22q11 Deletion Syndrome: A Genetic Subtype of Schizophrenia

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Abstract

Schizophrenia is likely to be caused by several susceptibility genes and may have environmental factors that interact with susceptibility genes and/or nongenetic causes. Recent evidence supports the likelihood that 22q11 Deletion Syndrome (22qDS) represents an identifiable genetic subtype of schizophrenia. 22qDS is an under-recognized genetic syndrome associated with microdeletions on chromosome 22 and a variable expression that often includes mild congenital dysmorphic features, hypernasal speech, and learning difficulties. Initial evidence indicates that a minority of patients with schizophrenia (~2%) may have 22qDS and that prevalence may be somewhat higher in subpopulations with developmental delay. This paper proposes clinical criteria (including facial features, learning disabilities, hypernasal speech, congenital heart defects and other congenital anomalies) to aid in identifying patients with schizophrenia who may have this subtype and outlines features that may increase the index of suspicion for this syndrome. Although no specific causal gene or genes have yet been identified in the deletion region, 22qDS may represent a more homogeneous subtype of schizophrenia. This subtype may serve as a model for neurodevelopmental origins of schizophrenia that could aid in delineating etiologic and pathogenetic mechanisms.

Keywords

Schizophrenia; genetics; subtype; neurodevelopment; chromosome 22; velocardiofacial syndrome

Introduction

Schizophrenia is likely to be caused by several susceptibility genes (genetic heterogeneity) and may have environmental factors that interact with susceptibility genes or non-genetic causes (etiologic heterogeneity) (Kendler and Diehl 1993; McGuffin et al 1995). Various attempts have been made to reduce heterogeneity in schizophrenia, primarily using clinical subtypes (Carpenter et al 1988) and sporadic/familial distinctions (Murray et al 1985). Recent evidence supports the likelihood that 22q11 Deletion Syndrome (22qDS) represents an identifiable genetic subtype of schizophrenia (Bassett et al 1998). This paper presents

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what is currently known about this syndrome, proposes clinical screening criteria, and outlines how this genetic subtype may serve as a neurodevelopmental model of schizophrenia and aid in delineating etiologic and pathogenetic mechanisms.

22q Deletion Syndrome (22qDS)

22qDS encompasses several genetic syndromes associated with microdeletions at chromosome 22q11.2, including velocardiofacial syndrome (VCFS) and DiGeorge syndrome (DGS) (Driscoll et al 1993; Kelly et al 1993; Lindsay et al 1995a; Scambler et al 1992). Learning disabilities, palatal anomalies, cardiac defects, and typical facial features are common, although the presentation is highly variable (Goldberg et al 1993; Shprintzen et al 1978; Shprintzen et al 1981; Yamagishi et al 1998). The syndrome was first described in the 1950s (Sedlackova 1967), delineated in the 1970s (Shprintzen et al 1978), and became more generally identified in pediatric populations in the 1990s through the availability of specialized chromosomal studies; routine karyotype analysis does not detect the deletion (Driscoll et al 1993; Lindsay et al 1995a). The estimated prevalence of the deletion is 1/4000 (du Montcel et al 1996), making 22qDS the second most common genetic syndrome after Down syndrome. 22qDS usually occurs as a sporadic mutation, but approximately 10% of cases are inherited from transmitting parents, who often have a less severe phenotype (Demczuk and Aurias 1995). Studies of 22qDS have usually involved infants and children because ascertainment has mainly been through pediatric specialty clinics. The variability of the phenotype and limited knowledge of the syndrome by medical practitioners mean that 22qDS remains largely undiagnosed, especially in adults where later onset behavioural manifestations may become prominent features.

Schizophrenia and Other Psychiatric Disorders in 22qDS

Researchers have reported a high prevalence of serious psychiatric illnesses in adult patients with 22qDS (Papolos et al 1996; Pulver et al 1994; Shprintzen et al 1992). In a study of 40 adults with 22qDS, the most common psychiatric disorder found on direct interview using DSM-IV criteria was schizophrenia (25%), followed by major depression (13%) and bipolar disorder (2.5%) (Murphy and Owen 1997). Four (31%) of 13 adults with 22qDS in another study had DSM-III-R schizophrenia or schizoaffective disorder (Pulver et al 1994). In contrast, there is no evidence of elevated rates of schizophrenia in other genetic syndromes with behavioral phenotypes (Turk and Hill 1995), and there are only mildly elevated rates of schizophrenia (~3%) in mental retardation (Turner 1989). The high rate of schizophrenia in 22qDS also does not appear to be related to major psychotic illness in first or second degree relatives (Bassett et al 1998; Pulver et al 1994). These early studies suggest that morbid risk of schizophrenia for a patient with 22qDS may be approximately 25 times the general population risk, and double the risk of a first degree relative of an individual with schizophrenia.

22qDS as a Subtype of Schizophrenia

Although there are no large scale epidemiologic studies of 22qDS yet available in psychiatric samples, the available evidence suggests that a small but significant subset of

patients with schizophrenia may have this syndrome. One study found 22q11.2 deletions in 2 of 100 random patients with schizophrenia screened for the deletion; minor facial features were subsequently identified in the deleted patients (Karayiorgou et al 1995). Consistent with this prevalence figure, a recent study of 32 well characterized subjects with childhood onset schizophrenia found 1 subject (3%) with a 22q11 deletion (Yan et al 1998). Subjects with IQ <70 were not included in either of these studies. The rate of detecting the deletion however may be higher in adults with a dual diagnosis of schizophrenia and developmental disabilities. One study found 22qDS in 2 (9%) of 22 such subjects (Murphy et al 1998). These preliminary studies indicate that the rate of 22qDS in schizophrenia may be approximately 80 times the estimated general population rate of 22q11.2 deletions (1/4,000) (du Montcel et al 1996). These compelling early findings have led to the proposal that 22qDS is a genetic subtype of schizophrenia (Bassett et al 1998; Propping and Nothen 1995).

Identifying 22qDS in Schizophrenia

Several groups (Bassett et al 1998; Gothelf et al 1997; Murphy et al 1998) have shown that 22qDS may be identified in clinical populations with schizophrenia who are screened for the presence of common syndromal features (see Table 1 for proposed clinical screening criteria). Age at onset, psychotic symptoms, and comorbid symptoms are consistent with those usually found in schizophrenia (Bassett et al 1998; Gothelf et al 1997; Pulver et al 1994). Behavioral and mood features (such as anxiety, depression, temper/aggressive outbursts, impulsive and compulsive behavior) observed in 22qDS-schizophrenia (Bassett et al 1998; Pulver et al 1994) are also commonly observed in schizophrenia (Häfner and an der Heiden 1997; Russell et al 1997). Although few data are yet available for adults with 22qDS, intellect appears to be most commonly in the borderline mental retardation range, with some subjects having low average intellect and a minority having mild mental retardation (Bassett et al 1998). This suggests that intellectual deficits may, in general, be more severe in a 22qDS subtype of schizophrenia. Comprehensive neuropsychological studies are needed to clarify whether the pattern of cognitive deficits is similar to that commonly found in schizophrenia (Green 1996).

Findings related to a neurodevelopmental hypothesis for schizophrenia and from genetic studies of schizophrenia provide further supportive evidence for a 22qDS subtype of schizophrenia.

Supportive Evidence: Neurodevelopmental

An observed increased prevalence of minor physical abnormalities (Green et al 1989; Guy et al 1983; O'Callaghan et al 1991) is considered supportive of a neurodevelopmental origin for schizophrenia (Murray and Lewis 1987; Weinberger 1997). In addition to major features (see Table 1), minor dysmorphic features are common in 22qDS (Bassett et al 1998; Goldberg et al 1993; Lipson et al 1991). Several of these, such as high arched palate, overlap with the minor physical abnormalities usually assessed in studies of schizophrenia (Green et al 1989; Griffiths et al 1998; Guy et al 1983; O'Callaghan et al 1991). Interestingly, physical features seen in 22qDS are similar to many of those listed by Kraepelin (Kraepelin 1971) as

common in schizophrenia: “small stature, youthful appearance, malformation of the cranium and of the ears, high and narrow palate, persistence of the intermaxillary bone, abnormal growth of hair, strabismus, deformities of the fingers or toes, polymastia, defective development and irregularity of the teeth.”

Developmental abnormalities reported to be elevated in the premorbid phase of schizophrenia also support a neurodevelopmental origin for schizophrenia (Done et al 1994; Jones et al 1994). These include developmental delays, speech difficulties, minor coordination deficits, blunted affect, and social withdrawal (Done et al 1994; Jones et al 1994). Similar features have also been reported to be prevalent in children with 22qDS (Golding-Kushner et al 1985; Haapanen and Somer 1993). One of the most common features in children with 22qDS is an intellectual deficit that results in decreased educational achievement (Golding-Kushner et al 1985; Kok and Solman 1995; Swillen et al 1997). Similarly, childhood cognitive deficits are significant features in schizophrenia and are considered further evidence of a neurodevelopmental origin for schizophrenia (Done et al 1994; Jones et al 1994).

Structural brain abnormalities are relatively frequent in schizophrenia and may be found at onset of illness, further supporting a neurodevelopmental hypothesis of schizophrenia (Weinberger 1997). Commonly reported brain anomalies include mild cortical atrophy, ventricular enlargement, decreased gray matter, and increased prevalence of midline developmental abnormalities, such as cavum septum pellucidum or cavum vergae (Degreef et al 1992; Johnstone et al 1976; Lewis and Mezey 1985; Zipursky et al 1998; Zipursky et al 1992). Preliminary results indicate similar anomalies in a 22qDS subtype of schizophrenia (Chow et al in press; Chow et al 1999) as well as increased hyperintensity signals, radiologic findings of unknown origin (Marsh et al 1996), that may be more specific to the subtype. Comparable findings have been reported in small studies involving mostly children with 22qDS (Haapanen and Somer 1993; Mitnick et al 1996; Mitnick et al 1994).

Syndromes with facial abnormalities are often associated with neurologic or psychiatric abnormalities (Winter 1996). This may be because facial development is dependent upon prosencephalic and rhombencephalic organizing centres or because specific genes are important both in the developing brain and face (Winter 1996). 22qDS is thought to originate during embryonic development. The pathogenesis has been hypothesized to involve abnormal neural crest cell migration (Demczuk and Aurias 1995; Mansour et al 1987; Nickel et al 1994; Scambler et al 1992; Thomas and Frias 1987). This proposed pathogenetic mechanism for 22qDS may overlap with the abnormal neuronal migration and other abnormalities of early neurodevelopment posited for schizophrenia (Bassett et al 1998; Bogerts 1993; Chow et al 1994; Weinberger 1987).

Supportive Evidence: Genetic

Like schizophrenia (Gottesman and Shields 1982), 22qDS most commonly presents as a sporadic occurrence in families, originating with a de novo mutation in the majority of cases (Dallapiccola et al 1996). 22qDS is inherited by autosomal dominant transmission in only about 10% of cases (Dallapiccola et al 1996; Lévy et al 1997). Interestingly, increased minor

physical abnormalities have recently been reported to be more prevalent in “sporadic” schizophrenia (Griffiths et al 1998). Consistent with family and twin studies of schizophrenia that indicate reduced penetrance and variable expression, (Kendler and Diehl 1993), the psychiatric phenotype in 22qDS appears to be associated with schizotypal features and psychiatric disorders other than schizophrenia, including schizoaffective disorder, major depression and bipolar disorder (Murphy and Owen 1997; Papolos et al 1996; Pulver et al 1994). Affective disorders do not appear to be as prevalent as schizophrenia in adults (Murphy and Owen 1997; Pulver et al 1994) but may occur as early manifestations in an evolving psychiatric phenotype (Papolos et al 1996). This may be comparable to depressive features that often appear early in a first psychotic episode of schizophrenia (Lieberman 1995).

With respect to genetic linkage studies of schizophrenia, there are weak linkage findings implicating the 22q12 region (Schizophrenia Collaborative Linkage Group for Chromosome 22 1998), several million base pairs distal to the 22q11.2 deletion region. Nonsignificant LOD scores despite large sample sizes suggest that few families may be linked or a mutation in a susceptibility gene or genes located on distal chromosome 22 may have a small effect (Moldin and Gottesman 1997), consistent with the genetic heterogeneity expected in schizophrenia. Also, linkage studies use families with two or more affected relatives, most often siblings. Individuals with schizophrenia in these studies would therefore be particularly unlikely to have 22qDS since the deletion usually occurs as a sporadic mutation.

Molecular Background on 22qDS

22q11.2 Microdeletion

The fluorescence in-situ hybridization (FISH) technique uses a fluorescently labeled probe from the 22q11.2 region to unequivocally identify chromosomes that do not fluoresce, i.e., those with submicroscopic deletions (Karayiorgou et al 1995; Kucherlapati et al 1995; Lindsay et al 1995a). FISH has therefore come to play a major role in clinical laboratory testing for microdeletions (Hall 1993). About 80% of patients with VCFS or related syndromes are found to have a 22q microdeletion; there are three main types (Kurahashi et al 1996; Morrow et al 1995). The largest (type 1) is the most common, with an estimated deletion size of 2–3 megabases (Mb). A smaller deletion (type 2) overlaps the proximal region of type 1 deletions. The D22S75 (N25) marker commonly used in clinical diagnostic FISH laboratories to diagnose the 22q microdeletion maps to the region overlapped by types 1 and 2 deletions (Morrow et al 1995), both of which have been reported in schizophrenia (Karayiorgou et al 1995). A third smaller deletion (type 3) that appears to overlap with the distal end of the largest deletion is very rare and requires a different probe for detection (Kurahashi et al 1996). The monosomy, or reduced dosage of genes within the 22q11.2 deleted region, is believed to cause the 22qDS phenotype.

Candidate Genes

There are many interesting candidate genes in the 22q11.2 region. One of these, catechol-*O*-methyltransferase (COMT), is an enzyme involved in catecholamine inactivation. Studies indicate that 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). There is preliminary evidence for the role of the low activity form of this gene in violent behavior (Lachman et al 1998). Other genes of interest in the deletion region include: TUPLE1, a transcription factor (Halford et al 1993); DGCR2, an adhesion receptor protein (Budarf et al 1995; Demczuk et al 1995), CLTD, a clathrin heavy chain gene (Sirotkin et al 1996); TMVCF, a transmembrane protein (Sirotkin et al 1997), and a developmentally expressed ubiquitination gene (Pizzuti et al 1997). Some of these have been found by screening fetal brain cDNA libraries. No point mutations have been detected in the candidate genes identified to date, even those disrupted by translocation breakpoints. This suggests that disruption of a sequential group of genes, perhaps involving disruption of regional regulation, is more likely than a single gene in causing 22qDS (Kurahashi et al 1996; Sutherland et al 1996).

Etiologic Heterogeneity

Approximately 20% of patients with syndromal features do not have a detectable deletion using the D22S75 probe (Carlson et al 1997; Lindsay et al 1995a; Morrow et al 1995). This indicates that in a minority of patients there are likely to be other causes of the syndrome, possibly involving point mutations in key genes in the 22q11 region that have yet to be identified (Lindsay et al 1995a). Other chromosomal regions, including 10p13 and 18q21, have been associated with some DGS features (Daw et al 1996; Greenberg 1993; Monaco et al 1991) but facial features appear to be different (Demczuk and Aurias 1995). Non-genetic causes of syndromal features are also possible (Hall 1993). These include exposure during pregnancy to teratogens such as alcohol and retinoids (Nickel et al 1994), that can cause similar appearing phenotypes, possibly because of effects on neural crest cell migration in embryonic development (Demczuk and Aurias 1995). Interestingly, a recent study of adults with fetal alcohol syndrome and fetal alcohol effects indicates an increased prevalence of psychotic disorders (Famy et al 1998).

Clinical Heterogeneity

The phenotype is highly variable both between and within families (Leana-Cox et al 1996; Lindsay et al 1995a; Lipson et al 1991; McLean et al 1993; Meinecke et al 1986), even when the same molecular genetic defect is apparently present (Motzkin et al 1993). Monozygotic (identical) twins with VCFS have also been reported to have variable phenotypes (Fryer 1996; Hatchwell 1996). There is no apparent correlation between the severity or pattern of the expressed phenotype and the extent of the deletion for 22qDS (Carlson et al 1997). The factors responsible for the phenotypic diversity are unknown, but are likely to involve variability in the many genes expressed on the normal 22q11.2 chromosomal segment (Demczuk and Aurias 1995; Sirotkin et al 1996). Interacting or additive environmental factors such as teratogens, somatic mosaicism (e.g., deletions in some cells and not others) (Pinto-Escalante et al 1998) or stochastic (chance) effects could also play a role in clinical heterogeneity.

Developing an Index of Suspicion for 22qDS in Adults with Schizophrenia

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). The best features to use in screening adult populations have yet to be determined. Several studies suggest that patients with features of variable severity from 2 or 3 of the systems usually involved in 22q11 deletion syndromes, especially minor dysmorphic features and hypernasal speech, are likely to carry the deletion (Bassett et al 1998; Finkelstein et al 1993; Goldberg et al 1993; Gothelf et al 1997; Lipson et al 1991; Ravnan et al 1996) (see Table 1). Nonsyndromic patients with only one feature, such as cleft palate (Debrus et al 1996; Mingarelli et al 1996) or congenital heart defect (Amati et al 1995; Takahashi et al 1995), do not appear to have associated 22q11 deletions. Careful examination for congenital features is essential, since some phenotypic features may be influenced by age (Jones 1997) or antipsychotic medications. For example, hypotonia could be obscured and kyphosis and scoliosis may be worsened by the parkinsonian side effects of conventional anti-psychotic medications.

Using medical history and a standardized physical examination for 103 minor dysmorphic features (SPEDF) developed by our group, we have demonstrated that we can identify 22qDS in adult patients with schizophrenia who meet clinical referral criteria (Bassett et al 1998). In 9 (32%) of 28 patients with schizophrenia referred from psychiatric sources who had two or more of the features outlined in Table 1, FISH studies using a standard probe at locus D22S75 confirmed a 22q11.2 deletion (unpublished data). These preliminary results represent a 16-fold increase in deletion detection over the prior probability of approximately 2% (Karayiorgou et al 1995). Although subjects with a 22q11.2 deletion had a greater total number of minor dysmorphic features than non-deleted subjects, no one feature was pathognomonic for deleted subjects (unpublished data). Further studies are needed to determine a set of clinical screening criteria for 22qDS with high sensitivity, specificity, and positive predictive value.

Developmental, medical, and family histories may be useful adjuncts in identifying patients who may have 22qDS. Developmental medical history may include neonatal seizures due to hypocalcemia that is secondary to hypoparathyroidism (Cuneo et al 1997), or repeated infections, due to defective cellular immunity. These features, typical of DGS, occur most often in infants and children and are usually transient (Goldberg et al 1993; Lindsay et al 1995b; Ravnan et al 1996). Any system may be affected, including musculoskeletal, renal, gastrointestinal, and haematologic (e.g., thrombocytopenia [low platelets]) (Lévy et al 1997; Ryan et al 1997). In the case of a transmitted deletion, the family history may include siblings with early infant death or stillbirth. Features to consider are shown in Table 2.

Clinical Considerations

There are several clinical imperatives to consider if 22qDS is diagnosed in an adult patient. First, patients with 22qDS will benefit from a consultation with a medical geneticist. Ongoing monitoring for onset of associated psychiatric illness, hypocalcemia, and hypothyroidism, that may occur in later years, has been recommended (Bassett et al 1998;

Cuneo et al 1997). These are treatable conditions and patients would benefit from early diagnosis and treatment that could lead to improved long-term outcomes. There is supportive evidence for this in schizophrenia (Lieberman 1995). Other medical conditions, such as cerebellar degeneration (Lynch et al 1995) may also be later occurring features of 22qDS. There are no published data on late-life or long-term outcome in 22qDS. Second, the 22qDS patients, and possibly family members should be offered genetic counseling (Driscoll et al 1993; Ryan et al 1997). 22qDS demonstrates autosomal dominant transmission, therefore patients with the syndrome have a 50% risk of passing on the deletion to offspring. Counseling is difficult because of the variability of the phenotype and there are no data yet on the likelihood of transmitting individual features, including psychiatric disorders. Reproductive fitness is likely to be unaffected by the syndrome in many cases; adults with 22qDS are often identified because they have had children severely affected with 22qDS (Leana-Cox et al 1996). As part of standard clinical recommendations, parents of patients identified to have a 22q11.2 deletion should be tested to determine if the deletion was transmitted (Ryan et al 1997). Third, receiving a genetic diagnosis may relieve parents of guilt or inappropriate blame for causing behavioral manifestations of the condition, and families may further benefit from 22qDS peer support networks, where available (Turk and Hill 1995).

Research-Related Advantages of Identifying a 22qDS Subtype of Schizophrenia

Schizophrenia has usually been subtyped on the basis of symptom patterns (e.g., paranoid, disorganized, catatonic; or deficit syndrome) (Carpenter et al 1988) or familial (considered more genetic) and “sporadic” (considered relatively nongenetic or more environmental), based on family history of schizophrenia (Murray et al 1985). The principal rationale for subtyping is to reduce heterogeneity in the syndrome, and determine clinically meaningful divisions that have prognostic or etiologic significance. Identifying a 22qDS subtype of schizophrenia may have several advantages.

First, a 22qDS subtype could serve as a neurodevelopmental model for schizophrenia and could therefore lead to a better understanding of pathogenesis. This would include an enhanced ability to determine environmental risk factors that interact with genetic risk. Studies involving a 22qDS subtype could clarify neurodevelopmental mechanisms by helping to determine which factors considered to be due to environmental insults, such as minor physical abnormalities (Cannon and Murray 1998), are more likely to be secondary to abnormal fetal development of genetic origin. Also, knowledge about a 22qDS subtype of schizophrenia may be useful to reexamine results from studies investigating “sporadic” schizophrenia, as this term may pertain to subjects with a genetic etiology.

Second, identifying a genetic subtype of schizophrenia would be an important first step in reducing the heterogeneity associated with the disorder. Investigations of subjects with an etiologically homogeneous form of the disorder could reduce the usually high variance associated with virtually any measure. If specific clinical parameters, such as symptoms, course and treatment response, were found to be different in a 22qDS subtype from other

patients with schizophrenia, this could have significant bearing on predicting outcome. Alternatively, if clinical features were found to be as variable in 22qDS as they are in other forms of schizophrenia this may suggest similar mechanisms for clinical heterogeneity. Other areas of research, such as imaging and neurophysiological studies, could also benefit from the potential reduction in heterogeneity conveyed by identification of a subtype. Many existing studies may screen 22qDS patients out with criteria that exclude patients with learning difficulties or associated medical conditions.

Third, ascertaining patients with a 22qDS subtype of schizophrenia could prove important in the search for genetic etiologies of schizophrenia. Genes located in the 22q11.2 deletion region may be involved in causing schizophrenia in some cases. A deletion provides a physical location for disease genes that statistical linkage studies of this complex disorder cannot. Localizing one gene for even a rare subtype of schizophrenia could lead to identification of related genes relevant to more common subtypes of the illness. Down Syndrome (DS), which is usually caused by trisomy of chromosome 21, provides a model for such an approach. The finding of a late-occurring psychiatric manifestation in DS, dementia of the Alzheimer type (AD), helped lead to the discovery of a gene (amyloid precursor protein) located on chromosome 21 which is involved in causing a rare form of familial AD (Masters et al 1985; Wisniewski et al 1985). Alternatively, a 22q11.2 gene may interact with another gene on chromosome 22q, within the deletion region or outside it, or on another chromosome, to cause schizophrenia.

Conclusion

A 22qDS subtype of schizophrenia is an important but currently under-recognized entity. The means are now at hand to begin to identify patients with this subtype. Many investigations are needed to determine the relationship of a 22qDS subtype to the heterogeneous entity known as schizophrenia. These 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. An identifiable subtype with potential importance for delineating a genetic etiology and neurodevelopmental mechanisms of schizophrenia provides an exciting opportunity for researchers and clinicians.

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Table 1**Screening Criteria to Identify Patients with Schizophrenia at Increased Risk for 22q Deletion Syndrome**

Two or more of the following features ^a	
1	Hypernasal speech, history of speech therapy, velopharyngeal incompetence, cleft palate (usually submucosal)
2	Characteristic facial features: e.g., long, narrow face, narrow palpebral fissures, flat cheeks, prominent nose, small ears, small mouth, retruded chin
3	Learning difficulties, history of special education, mental retardation (borderline to mild)
4	Congenital heart defect: e.g., ventricular septal defect, tetralogy of Fallot, right aortic arch, double aortic arch
5	Other significant congenital anomaly: e.g., talipes (club foot), polydactyly (extra finger or toe), kyphosis/scoliosis, renal anomaly, hypospadias
6	History of hypocalcemia (neonatal, childhood, adolescence or adult onset) and/or hypoparathyroidism
7	History of athymia (absent thymus gland) or severe immune deficiency in infancy

^aThe 22qDS phenotype is variable. Examples are provided of features reported in adults with schizophrenia; specific features listed may not be present or others may be identified in an individual patient.

Table 2
History and Physical Examination Features^{a,b} That Should Increase the Index of Suspicion for 22q Deletion Syndrome

Physical examination (limited) ^b	Neuropsychiatric features	Family history	Developmental history	Medical history	Laboratory
Hypomastic speech Different looking facial features (long, narrow face, small chin, narrow or slanted palpebral fissures, prominent nose, small mouth, small ears) Slender, tapered fingers Scoliosis or Kyphosis Any congenital anomaly (e.g., talipes [club foot]) Height different from siblings	Borderline to mild mental retardation Temper outbursts Preservative speech Compulsive behavior Hearing deficit	Miscarriages, stillbirths, early infant deaths, congenital heart defects (especially siblings) Learning or speech difficulties Note: usually no history of psychosis	Neonatal convulsions Difficulties feeding Repeated infections Developmental delays especially speech delay Speech therapy Learning difficulties or special education Absence of alcoholism or high dose retinoic acid during gestation	Palatal repair of velopharyngeal insufficiency or cleft Congenital heart defect such as ventricular septal defect, right-sided aortic arch, tetralogy of Fallot Any other congenital defect	Low calcium Low platelet count

^a Individual features are nonspecific; a pattern of several features may warrant a referral to medical genetics.

^b Features are congenital, not acquired.