

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

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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.¹ It was first described by Shprintzen et al² and has an estimated prevalence of 1 in 4000 births.³

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.⁴ As many of the tissues and organ systems affected in VCFS are embryologically derived from neural crest cells,⁵ 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.⁶

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 in-

dividuals. 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.⁷ In a follow-up study of adults (aged ≥ 17 years) using *DSM-III-R* criteria, Pulver et al⁸ 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. More recently, Papolos et al³ reported that 4 (16%) of their sample of 15 children and 10 adults had psychotic symptoms and 16 (64%) met *DSM-III-R* criteria for a spectrum of bipolar affective disorders. While none had schizophrenia, the 2 oldest members of their patient cohort (aged 29 and 34 years) both had schizoaffective disorder.

Disturbances in dopamine neurotransmission have long been postulated to play a key role in the etiology of psychotic disorders, particularly schizophrenia.⁹ The gene for catechol-O-methyltransferase (*COMT*), an enzyme involved in the degradation of dopamine, maps to the region of chromosome 22q11 deleted in

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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 22q11,¹³ 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.¹⁴ 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.¹⁵

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.¹⁶ 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).

VCFS.¹⁰ An amino acid polymorphism (Val-108-Met) determines high and low activity of this enzyme.¹¹ Dunham et al¹² 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.

MEASURES OF PSYCHOPATHOLOGY

Diagnoses were based on all available clinical information including in every case a semistructured interview (Schedules for Clinical Assessment in Neuropsychiatry¹⁷ or Psychiatric Assessment Schedule for Adults with Developmental Disability¹⁸ if IQ < 50 [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 diagnoses¹⁹ 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)²⁰ and Negative (SANS)²¹ Symptoms incorporated into the Diagnostic Interview for Genetic Studies²² and the Global Assessment Scale²³ were completed for each individual on a lifetime-worst basis from all available clinical information.

The versions of SAPS²⁰ and SANS²¹ and the Global Assessment Scale²³ were also administered to a control group of unrelated individuals with schizophrenia without VCFS (SZ group).

The 63-item King's Schizotypy Questionnaire,²⁴ 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.²⁴

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 previously²⁵ and identifies an *Nla*III 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 χ^2 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.²⁶

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-

Table 1. Comparison of Demographic and Phenotypic Variables in Psychiatric Disorder Subgroups*

	Total Sample (N = 50)	VCFS With Psychosis (n = 15)	VCFS Without Psychosis (n = 35)	VCFS Without Major Psychiatric Disorder (n = 29)
Age, y				
Mean (SD)	31 (10)	34 (12)†	29 (9)†	29 (10)
Range	17-52	17-52	17-50	17-50
Sex, M/F	15/35	5/10‡	10/25‡	10/19
IQ				
Mean (SD)	77 (14)	73 (13)§	79 (14)§	78 (14)
Range	38-104	45-90	38-104	38-104
IQ <70	16 (33)	7 (47)	9 (26)	8 (28)
Congenital heart disease	21 (42)	4 (27)¶	17 (49)¶	14 (48)
Ventricular septal defect	...	2 (13)	11 (31)	9 (18)
Atrial septal defect	...	1 (6)		
Tetralogy of Fallot	...		3 (8)	2 (6)
Double outlet right ventricle	1 (2)	1 (3)
Truncus arteriosus	1 (2)	1 (3)
Aberrant right subclavian artery	...	1 (6)		
Unspecified	1 (2)	1 (3)
Cleft palate (overt or submucous)	13 (26)	6 (40)#	7 (20)#	7 (24)
Offspring	27 (54)	5 (33)**	22 (63)**	17 (59)**
Ascertainment				
Via VCFS offspring	26 (52)	5 (33)††	21 (60)††	16 (55)
Via other sources	24 (48)	10 (67)	14 (40)	13 (45)

*Data are presented as number (percentage) unless otherwise indicated. VCFS indicates velo-cardio-facial syndrome.

† $t_{48} = -1.55, P = .10$.

‡ $\chi^2_1 = 0.11, P = .70$.

§ $t_{48} = 1.30, P = .20$.

|| $\chi^2_1 = 2.47, P = .20$.

¶ $\chi^2_1 = 2.07, P = .20$.

$\chi^2_1 = 2.18, P = .10$.

** $\chi^2_1 = 3.68, P = .05$.

†† $\chi^2_1 = 2.99, P = .08$.

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) hemizygoty 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 ($\chi^2_1 = 0.48, P = .50$) 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) ($t_{48} = -4.19, P < .001$) and were also significantly more likely to be female (85% vs 54%) ($\chi^2_1 = 5.50, P = .02$). However, there were no significant differences in IQ ($t_{46} = 1.53, P = .13$), presence of major psychiatric disorder ($\chi^2_1 = 0.28, P = .60$), or mean schizotypy score ($t_{30} = 0.24, P = .80$) 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.¹⁹ 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-

Table 2. Mean Schizotypy Scores of Subjects With VCFS, Their First-Degree Relatives, and Controls*

	KSQ Completed, No. of Subjects	Mean (SD) Age, y	Sex, M/F	Mean (SD) Schizotypy Score†
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 (6.8)
Controls	316	40 (12)	176/140	11.6 (8.5)

*VCFS indicates velo-cardio-facial syndrome; KSQ, King's Schizotypy Questionnaire.²⁴

†P < .05.

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, or 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 75 (SD = 11 points). Six (50%) of the 12 had an IQ of less than 70. There were no significant differences in age ($t_{48} = -1.36, P = .20$), sex ($\chi^2_1 = 0.08, P = .80$), or IQ ($t_{46} = 0.63, P = .53$) between subjects with VCFS with or without schizophrenia.

The SZ/VCFS group had a significantly later age of onset of schizophrenia (mean age of onset = 26 years, SD = 9 years; 95% confidence interval [CI], 20-32 years, range = 16-41 years) compared with the SZ group (mean age of onset = 19 years, SD = 4 years; 95% CI, 16-22 years, range = 15-30 years) ($t_{22} = -2.47, P = .02$).

Analysis of the composite SAPS ratings between the SZ/VCFS group (mean = 41, SD = 14) and the SZ group (mean = 48, SD = 26) revealed that there were no significant differences ($t_{22} = 0.84, P = .40$) between them. However, analysis of the composite SANS ratings revealed significantly lower scores in the SZ/VCFS group (mean = 10, SD = 9; 95% CI, 4-15) than in the SZ group (mean = 31, SD = 18; 95% CI, 19-42) ($t_{18} = 3.55, P = .002$).

There were no significant differences in scores on the Global Assessment Scale between the SZ/VCFS (mean

score = 26, SD = 4) and the SZ groups (mean score = 20, SD = 11) ($t_{22} = -1.65, P = .10$). Treatment-resistant schizophrenia, defined as lack of satisfactory clinical improvement despite the use of adequate doses of at least 2 conventional neuroleptics prescribed for adequate durations, was found in 1 patient (8%) in both the SZ/VCFS and SZ group.

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 ($F_{4,420} = 13.6, P < .001$) (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 ($P < .05$).

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 ($t_{34} = 0.7, P = .50$).

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.²⁷ Consequently, 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-

lence 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%²⁸ 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 hemizygoty 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.²⁹ 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.⁶

How important is chromosome 22q in the etiology of schizophrenia as a whole? Karayiorgou et al³⁰ 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 al³² 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 al³ 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 N25 who are not deleted for *COMT*, 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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