease, and learning disabilities, although considerable phenotypic variability occurs. This phenotypic variability is further confounded by many published series reporting varying rates of major features, which may reflect different ascertainment strategies. As many of the tissues and organ systems affected in VCFS are embryologically derived from neural crest cells, it has been suggested that disturbed neural crest cell migration may play a significant role in the pathogenesis of the cardiac, facial, and psychiatric phenotypes in individuals with VCFS.

As the first recognized cohort of children with VCFS was followed up into adolescence and early adulthood, evidence began to accumulate for a high prevalence of major psychiatric disorders in these individuals. Early reports suggested that more than 10% had developed psychiatric disorders that mostly resembled chronic schizophrenia with paranoid delusions, although operational criteria were not used. In a follow-up study of adults (aged ≥17 years) using DSM-III-R criteria, Pulver et al reported that 11 (79%) of their sample of 14 patients were given a psychiatric diagnosis: 29% had schizophrenia (22%) or schizoaffective disorder (7%), 29% had simple or social phobia, 21% had depression, and 14% had obsessive-compulsive disorder.

Disturbances in dopamine neurotransmission have long been postulated to play a key role in the etiology of psychotic disorders, particularly schizophrenia. The gene for catechol-O-methyltransferase (COMT), an enzyme involved in the degradation of dopamine, maps to the region of chromosome 22q11 deleted in...
SUBJECTS AND METHODS

SUBJECTS AND CONTROLS

Fifty adults with VCFS aged 17 years and older were identified and enrolled in this study. All individuals were referred to their local department of medical genetics and a clinical diagnosis of VCFS was made in all cases by a clinical geneticist. Of the 50 individuals recruited, 48 were shown to have a chromosome 22q11 deletion using fluorescence in situ hybridization with the N25 probe (Oncor Inc, Gaithersburg, Md). Patients with VCFS who did not demonstrate a deletion with the N25 probe may carry a different small deletion on 22q11, a point mutation in a critical gene on 22q11, a deletion or mutation in another chromosomal region, or they may be “phenocopies,” whose disease has a nongenetic etiology. All individuals were white and were born in the United Kingdom. Of these, 34 (68%) were recruited from numerous departments of medical genetics throughout England and Wales. Five (10%) were recruited from the VCFS Support Group in the United Kingdom, 6 (12%) were recruited from psychiatric services, 4 (8%) were recruited from the local cardiology department, and 1 (2%) was self-referred to the study. Some clinical information on 2 of the individuals with VCFS recruited from an institution for the mentally retarded has recently been reported. After a complete description of the study, written informed consent was obtained from all subjects or their nearest relatives. Social and demographic information was obtained from subjects or their relatives at interview. Subjects’ IQ was assessed using the Quick Test.

Individuals with VCFS and schizophrenia (SZ/VCFS group) were compared with a control group of unrelated individuals with schizophrenia (SZ group) who were shown not to have a chromosome 22q11 deletion using the N25 probe. Using similar methods on a lifetime-worst basis as described elsewhere, data were obtained from subjects who had previously been recruited from inpatient and day hospital facilities throughout the United Kingdom for a genetic study of schizophrenia. One of us (K.C.M.) was a member of the clinical assessment team for this earlier study. Controls were white and were individually matched for age (±1 year), sex, marital status, and reproductive status with the SZ/VCFS group on a case-by-case basis. The SZ control group comprised 8 women and 4 men with a mean age of 34 years (SD = 12 years). Five (42%) had been married or had lived as married and 5 (42%) had had children. A further series of unrelated normal controls (n = 316) was recruited from a local branch of the National Blood Transfusion Service. All were white and the group comprised 140 women and 176 men with a mean age of 40 years (SD = 12 years).

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MEASURES OF PSYCHOPATHOLOGY

Diagnoses were based on all available clinical information including in every case a semistructured interview (Schedules for Clinical Assessment in Neuropsychiatry or Psychiatric Assessment Schedule for Adults with Developmental Disability if IQ < 30 [n = 2]), examination of all appropriate case records, and information from relatives and mental health professionals. All interviews were performed by one of us (K.C.M.) and data were compiled into case vignettes for each individual. These case vignettes were used to generate consensus DSM-IV diagnoses by 2 other raters (L.A.J. and M.J.O.) who were blind to the deletion status of the sample. Age of illness onset was defined as the earliest age at which medical advice was sought for psychiatric reasons. Where a diagnosis of schizophrenia was made (SZ/VCFS group), the versions of the Schedules for the Assessment of Positive (SAPS) and Negative (SANS) Symptoms incorporated into the Diagnostic Interview for Genetic Studies and the Global Assessment Scale were completed for each individual on a lifetime-worst basis from all available clinical information.

The versions of SAPS and SANS and the Global Assessment Scale were also administered to a control group of unrelated individuals with schizophrenia without VCFS (SZ group).

The 63-item King’s Schizotypy Questionnaire, which measures schizotypal personality disorder by giving a quantitative score for schizotypal traits, was administered to individuals with VCFS, their first-degree relatives, and a series of unrelated normal controls. The questions, requiring either a positive or negative reply, were posed to the individual and a score calculated. The King’s Schizotypy Questionnaire has been shown to have high internal consistency, test-retest reliability, and convergent validity compared with other questionnaire methods.

GENETIC ANALYSES

High-molecular-weight DNA from all individuals with VCFS deleted for the N25 probe (n = 48) was isolated from lymphocytes by routine procedures. The polymerase chain reaction assay used has been described previously and identifies an NlaIII polymorphism, the restriction endonuclease site being present in the low-activity COMT allele and absent in the high-activity COMT allele. Individual genotypes were read by 2 independent raters who were unaware of the subjects’ clinical status.

STATISTICAL ANALYSES

We used 2-tailed tests of significance (at an α level of .05) for all comparisons. We also calculated χ² statistics using the Fisher exact test when cell sizes were small. Analyses of variance were performed for the schizotypy scores of individuals with VCFS, their first-degree relatives, and controls. Post hoc testing was then performed using the Tukey honestly significant difference procedure, which corrects for multiple comparisons.

VCFS. An amino acid polymorphism (Val-108-Met) determines high and low activity of this enzyme. Dunham et al have hypothesized that individuals hemizygous for COMT and carrying a low-activity allele on their nondeleted chromosome may be predisposed to the development of psychosis by a resulting increase in brain dopamine levels.

In view of previous reports of a high prevalence of psychosis in VCFS, we undertook the present study to characterize the psychiatric phenotype in the largest interviewed series to date of adults with VCFS. In addition, we tested the following hypotheses: (1) a clinical subtype of schizophrenia occurs in VCFS compared with a matched series of individuals with schizophrenia with-
out VCFS; (2) the presence of schizophrenia is associated with lower IQ, presence of congenital heart disease, or presence of cleft palate in persons with VCFS; (3) individuals with VCFS have higher rates of schizotypal personality traits as compared with their first-degree relatives and unrelated normal controls; and (4) hemizygosity for the low-activity \( COMT \) allele is associated with psychosis in individuals with VCFS.

### RESULTS

#### SOCIAL AND DEMOGRAPHIC DATA

Results are summarized in Table 1. The VCFS sample consisted of 50 individuals. Forty (80%) were younger than 40 years and 9 (18%) were younger than 20 years. Sixteen subjects (33%) had mental retardation (IQ <70), 19 (40%) had borderline retardation (IQ 71–85), and 13 (27%) had normal IQ (IQ >85). Of those with an IQ less than 70, the majority (n = 13) had mild mental retardation (IQ 50–70), while only 2 patients had moderate mental retardation (IQ <50). Two subjects with VCFS were unwilling to participate in IQ assessment.

Although more detailed characteristics of the physical phenotype will be described elsewhere, information on cleft palate and congenital heart disease is summarized in Table 1. There was no association between the presence of a cardiac defect (\( \chi^2 = 0.48, P = .50 \)) or cleft palate (Fisher exact test, \( P = .06 \)) and schizophrenia.

Twenty-seven subjects (54%) had had children, and women (n = 23) were significantly more likely to have reproduced than men (n = 4) (Fisher exact test, \( P = .01 \)). Individuals with VCFS ascertained by having an affected child were significantly older (mean age = 36 years, SD = 8 years) than those ascertained by other strategies (mean age = 25 years, SD = 10 years) (t\(_{46} = -4.19, P < .001 \)) and were also significantly more likely to be female (85% vs 54%) (\( \chi^2 = 5.50, P = .02 \)). However, there were no significant differences in IQ (\( t_{46} = 1.53, P = .10 \)) between these groups.

#### PSYCHIATRIC DIAGNOSIS

Twenty-one individuals (42%) with VCFS had a history of major psychiatric disorder and of these 15 (30% of the total sample) had a history of psychosis. Twelve (24%) satisfied DSM-IV criteria for schizophrenia, 1 (2%) had DSM-IV schizoaffective disorder (bipolar), 1 (2%) had DSM-IV bipolar disorder (rapid cycling), and 1 (2%) had DSM-IV psychosis not otherwise specified. In addition, 6 (12%) had DSM-IV major depressive disorder without psychotic features and of these 3 had recurrent depressive episodes and 2 were currently prescribed antidepressants. No individual fulfilled DSM-IV criteria for current major depressive episode at interview. Three subjects (6%) had DSM-IV minor depressive disorder. Twelve (24%) were prescribed neuroleptics and 5 (10%) were prescribed antide-
pressants at the time of the interview. Of the 21 subjects with VCFS and major psychiatric disorder, all except 1 (with major depressive disorder) were deleted for the N25 probe.

**INDIVIDUALS WITH VCFS AND PSYCHOSIS**

Fifteen patients (30%) had a history of psychosis (Table 1). The age of onset of psychosis ranged from 15 to 46 years with a mean age of 26 years (SD = 10 years). Eight subjects (53%) were ascertained from departments of medical genetics, 6 (40%) from departments of psychiatry, and 1 (7%) from the VCFS support group. There were no significant differences in age, sex, IQ between individuals with VCFS with or without psychosis (Table 1).

**INDIVIDUALS WITH VCFS AND SCHIZOPHRENIA**

We examined the 12 patients with both schizophrenia and VCFS (SZ/VCFS group) in an attempt to further characterize the nature of the schizophrenia phenotype in these individuals. The SZ/VCFS group comprised 8 women and 4 men with a mean age of 34 years (SD = 12 years). Five (42%) of the 12 individuals had been married or had lived as married and 5 (42%) had had children. The IQ of the SZ/VCFS group ranged from 56 to 90, with a mean IQ of 80 (SD = 9 years; 95% confidence interval [CI], 70-90 years). Analysis of variance (ANOVA) was performed that revealed highly significant differences in mean schizotypy scores between subjects with VCFS with and without psychosis, their first-degree relatives, and controls (F4,420 = 13.6, P < .001 (Table 2). Post hoc testing (Tukey honestly significant difference) showed significant differences between the mean schizotypy scores of VCFS patients with psychosis, VCFS patients without psychosis, and controls (P < .05).

**SCHIZOTYPY**

The King’s Schizotypy Questionnaire was administered to 41 adults with VCFS, 68 of their first-degree relatives (48 parents, 16 siblings, and 4 children) and 316 controls. Nine individuals with VCFS (including 6 with psychosis) were unable to complete the questionnaire because of mental retardation (n = 5), severe mental illness (n = 3), or refusal (n = 1). Analyses of variance (ANOVA) were performed that revealed highly significant differences in mean schizotypy scores between subjects with VCFS with and without psychosis, their first-degree relatives, and controls (F1,312 = 13.6, P < .001) (Table 2). Post hoc testing (Tukey honestly significant difference) showed significant differences between the mean schizotypy scores of VCFS patients with psychosis, VCFS patients without psychosis, and controls (P < .05).

**COMT GENE**

No significant differences were found between allelic distributions of the COMT NlaIII polymorphism in VCFS individuals with and without psychosis (Fisher exact test, P = .70). In addition, we found no correlation between allelic distribution and schizotypy scores of all individuals with VCFS (t31 = 0.7, P = .50).

**COMMENT**

The most important observations of this study, the largest of its kind yet performed, were the high rates of psychotic illness (especially schizophrenia) and schizotypy found in individuals with VCFS.

There are several possible explanations for the high rates of psychosis observed in this study. First, it is well-recognized that published rates of major features of VCFS may vary with different ascertainment strategies. Consequences, the high prevalence of psychosis in this sample could be a result of ascertainment bias, as referrals from psychiatric services may have artificially inflated the preva-

| Table 2. Mean Schizotypy Scores of Subjects With VCFS, Their First-Degree Relatives, and Controls* |
|-----------------|-----------------|-----------------|-----------------|
| **No. of Subjects** | **Mean (SD)** | **Sex, M/F** | **Mean (SD)** |
| VCFS with psychosis | 9 | 35 (12) | 2/7 | 29.4 (9.2) |
| VCFS without psychosis | 32 | 30 (9) | 7/25 | 17.6 (9.2) |
| VCFS without major psychiatric disorder | 26 | 29 (10) | 7/19 | 16.3 (9.3) |
| First-degree relatives with psychosis | 21 | 48 (13) | 13/8 | 10.2 (8.2) |
| First-degree relatives without psychosis | 47 | 51 (15) | 17/30 | 11.3 (6.8) |
| First-degree relatives without major psychiatric disorder | 44 | 50 (14) | 16/28 | 11.4 (6.6) |
| Controls | 316 | 40 (12) | 176/140 | 11.6 (8.5) |

*VCFS indicates velo-cardio-facial syndrome; KSQ, King’s Schizotypy Questionnaire.
†P < .05.

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ence of psychiatric disorder in the sample as a whole. Of the subjects with VCFS and psychosis, 6 were referred by psychiatric services. However, excluding these from the sample reveals a prevalence of psychosis of 18%, which remains much higher than expected.

Second, as 16 (33%) of individuals with VCFS in this sample had (predominantly mild) mental retardation, the high prevalence of schizophrenia observed might reflect a nonspecific association with mental retardation. However, as it is generally estimated that the prevalence of schizophrenia in those with mental retardation is 3%\(^2\) compared with a risk in the general population of 1%, this alone does not adequately explain the high prevalence of schizophrenia (24%) seen in this sample.

Third, the high prevalence of psychosis might result from hemizygosity for a gene or genes at chromosome 22q11. Several researchers favor the view that schizophrenia is a neurodevelopmental disorder, associated with a defect in early brain development in a significant proportion of cases.\(^5\) In VCFS, defective development and migration of mesencephalic and cardiac neural crest cells are believed to play a significant role in the pathogenesis of midfacial and cardiac abnormalities.\(^5\) Consequently, it has been postulated that a gene or genes causing disruption of neural cell migration may be a common neurodevelopmental mechanism for both VCFS and schizophrenia.\(^8\)

How important is chromosome 22q in the etiology of schizophrenia as a whole? Karayiorgou et al.\(^30\) reported that 2 of 100 randomly ascertained individuals with schizophrenia were found to have a 22q11 deletion. In addition, when subjects with schizophrenia have been selected for the presence of clinical features consistent with VCFS, 22q11 deletions have been identified in 20% to 59% of cases.\(^31,32\) These findings suggest that a small proportion of cases of schizophrenia may result from deletions of 22q11. Results of linkage studies also provide supportive evidence for a schizophrenia susceptibility locus on 22q. Although markers telomeric to the VCFS region have been implicated in most of these studies,\(^33-34\) several groups have also reported modest evidence for linkage in the VCFS region.\(^35-37\)

We found that individuals with VCFS and schizophrenia in our sample seemed to show significantly fewer negative symptoms and had a significantly later age of onset compared with controls. Using different ascertainment strategies, however, Bassett et al.\(^37\) reported that their sample of subjects with VCFS and schizophrenia (n = 10) had a mean age of onset of 19 years. It could therefore be argued that our findings of an apparent mild clinical subtype of schizophrenia in VCFS might reflect the fact that we have recruited a highly functioning subset of subjects with VCFS (with fewer negative features), as 52% were ascertained on the basis of having affected children. As reproductive fitness is significantly reduced in schizophrenia,\(^38\) patients with more severe schizophrenic illnesses might not have been recruited as they might have been less likely to have reproduced. However, as both the SZ/VCFS and SZ groups had equal distributions of marital status and reproduction rates, this alone does not adequately explain the apparent mild clinical subtype observed in this study.

We found that individuals with VCFS and psychosis had the highest schizotypy scores while those without psychosis had intermediate schizotypy scores compared with controls. This suggests that while deletion of 22q11 predisposes to psychosis, other genetic or environmental factors are required if psychosis is to develop. In addition, some of the VCFS patients with high schizotypy scores might develop psychosis in the future, as 80% were younger than 40 years and are therefore still within the age of risk. If this is the case, the true lifetime prevalence of psychosis in VCFS may be considerably higher than the 30% observed in the present study.

We were unable to replicate the findings of Papolos et al.\(^3\) of a high prevalence of bipolar spectrum disorders in VCFS. However, social withdrawal and affective disorder are features that often precede the onset of psychosis in schizophrenia.\(^39\) We suggest that the psychiatric phenotype observed in children and adolescents with VCFS (containing prominent affective symptoms) may in some cases evolve into schizophrenia or schizoaffective disorder as the children get older and we recommend that prospective studies should be performed to test this hypothesis.

While we and others have previously found no evidence for an association between COMT genotype and schizophrenia,\(^25,40,41\) we also found no association between the low-activity COMT allele and schizophrenia or schizotypy score in our series of individuals with VCFS. However, although we know of no individuals with interstitial deletions of 22q11 who have not been included in the COMT cohort, it is theoretically possible that some individuals rated as hemizygous may in fact be homozygous for the COMT allele. In addition, the power of our sample to detect a moderate allelic association (odds ratio = 20) at an α level of .05 was 0.71, suggesting that we are unable to exclude a minor effect for the genetic variation in COMT in the development of schizophrenia in VCFS.

While we provide preliminary evidence for a clinical subtype of schizophrenia in VCFS, we suggest that these results must be interpreted with caution owing to possible ascertainment bias and small sample sizes. Future work in an extended sample will be required to determine whether a clinical subtype of schizophrenia occurs in VCFS and, if so, whether it is associated with linkage to chromosome 22q11 in individuals with schizophrenia in the wider population.

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Corresponding author: Kieran C. Murphy, MB, MRCPsych, Department of Psychological Medicine, Institute of Psychiatry, DeCrespigny Park, Denmark Hill, London SE5 8AF, England (e-mail: k.murphy@iop.kcl.ac.uk).


