22q11 Deletion Syndrome in Adults With Schizophrenia

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Abstract

Genetic syndromes associated with deletions at chromosome 22q11 generally have been diagnosed during childhood based on a constellation of physical features. To investigate a reported association of velocardiofacial syndrome with psychotic disorders in adults, we assessed subjects with DSM-IV schizophrenia or schizoaffective disorder who were referred with two or more syndromal features (palatal, cardiac, facial, or other congenital anomalies, and/or learning difficulties). We report on 10 subjects (5 men and 5 women), mean age 27.2 (SD 6.0) years, who were found to have a 22q11 deletion at locus D22S75 using fluorescence in-situ hybridization (FISH). The mean age at onset of psychosis was 19.6 (SD 4.6) years. Symptoms and course of the psychotic illnesses were unremarkable, but additional signs such as temper outbursts were common. These adult subjects had significantly fewer major palatal ($P = .0001$) and conotruncal cardiac ($P = .05$) anomalies but the same high rate of learning difficulties as a sample with deletion 22q11 ascertained through a pediatric clinic [Lindsay et al. (1995): *Am J Med Genet* 57:514–522]. Minor congenital features and rate of transmitted cases were similar to those previously reported. These results replicate the association of a 22q11 deletion syndrome with schizophrenia and confirm the importance of ascertainment in influencing the phenotype found. The findings support a developmental gene in the 22q11 deletion region causing a complex phenotype which may include significant behavioral components that emerge over time. We support using the term “22q11 deletion syndrome (22DS),” which would encompass physical and psychiatric features, and could also be applied to describe a genetic subtype of schizophrenia.

Keywords

chromosome 22q11; velocardiofacial syndrome; schizophrenia; psychosis; genetic syndrome

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INTRODUCTION

There are several genetic syndromes and anomalies associated with interstitial deletions at chromosome 22q11, including velocardiofacial syndrome (VCFS) [Scambler et al., 1992; Driscoll et al., 1993; Kelly et al., 1993; Lindsay et al., 1995], DiGeorge syndrome (DGS), and conotruncal anomaly face syndrome [Demczuk and Aurias, 1995; Gong et al., 1996]. The estimated prevalence of the deletion is 1/4,500 [du Montcel et al., 1996], with sporadic occurrence in the majority and autosomal-dominant transmission in the minority of cases [Driscoll et al., 1993; Dallapiccola et al., 1996]. The collective acronym, CATCH 22 (Cardiac anomalies, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcemia) has been suggested, emphasizing severe congenital features associated primarily with DGS [Hall, 1993; Wilson et al., 1993]. However, case series have documented a variable phenotype with features involving several other systems [Shprintzen et al., 1978, 1981; Lipson et al., 1991; Finkelstein et al., 1993; Goldberg et al., 1993; Ravnan et al., 1996], and rates of major features may vary with different ascertainment strategies [Motzkin et al., 1993]. Despite this, most cases reported to date have had four main features considered characteristic of VCFS [Shprintzen et al., 1978, 1981; Goldberg et al., 1993]: learning disabilities, palatal anomalies (especially overt and submucous cleft palate), cardiac defects (especially of conotruncal origin), and typical facial features: a long face with prominent nose (broad nasal root and squared-off tip), malar hypoplasia, retrognathia, and minor ear anomalies. Recently, serious psychiatric illnesses have been reported in adult patients with VCFS, suggesting that later-onset conditions may be causally connected with 22q11 deletions [Chow et al., 1994; Karayiorgou et al., 1995; Papolos et al., 1996], and that 22q11 deletions may be found in adults with psychiatric disorders.

The first study of a possible association between psychiatric illness and the clinical syndrome [Shprintzen et al., 1992] found that 4 of 13 adults with VCFS had schizophrenia or schizoaffective disorder [Pulver et al., 1994]. A subsequent study on an overlapping sample reported that 4 of 7 adults with 22q11 deletions and VCFS had schizoaffective disorder or bipolar disorder with psychosis [Papolos et al., 1996]. In a complementary study, 2 of 100 randomly selected patients with schizophrenia were found to have a 22q11 deletion and, on retrospective assessment, facial features of VCFS [Karayiorgou et al., 1995]. In total, studies by this group of researchers [Pulver et al., 1994; Karayiorgou et al., 1995; Lindsay et al., 1995; Morrow et al., 1995; Papolos et al., 1996; Carlson et al., 1997] have reported 8 adult patients with VCFS, a 22q11 deletion, and a major psychotic disorder. A recent study found 3 adults with schizophrenia and a 22q11 deletion [Gothelf et al., 1997]. The association between psychotic disorders and deletion 22q11 deserves replication and clarification of the clinical presentation [Propping and Nothen, 1995]. Delineation of an adult phenotype would help to increase the probability of identifying deletion 22q11-related syndromes in adults. Furthermore, since most identified patients are currently infants and children, investigation of a possible connection between syndromes associated with 22q11 deletions and later-onset psychotic illnesses appears warranted.

We hypothesized that we could identify adults with VCFS and a 22q11 deletion by recruiting patients with a major psychiatric disorder and with phenotypic features associated with VCFS. We further hypothesized that these adult patients would have fewer major

physical anomalies than a large group of subjects with 22q11 deletion and VCFS as reported in the literature [Lindsay et al., 1995].

This report examines 10 adults with schizophrenia or schizoaffective disorder who have VCFS features associated with a 22q11 deletion. We replicate an association of the syndrome with serious behavioral and psychiatric features, delineate the adult phenotype expressed in individuals ascertained from a psychiatric sample, and identify a similar but somewhat milder physical phenotype than that usually reported in children. To encompass these and other extensions to the phenotype, we suggest the designation “deletion 22q11 syndrome” in preference to CATCH 22 [Thomas et al., 1997].

MATERIALS AND METHODS

Psychiatrists initially referred 15 adult patients with schizophrenia or schizoaffective disorder and features from two or more of the following five areas: palatal (hypernasal speech or history of cleft palate), cardiac (history of congenital cardiac anomalies), craniofacial (dysmorphic facies), learning difficulties (history of special education or mental retardation), or other physical congenital abnormalities (e.g., talipes or slender hands with tapered fingers). Two additional subjects with VCFS and 22q11 deletion were referred by geneticists. All initially referred subjects provided informed consent, supplemented by surrogate consent from a guardian where necessary. Medical and psychiatric records were obtained for each subject.

In all cases, subjects were diagnosed with schizophrenia or schizoaffective disorder. Confirmation of these diagnoses using DSM-IV criteria [American Psychiatric Association, 1994] and the Structured Clinical Interview for DSM-IV (SCID-I) [First et al., 1997] were made by two experienced psychiatrists (A.S.B. and E.W.C.C.), based on interviews with subjects, available clinical records, and extensive collateral information. Diagnoses were made for both past, including childhood, and current psychiatric conditions. The possible causal connection of the psychiatric disorders to a 22q11 deletion was ignored, since according to DSM-IV criteria all psychiatric diagnoses would then be in the category of “Mental Disorders Due to a General Medical Condition.”

Subjects were examined using a standardized physical examination protocol developed by us (A.S.B. and R.W.) to aid in the assessment of subtle congenital physical features in adult patients with schizophrenia (unpublished data). The physical examination was performed by physicians (A.S.B. and E.W.C.C.) trained by a dysmorphologist (R.W.) to identify minor congenital dysmorphic features and distinguish these from acquired features. Anomalies that were consistent with VCFS were later confirmed by the dysmorphologist, who made the clinical diagnosis of probable VCFS. Because of the variability of the phenotype, especially in the underreported adult population, only subjects with confirmed 22q11 deletions were included in the current study.

Rates for features of 22q11 deletion syndrome were compared, using two-tailed Fisher’s exact tests, to those reported for VCFS subjects with deletions in the largest sample from a single group [Lindsay et al., 1995]. The following features were used: learning disability,

cleft palate (overt or submucosal), and congenital conotruncal cardiac anomalies; the number of subjects with data available varied for each feature [Lindsay et al., 1995]. Other features, including “typical VCFS facies,” were felt to be of insufficient reliability to permit statistical comparisons.

Detailed psychiatric, medical, family, and developmental histories were obtained from subjects and families. All physical, congenital, and acquired conditions were reviewed by R.W., and those potentially related to VCFS, e.g., hypothyroidism, were tabulated. Age at onset (AAO) of psychosis was the age at which the subject first had an episode of hallucinations and/or delusions requiring treatment. Psychiatric signs and symptoms occurring in the premorbid period and/or in addition to diagnostic criteria were recorded. The best level of global functioning for the previous year was assessed using the standardized Global Assessment of Functioning Scale (GAF) [American Psychiatric Association, 1994].

Standard fluorescence in situ hybridization (FISH) analysis, using probe N25 [Driscoll et al., 1993] at the D22S75 locus and a control probe, pH17 at D22S39 (Oncor, Inc., Gaithersburg, MD), was used to detect deletions at 22q11. Seven patients with dysmorphic features and schizophrenia who did not show a 22q11 deletion using these methods were excluded and will be described elsewhere. Ten subjects met the inclusion criterion of having a detectable 22q11 deletion. To determine whether deletions were transmitted, a blood sample was drawn from available parents of the 10 subjects for FISH analysis, using the same probes.

RESULTS

Ten (5 female and 5 male) Caucasian subjects with schizophrenia or schizoaffective disorder, syndromal dysmorphic features, and 22q11 deletions were investigated (Tables I and II). Their mean age at assessment was 27.2 years (SD 6.0). Seven subjects were diagnosed with VCFS during the course of our evaluation, one subject (subject 3) was referred simultaneously to us and to medical genetics, and 2 subjects were referred from genetics following a diagnosis of VCFS (see Table I). Subjects were referred from psychiatric sources because of learning difficulties ($n = 8$), hypernasal speech ($n = 8$), dysmorphic facies ($n = 7$), other observed or historical physical congenital abnormalities ($n = 6$; slender/tapered fingers, short stature, talipes, or herniae), and/or history of congenital heart defects ($n = 1$). Each subject referred had three or four of these features. All subjects were diagnosed with VCFS as adults at a mean age of 25.7 years (SD 6.5). One subject (subject 1) was briefly described previously [Chow et al., 1994].

Psychiatric and Neurological Features

Table I outlines psychiatric, neurological, and audiological features for the 10 subjects. In 9 cases the onset of psychosis preceded the diagnosis of VCFS. The AAO of psychosis ranged from 15–29 years with a mean of 19.6 years (SD 4.6), and there was no difference between males and females ($t = -0.26$, $P = 0.80$). One subject had schizoaffective disorder; the others had schizophrenia. These disorders were severe, defined by psychotic symptoms (delusions and hallucinations), social withdrawal, and serious impairment in role functioning; the 10 subjects demonstrated all of these features. Subjects had a mean of 5.2 (SD 4.3) psychiatric

hospitalizations and a mean duration of major psychotic illness of 7.6 (SD 3.2) years. All were receiving antipsychotic medications.

There were a number of associated behavioral features. These included impulsivity or unpredictability, particularly in behavior and mood, with frequent temper outbursts, and not uncommonly, physical aggression. Collateral history indicated that these behaviors were not necessarily related to psychotic symptoms. Only one subject had an alcohol abuse disorder. Other features included anxiety, sometimes to the point of panic attacks, and compulsive behavior or speech (perseverations). Social withdrawal and depression (see Table I) are features that often precede the onset of psychosis in schizophrenia [American Psychiatric Association, 1994; Häfner and van der Heiden, 1997]. The average level of global functioning ranged from low (corresponding to moderately severe symptoms, and moderate impairment of social and/or occupational functioning) to fair (corresponding to few persistent symptoms, and mild difficulties with functioning). One subject had a steady boyfriend; none were married or had children. Most had stable relationships with caregivers; fewer had close relationships with peers. Two subjects worked in a semisheltered workplace, and several others participated regularly in day programs for psychiatric patients. Six subjects were living in supervised boarding homes, 3 in their parents' homes, and 1 independently.

The observed levels of functioning likely reflected both the subjects' psychiatric disorders and learning disabilities. Most subjects attended school to age 20; all required some special education. Grade 11 was the maximum education level attained in a vocational program. Learning difficulties were usually detected in grades 5 or 6, although mild language delays and articulation difficulties were often observed much earlier. These were sometimes attributed to hearing deficits, either conductive, related to multiple ear infections, or sensorineural origins (see Table I). Five individuals received speech therapy in childhood. Other neurological problems included those of congenital origin, such as ptosis, and those that became clinically significant during adolescence or early adulthood, such as hemiparesis.

Physical Features

Table II outlines the physical phenotype for each of the 10 adult VCFS-schizophrenia subjects. The results show variability of features between subjects and no trends by sex or age. Eight subjects (subjects 1–4, and 7–10) were considered to have “typical” VCFS facies. Examples of the range of facial appearance are presented in Figure 1. Two subjects had had facial surgery, one to improve retrognathia (subject 4), and the other to improve a cleft nasal tip (subject 9). Associated craniofacial features included both hypotelorism and hypertelorism. All subjects had hypernasal speech to varying degrees, which was an expected finding given the referral criteria. However, only one subject had an overt cleft palate (surgically corrected in infancy). One subject had a pharyngoplasty to correct a short (non-cleft) palate, and 2 others had documented velopharyngeal incompetence by direct examination in childhood. Five subjects had had adenoidectomies with tonsillectomies. Five subjects had a history of cardiac anomalies, with conotruncal defects in 4 cases (subjects 1, 6, 8, and 9). Only one (subject 1) had required surgical correction; the others were detected

in childhood because of symptoms (e.g., murmur, bradycardia) (subjects 6 and 7), or as adults following identification of syndromal features in the current study (subjects 8 and 9).

Every subject had one or more minor dysmorphic features of the limbs, although these were often flexion contractures rather than the slender hands usually described [Jones, 1997]. High arches of the feet were relatively common, and 2 subjects had a history of surgically corrected talipes. There were other features related to abnormalities of the musculoskeletal system and/or connective tissue. A degree of scoliosis and/or kyphosis was common. However, only 2 subjects (subjects 2 and 4) had previously been assessed for scoliosis by an orthopedic surgeon, and neither had required treatment. Two subjects had a history of herniae repaired as children. One subject had a history of surgically corrected unilateral postaxial polydactyly, another had pectus excavatum, and yet another had a single palmar crease and congenital torticollis.

Other systems were also involved. Eight subjects had acne or unspecified dermatitis of the scalp and/or face, often severe, requiring referral to dermatologists and ongoing medications. There was evidence of either mild thrombocytopenia (clinically insignificant) or recurrent epistaxis (requiring treatment) in half of the subjects. Ongoing difficulties with recurrent vomiting, accompanied by a hyperactive gag reflex, were present in 2 subjects, requiring referral to gastroenterologists. Several subjects had histories of gastrointestinal symptoms as infants requiring pediatric consultations: feeding difficulties, constipation, and/or diarrhea. One subject had had ophthalmological interventions for bilateral keratoconus. With respect to hormonal or metabolic abnormalities, one female subject had hypothyroidism with onset at age 20, and another had evidence of high testosterone levels with polycystic ovaries, diagnosed at age 28. There was no history of hypocalcemia in any of these adult subjects.

Comparison of Features to a Literature Sample

The adult subjects in the current study had significantly lower rates of cleft palate (1/10 vs. 29/41; $P < 0.0001$) and conotruncal cardiac anomalies (4/10 vs. 33/43; $P = .05$) than a literature sample of mostly pediatric subjects with VCFS and 22q11 deletion [Lindsay et al., 1995]. However, the rate of special education/learning disabilities (10/10 vs. 26/27) was very similar ($P = 1.0$) (see Table I). Although the subjectivity of minor dysmorphic features precluded statistical comparisons, rates for several of the more common features appeared comparable between our sample and a pediatric VCFS literature sample [Goldberg et al., 1993], respectively: minor ear anomalies (90% vs. 70%); slender/tapered fingers (70% vs. 63%); and malar flatness (60% vs. 70%). The rate of mild mental retardation (40%) was identical, but microcephaly (10% vs. 40%) and short stature (10% vs. 33%) were less frequent in the adult sample.

Family History and Transmission

There was no consanguinity between any of the subjects' parents. Fathers and mothers of 8 subjects had FISH testing for a 22q11 deletion. Two subjects had no parents available for testing, and for one of these a sib was found to be a noncarrier. Of the 16 parents tested, only one, the 69-year-old mother of subject 10, was positive for the deletion. Her pregnancy history included an infant death with congenital cardiac anomalies, a stillbirth, and a

spontaneous abortion. On examination she had mild VCFS facies (long, narrow face, malar hypoplasia, prominent nose with bulbous tip, and minor ear anomalies), hypernasal speech, and small slender hands. She had a history of a minor learning disability, recurrent epistaxis, moderate smoking, ischemic bowel disease, and hypertension. She had suffered a stroke at age 65 and had a subsequent mild anxiety disorder with irritability, but there was no history of major psychotic illness. The father of another subject had a history of alcohol dependence and a violent temper; the mother of a third subject had a history of panic disorder. There was no other history of psychiatric illness or any history of learning disability, mental retardation, cleft palate, hypernasal speech, or congenital heart defect in first- or second-degree relatives of any of the subjects. There was also no family history of polydactyly, keratoconus, or polycystic ovaries.

DISCUSSION

These results replicate the reported association of VCFS, 22q11 deletion, and psychotic disorders in adults [Shprintzen et al., 1992; Karayiorgou et al., 1995; Papolos et al., 1996]. The findings suggest that investigating patients with schizophrenia, if they have other syndromic features, may identify adults with a 22q11 deletion. Although included in the ascertainment criteria used, the results indicate that patients with a 22q11 deletion identified from an adult psychiatric population do not have the high rates of cardiac or palatal malformations seen in VCFS patients ascertained through pediatric clinics [Lipson et al., 1991; Goldberg et al., 1993; Lindsay et al., 1995]. Other than a milder physical phenotype, the clinical features of these adult patients appeared similar to those usually found in the 22q11 deletion syndrome.

Psychiatric and Neurodevelopmental Phenotype

This sample of 22q11 deletion syndrome patients appeared to have a typical form of schizophrenia or schizoaffective disorder, as indicated by their level of functioning, and need for psychiatric hospitalizations and antipsychotic treatment. The mean age at which psychotic symptoms first appeared was slightly younger than that usually reported for schizophrenia, especially for women [Häfner and van der Heiden, 1997]. This is consistent with evidence that younger AAO in schizophrenia is associated with greater severity of illness, genetic risk, and level of cognitive deficits [Häfner and van der Heiden, 1997; Russell et al., 1997]. The behavioral and mood features reported in this sample are common premorbid and comorbid features in schizophrenia [Häfner and van der Heiden, 1997; Russell et al., 1997], and are consistent with behavioral features and mood disorders reported in children [Golding-Kushner et al., 1985] and young adults with VCFS [Shprintzen et al., 1992; Pulver et al., 1994; Papolos et al., 1996], including notable prevalence of compulsive features [Pulver et al., 1994]. However, the quality and relatively brief duration of mood symptoms compared to psychotic symptoms meant that they did not meet criteria for DSM-IV mood and anxiety disorders.

Rates of learning disabilities and mental retardation in this adult sample were similar to those in studies using different ascertainment strategies [Goldberg et al., 1993; Swillen et al., 1997]. This suggests that cognitive abnormalities are a fundamental component of the

syndrome. Further studies are necessary to delineate if there is a common pattern of deficits, as there appears to be for other microdeletion syndromes such as Williams syndrome [Udwin and Yule, 1991]. Cognitive deficits are common in schizophrenia, and their presence many years prior to onset of psychosis is taken to be evidence of a neurodevelopmental origin for schizophrenia [Done et al., 1994; Jones et al., 1994]. Speech articulation deficits, common in VCFS [Haapanen and Somer, 1993], are another premorbid neurodevelopmental feature of schizophrenia [Done et al., 1994].

Physical Phenotype and Ascertainment

Adult subjects ascertained had a phenotype consistent with a 22q11 deletion. The rate of autosomal-dominant transmission was 12.5%, which is comparable with previous estimates for VCFS in children [Driscoll et al., 1993; Dallapiccola et al., 1996]. The phenotype was variable within the group, but, in addition to central nervous system (CNS) abnormalities, all subjects had features of variable severity from two or three of the systems usually involved in 22q11 deletion syndromes, especially minor dysmorphic features and hypernasal speech [Lipson et al., 1991; Finkelstein et al., 1993; Goldberg et al., 1993; Ravnan et al., 1996]. However, only one subject had a cleft palate, and no subject was treated for hypocalcemia or absent thymus. This suggests that several of the “CATCH 22” [Wilson et al., 1993] features, which are based on congenital features in children with DiGeorge Syndrome and which have been proposed as screening criteria for schizophrenic patients [Murphy and Owen, 1996], may not be helpful in identifying adults with 22q11 deletions. Instead, a high index of suspicion and a careful clinical assessment should help to identify patients with schizophrenia and a 22q11 deletion, as has been shown in populations of patients with cleft palate [Mingarelli et al., 1996] and cardiac defects [Amati et al., 1995]. Notably, the rate of associated 22q11 deletions found in the current study (8/15 psychiatric referrals tested) was comparable to that found in these and other studies of patients with syndromic features [Driscoll et al., 1993], while nonsyndromic patients with only one feature, such as cleft palate [Debrus et al., 1996; Mingarelli et al., 1996] or conotruncal cardiac defect [Amati et al., 1995; Takahashi et al., 1995], do not appear to have associated 22q11 deletions.

Many of the low-frequency associated physical findings found in our sample have been reported previously: thrombocytopenia [Budarf et al., 1995; Carlson et al., 1997; Lévy et al., 1997], recurrent epistaxis [Budarf et al., 1995], hypothyroidism [Lindsay et al., 1995], sensorineural hearing loss [Wilson et al., 1993], talipes [Lipson et al., 1991; Wilson et al., 1993], polydactyly [Finkelstein et al., 1993], and cleft nose [Lynch et al., 1995]. Other clinically significant features, however, may be additions to the 22q11 deletion syndrome phenotype. These include: severe acne or dermatitis, keratoconus, and polycystic ovaries. Follow-up studies of young patients with 22q11 deletions will determine whether these features may be underreported because of later onset or coincidental occurrence.

Limitations

Although this is the largest sample of adults with 22q11 deletion syndrome and psychotic disorders studied to date, the small sample size remains a limitation. The referral criteria used in this study may have confounded results on certain phenotypic characteristics. For example, the referral method likely ensured that subjects with more severe physical

phenotypes and learning disorders were referred. Although this strengthens findings with respect to low rates of major cardiac and palatal anomalies, milder physical and psychiatric phenotypes may be found in future studies. Clarification is required as to whether psychiatric disorders associated with 22q11 deletions are always accompanied by the presence of learning disabilities, which was one of the five referral criteria. Individuals with 22q11 deletion syndrome may have died in infancy, not living to develop psychiatric illnesses, especially before successful surgical correction of severe congenital heart defects became available. While this could have been the reason all subjects ascertained in the current study were born in the past four decades, effects on results should be minimal. Conversely, very mild cardiac defects may have been missed, but major cardiac anomalies are those predominantly reported in other studies [Lindsay et al., 1995]. Clinical features that were manifest before the mean age of assessment of 27 years were identified, but further investigation is required to reveal asymptomatic abnormalities that may be present, such as latent hypoparathyroidism, which was reported in a family with 22q11 deletion and psychotic illness [Cuneo et al., 1997]. Also, some phenotypic features may have been influenced by age [Jones, 1997] and/or antipsychotic medications. For example, hypotonia could be obscured and kyphosis and scoliosis may be worsened by the parkinsonian side effects of conventional antipsychotic medications.

The comparison sample [Lindsay et al., 1995] was relatively small, included 9 adults, and used a molecular method to determine deletions. A recently assembled multicenter sample of 22q deletion syndrome patients [Ryan et al., 1997] reported rates for congenital heart defects as high as those in Lindsay et al. [1995], but cleft palate rates more similar to those found in our schizophrenia sample. Unfortunately, there are relatively few studies of adults with 22q11 deletions, the presence or absence of psychiatric illnesses is rarely noted, descriptions of the physical phenotype are often scanty [Propping and Nothen, 1995], and the majority reported are transmitting parents ascertained through their affected offspring [Leana-Cox et al., 1996]. Further studies are needed to investigate patients with features typical of the syndrome but without detectable 22q11 deletions. Lastly, the 22q11 deletion in our 10 subjects, while known to be within the minimal critical region [Gong et al., 1996], requires investigation of its extent and variability. However, another study has shown no correlation between the psychiatric phenotype and length of 22q11 deletion [Karayiorgou et al., 1995].

Implications

Results of the current study have several important implications for both VCFS and schizophrenia. First, the results confirm that an identifiable subtype of schizophrenia is associated with VCFS and a 22q11 deletion. VCFS may be the most common genetic syndrome or aneuploidy associated with schizophrenia [Bassett, 1992], as it is for tetralogy of Fallot [Amati et al., 1995] and cleft palate that is not associated with cleft lip [Shprintzen et al., 1985]. This subtype requires further investigation to determine its relationship to the heterogeneous entity known as schizophrenia. This will involve studies of symptom patterns, associated psychiatric disorders, cognitive deficits, structural and functional brain abnormalities, clinical and molecular epidemiology, and eventually etiology and pathogenesis. There are suggestive linkage results pertaining to major psychotic illnesses

and chromosome 22q, but these involve markers telomeric to the 22q11 deletion region [Schizophrenia Collaborative Linkage Group (Chromosome 22), 1996]. One candidate gene within the 22q11 region which is usually deleted is catechol-O-methyltransferase (COMT), an enzyme involved in catecholamine inactivation, which could modify the psychiatric phenotype. However, there is no allelic association with schizophrenia [Daniels et al., 1996], and both low- and high-activity COMT alleles occur in adult patients with 22q11 deletions and psychosis [Lachman et al., 1996]. A more parsimonious hypothesis would be a gene disrupting neurodevelopmental pathways. The CNS and multiple other anomalies associated with the 22q11 deletion implicate a defective developmental gene and/or a gene involved in neural crest migration [Demczuk and Aurias, 1995]. Either possibility would be consistent with strong evidence for genetic origins [McGuffin et al., 1995] and the proposed neurodevelopmental pathogenesis of schizophrenia [Murray and Lewis, 1987; Weinberger, 1996].

Second, this study has clinical implications for both adults and children with a 22q11 deletion syndrome. Adults identified in psychiatric populations with this syndrome require follow-up for associated physical conditions, and genetic counseling should be offered to them and their families [Driscoll et al., 1993]. In addition, the results suggest that children with a 22q11 deletion should be followed for early signs of psychotic illness, since early intervention has been shown to lead to improved functioning [Loebel et al., 1992]. Even though most patients with 22q11 deletion syndrome will likely not develop major psychotic disorders, when present these disorders may interfere with quality of life far more than physical symptoms or learning difficulties, and they require comprehensive treatment.

In summary, the current study highlights the importance of ascertainment in determining the features of a genetic syndrome. It is likely that many individuals with the 22q11 deletion syndrome remain to be detected [du Montcel et al., 1996]. Our results suggest that identifying adults with 22q11 deletions should involve a broad ascertainment strategy, including careful examination for the presence of two or more features from five main areas: CNS abnormalities (cognitive and/or psychiatric), palatal and/or speech anomalies, craniofacial dysmorphisms, anomalies of the heart and/or major vessels, and miscellaneous anomalies (including hypocalcemia, slender tapered fingers, or thymic hypoplasia). We propose that the acronym “CATCH 22” no longer be used, as it may impede the identification of adults with 22q11 deletion syndromes by placing emphasis on the more severe congenital physical anomalies, ignoring important cognitive and behavioral components of the phenotype which may emerge over time. We support the use of the term “22q11 deletion syndrome,” as suggested by Thomas et al. [1997].

Acknowledgments

We appreciate the assistance of the following psychiatrists: Dr. K. Boyd (McMaster University, Hamilton, Ontario, Canada), Drs. W. MacEwan and W. Honer (University of British Columbia, Vancouver, British Columbia, Canada), Dr. T. O'Neill (Nova Scotia Hospital, Dartmouth, Nova Scotia, Canada), Dr. Shammi (Whitby Mental Health Centre, Whitby, Ontario, Canada), Drs. S. Tewfik and M. Wainberg (Queen Street Mental Health Centre, Toronto, Ontario, Canada), Dr. C. Welton (Hamilton Psychiatric Hospital, Hamilton, Ontario, Canada), and Drs. R. Zipursky and Fu (Clarke Institute of Psychiatry, Toronto, Ontario, Canada). We also acknowledge the referring geneticists, Drs. T. Costa and J. Siegel-Bartelt (Hospital for Sick Children, Toronto, Ontario, Canada). Grateful thanks go to the patients and their families.

Contract grant sponsor: Ontario Mental Health Foundation; Contract grant sponsor: Scottish Rite Schizophrenia Research Program; Contract grant sponsor: National Alliance for Research on Schizophrenia and Depression.

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Fig. 1. Four adult subjects, two men (top row) and two women (bottom row), with schizophrenia and 22q11 deletion syndrome. These subjects illustrate the variability of facial features in individuals with this genetic syndrome.

TABLE I
Psychiatric, Developmental, and Neurological Features in 10 Subjects With Schizophrenia and 22q11 Deletion Syndrome^{*}

Subject	1	2	3	4	5	6	7	8	9	10
Age at examination, sex	28, F	30, F	22, F	34, F	34, F	20, M	21, M	23, M	24, M	36, M
Referral source	Genet.	Genet.	Psych.	Psych.	Psych.	Psych.	Psych.	Psych.	Psych.	Psych.
VCFS age at diagnosis	18	25	22	34	34	20	21	23	24	36
AAO of psychosis	22	18	15	20	25	16	15	17	19	29
Psychiatric features										
Additional diagnoses (DSM IV)	PDD NOS	-	-	-	-	-	-	-	OCD, PD, AA, CD	-
Aggression/temper outbursts	+	+	+	+	+	+	+	+	+	+
Suicidal ideation/behavior	+	-	-	-	+	+	+	+	-	+
Emotional lability	+	+	+	+	-	-	+	+	-	-
Compulsions/perseveration	+	+	+	-	-	-	-	+	+	-
Anxiety/depressive symptoms	+	+	-	-	-	+	-	+	+	-
Social withdrawal/isolation	+	+	-	+	-	+	+	+	+	+
Childhood learning difficulties/developmental delay										
Special education	+	+	+	+	+	+	+	+	+	+
Mental retardation	Mild	BL	Mild	BL	Mild	-	BL	Mild	BL	BL
Articulation disorder	-	+	+	+	-	-	+	+	+	-
Neurological/audiological features										
Handedness	Right	Right	Right	Right	Right	Right	Left	Left	Right	Right
Neurological	-	- ^a	-	+	-	-	+	-	-	-
Hearing loss	+	-	-	+	+	++FS	-	++SN	-	-
Recurrent ear infections	-	-	-	+	-	+	+	+	+	-

^{*} Genet., genetics; Psych., psychiatry; PDD NOS, pervasive developmental disorder not otherwise specified (atypical autism); OCD, obsessive compulsive disorder; PD, panic disorder; AA, alcohol abuse; CD, childhood conduct disorder; BL, borderline; SN, sensorineural; FS, fixed stapes.

^aLeft hemiparesis.

^bMoebius sequence.

^cProsis.

TABLE II
Physical Features in 10 Adults With Schizophrenia and 22q11.2 Deletion Syndrome*

Subject	1	2	3	4	5	6	7	8	9	10
Stature (centile) ^a	165.0 (65)	158.0 (25)	152.0 (7)	157.2 (25)	160.5 (50)	166.5 (10)	159.0 (<3)	188.0 (97)	165.0 (10)	165.2 (10)
OFC (centile for height) ^b	52.5 (3)	55.0 (60)	54.6 (60)	54.9 (60)	55.0 (55)	56.5 (50)	55.0 (20)	59.4 (80)	56.7 (55)	58.0 (85)
Craniofacial										
Long face	+	+	-	-	-	-	+	-	-	-
Palpebral fissures ^c	+	+HT ^d	+	+	+	+	+HT ^d	+HRT ^e	+	+
Minor ear anomalies	+	+	+	+	-	+	+	+	+	+
Prominent nose	+	+	+	+	+	+	+	+	+	+
Flat cheeks	+	+	-	-	+	-	+	-	+	+
Small mouth	-	+	-	-	+	-	+	-	+	+
Micro/retrognathia	-	+	-	++	+	-	+	+	+	+
Irregular teeth	+	-	-	-	+	-	+	-	+	+
Coarse/thick hair	+	-	-	-	+	-	+	+	+	-
Palate										
High-arched	+	Short	+	+	+	+	+	+	+	+
Hypomnasal speech	+VPI	+	+VPI	+VPI	+	+	+	+	+	+
Cleft	-	-	-	+	-	-	-	-	-	-
Cardiac defects										
	VSD, ASD, BAV, MVP	-	-	-	-	VSD, RAA	MVP, AVB	VSD	DAA	-
Limbs										
Small hands	-	-	+	+	+	-	-	-	-	+
Slender/tapered fingers	+	+	+	-	+	+	-	+	-	+
Camptodactyly	-	+	-	++	+	-	-	++	-	+
Clinodactyly	-	-	-	-	+	-	-	+	-	+
Long feet/toes	+	-	-	-	+	-	-	+	-	-
High arches	+	+	-	+Tal	-	-	+	-	+Tal	+
Other										

Subject	1	2	3	4	5	6	7	8	9	10
Scoliosis/kyphosis	+	+	-	+	+	+	+	+	-	+
Herniae	-	-	-	-	-	+I	-	-	+I, U, E	-
Acne/dermatitis	++	+	-	+	+	-	+	++	+	++

* VPI, velopharyngeal insufficiency; VSD, ventricular septal defect; ASD, atrial septal defect; BAV, bicuspid aortic valve; MVP, mitral valve prolapse; RAA, right aortic arch; AVB, atrioventricular first-degree heart block with sinus bradycardia; DAA, double aortic arch; Tal, talipes; I, inguinal; U, umbilical; E, epigastric herniae.

^{a,b} Standard curves were used to estimate percentiles for height using norms for 18 years of age [Jones, 1997] and for occipitofrontal head circumference (OFC), using adult Caucasian norms for OFC corrected for height [Bushby et al., 1992]. Measurements that were <3rd centile were considered to be short stature and microcephaly, respectively.

^c Narrow or slanted palpebral fissures, and/or

^d HT (hypotelorism) or

^e HRT (hypertelorism) determined by inner canthal distance measurements of 2.64 cm and 3.65 cm, respectively, corresponding to values < and >2 SD from the mean for the oldest age available, i.e., 16 years [Hall et al., 1989].