Schizophrenia and 22q11.2 Deletion Syndrome

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Current Psychiatry Reports 2008, **10:**148–157
Current Medicine Group LLC ISSN 1523-3812

22q11.2 deletion syndrome (22qDS) is a genetic syndrome associated with a chromosome 22q11.2 deletion and variable phenotypic expression that commonly includes schizophrenia. Approximately 1% of patients with schizophrenia have 22qDS. The schizophrenia in 22qDS appears broadly similar to that found in the general population with respect to core signs and symptoms, treatment response, neurocognitive profile, and MRI brain anomalies. However, individuals with a 22qDS form of schizophrenia typically have distinguishable physical features, have a lower IQ, and may differ in auxiliary clinical features. IQ, length of 22q11.2 deletions, and *COMT* functional allele do not appear to be major risk factors for schizophrenia in 22qDS. Ascertainment biases and small sample sizes are limitations of most studies. Larger studies over the lifespan and continuing education about this underrecognized condition are needed. 22qDS-schizophrenia is an important genetic subtype and a valuable model of neurodevelopmental mechanisms involved in the pathogenesis of schizophrenia.

Introduction

Of schizophrenia's many genetic forms, some of which are inherited and many of which are new mutations, only one is recurrent, clinically recognizable, and has confirmatory genetic testing available: 22q11.2 deletion syndrome (22qDS) and its associated 22q11.2 deletion [1•]. This review provides an overview of the evidence for 22qDS as the first identifiable genetic subtype of schizophrenia, the available information about 22qDS-schizophrenia, and some of the implications of this underrecognized condition for clinical practice and research.

Common Features and Prevalence of 22qDS

22qDS has a highly variable clinical presentation with several dozen commonly associated features, including congenital and later-onset manifestations, such as psychiatric disorders [2••]. Classically associated features include mild facial dysmorphic features, learning difficulties, hypernasal speech, and congenital anomalies such as congenital heart defects and velopharyngeal insufficiency and/or submucous cleft palate [3]. Overt cleft palate is rare in 22qDS [2••]. Before the associated chromosomal deletion was identified, the variability of features had led to multiple names being used to describe the syndrome (eg, DiGeorge, velocardiofacial, conotruncal anomaly face syndromes).

The hemizygous 22q11.2 deletions (ie, on one chromosome 22) associated with 22qDS are too small to be seen using standard karyotyping methods. The molecular cytogenetic method, fluorescence in situ hybridization (FISH), which detects the commonly associated 22q11.2 deletions, became available to clinical laboratories in the mid-1990s. Some variability exists in the length and genomic extent of the 22q11.2 deletions, which are most commonly 3 million bases (Mb) long, but most are clinically detectable using FISH and a standard probe (eg, *TUPLE1*) from the typically deleted region [4]. The deletion is most commonly a spontaneous (de novo) mutation that occurs during gametogenesis (egg or sperm formation). However, in 5% to 10% of newly diagnosed cases of 22qDS, the mutation has been inherited from a parent with the syndrome who may have only mild manifestations.

The true prevalence of 22qDS in the general population is unknown and is likely to vary according to the population's demographic characteristics. Men and women are equally likely to be affected. Ethnic differences in prevalence may exist, but no studies have formally examined this issue. The best available estimates, based largely on infants with congenital anomalies leading to genetic testing, place the prevalence of 22qDS at about 1 in 4000 [5].

Evidence for the Association of 22q11.2 Deletions and Schizophrenia

A meaningful association between 22qDS and schizophrenia would be suggested if 1) patients with schizophrenia have elevated rates of 22q11.2 deletions and 2) an elevated rate of schizophrenia exists in individuals with 22q11.2 deletions [6]. Several studies have now contributed data to these issues, although rates observed vary considerably.

How common is 22qDS in schizophrenia?

Overall, studies investigating the prevalence of 22qDS and/or 22q11.2 deletions in samples of patients with schizophrenia and related psychotic disorders suggest that 22qDS is likely to be found in about 1 of 100 patients with schizophrenia (Table 1). Our group found that 2 (1.1%) of 178 patients with schizophrenia screened at a community clinic had 22qDS (Bassett and Chow, unpublished data). The observed prevalence is influenced by the characteristics of the sample population studied and the clinical and molecular methods used to detect the syndrome and/or deletion (Table 1). Samples with many individuals who have high intellectual levels, are physically healthy, are older, and/or have relatives with schizophrenia tend to have a lower prior probability of containing individuals with 22qDS. This is because although only a minority have mental retardation, most individuals with 22qDS have learning difficulties, have multiple physical health problems (eg, recurrent seizures), may be prone to premature death, and carry a de novo 22q11.2 deletion [2••]. One half would be expected to be women. Thus, many studies of schizophrenia would have inclusion and exclusion criteria and sampling strategies that would bias against ascertainment of individuals with 22qDS. However, high rates of 22qDS result from screening for patients with physical features of the syndrome and/or borderline to mild mental retardation [3] or childhood-onset schizophrenia (Table 1).

Risk for developing schizophrenia in 22qDS

The most prevalent psychiatric disorder in adults with 22qDS is schizophrenia [2••,7,8]. The only study using a sample that did not include psychiatric ascertainment, which was systematically collected from a congenital cardiac clinic, reported 22.6% (95% CI, 7.0% to 38%) of adults with 22qDS had schizophrenia or schizoaffective disorder [2••]. Other studies using mixed-ascertainment strategies that included psychiatric sources reported slightly higher rates of 27% (13/48) [7] and 31% (4/13) [8]. Other psychotic disorders are also found, but sample sizes are still small (Table 2). In contrast, rates of bipolar disorder appear to be similar to those in the general population [7]. One case of bipolar disorder was found in the 105 adults with 22qDS we assessed through our center; rates of anxiety, depressive, and attention-deficit disorders are higher than population expectations (Bassett and Chow, unpublished data).

These studies indicate the relative risk for schizophrenia in a patient with 22qDS is about 20 to 25 times the lifetime general population risk of 1% [6,9]. Therefore, 22qDS represents the highest known genetic risk group for schizophrenia development aside from two very rare groups of individuals: children of two parents with schizophrenia or monozygotic co-twins of affected individuals [6,9].

Comparability of 22qDS-Schizophrenia to Other Forms of Schizophrenia

Table 2 summarizes clinical features from studies involving nonoverlapping samples of four or more patients with 22qDS and schizophrenia. Results for a total of 82 individuals with 22qDS-schizophrenia reported to date indicate a range of clinical findings likely relating to inherent variability of expression and the small sample sizes obtained from diverse ascertainment sources.

Clinical signs and symptoms of schizophrenia

Several (but not all) reports [7,10] have indicated that with respect to schizophrenia's major clinical features, 22qDS-schizophrenia is largely indistinguishable from other forms of schizophrenia [11]. Ascertainment may play a role in differences observed. For example, median age at onset varies from 12 years for a sample restricted to childhood-onset schizophrenia [10] to 26 years when case identification involved parents who had transmitted the deletion to affected children [7]. The latter ascertainment strategy may also explain a finding of less severe negative symptoms [7] that was not found in a larger sample with no transmitting parents [12].

However, there may be some differences in auxiliary clinical features (eg, lower rates of comorbid substance use disorders) [12,13]. Also, some evidence indicates that patients with 22qDS-schizophrenia may have neurobehavioral characteristics other than schizophrenia's core symptoms [14]. These include greater severity of excitement and impulsivity [12] that may be associated with the short-lived temper or emotional outbursts commonly observed in patients with 22qDS-schizophrenia [11,14]. These features are not those of manic episodes, in which there are more prolonged mood changes. Consistent with this, a study of 86 children with 22qDS found no evidence of elevated rates of manic symptoms [15].

Management issues

Bassett et al. [2••] have proposed general clinical practice guidelines for adults with 22qDS. These include active monitoring for and treatment of commonly associated conditions with onset after infancy, including endocrinologic disorders. Genetic counseling for patients with 22qDS and schizophrenia [9] and management considerations specific to 22qDS are outlined in a recent book [1•].

Table 2 summarizes the limited information reported in the literature about antipsychotic treatment

Table 1. Prevalence of 22q11.2 deletions in SZ

22q11.2 deletion		Sample screened for 22q11.2 deletions						Molecular		Reference
%	*N*	Sample size	Mean age, *y* (range)	Male	MR	Population	Ascertainment issues	Screening	FISH confirmation	
Clinically screened and special population samples										
33.3	3	15	30 (16–67)	47%	47%	Israeli, SZ	Hospitalized record linkage (n = 7) or referred with suggestive 22qDS features (n = 8)	FISH	Yes	Gothelf et al. [42]
33.3	2	6	24 (18–54)	67%	17%	South African white, SZ	Patients (n = 6) with ≥ 2 22qDS features, of 85 patients assessed	FISH	Yes	Wiehahn et al. [43]
16.7	1	6	NI	NI	NI	Japanese (Okinawa), SZ	n = 6 selected by a geneticist, of 12 patients with facial features identified by psychiatrists (of 268 inpatients)	FISH	Yes	Sugama et al. [44]
7.1	2	28	NI	NI	All	Welsh, dual diagnosis, inpatient MR hospital	MR and psychotic illness	FISH	Yes	Murphy et al. [45]
5.3	4	75	NI	63%	Excluded	US, childhood-onset SZ (onset < 13 y)	No somatic illness	FISH	Yes	Sporn et al. [10]
More general samples										
2.4	2	85	31.8 (17–48)	61%	NI	South African white, SZ	Recontact of participants in a genetic study	SNP markers	Yes	Wiehahn et al. [43]
2	2	100	NI	78%	NI	US (Baltimore), mostly SZ	Recontact of participants in an epidemiologic study	FISH	Yes	Karayiorgou et al. [46]
1.1	3	265	NI	NI	NI	Polish, psychosis	NI	FISH	Yes	Pawlowska et al. [47]
0.9	6	634	45.8 (18–83)	63%	NI	Ashkenazi Jewish (Israel), SZ	Hospitalized patients, genetic association study	7 ms, 3 SNP markers from 600-kb *COMT* region	No	Horowitz et al. [48]
0.3	1	300	44.3 (19–78)	56%	NI	Japanese, SZ	Hospitals within 200 km of Tokyo	3 ms, 1 SNP (*COMT*) markers	Yes	Arinami et al. [49]

22qDS—22q11.2 deletion syndrome; FISH—fluorescence in situ hybridization; MLPA—multiplex ligation-dependent probe amplification; MR—mental retardation; ms—microsatellite; NA—not applicable; NI—no information; SNP—single nucleotide polymorphism; SZ—schizophrenia.

Table 1. Prevalence of 22q11.2 deletions in SZ *(Continued)*

22q11.2 deletion		Sample screened for 22q11.2 deletions						Molecular		Reference
%	*N*	Sample size	Mean age, *y* (range)	Male	MR	Population	Ascertainment issues	Screening	FISH confirmation	
0.2	1	470	NI	69%	Excluded	British (86 of 415 onset age < 18 y), SZ; Bulgarian (55 onset age < 18 y), SZ	Genetic association study	3-5–ms markers	No	Ivanov et al. [50]
0	0	177	47	54%	NI	Han Chinese (Taiwan), SZ	Private psychiatric hospital	4 *COMT* SNPs; 5 ms markers for 28 homozygous patients	NA	Chen et al. [51]
0	0	311	41	74%	NI	Dutch, SZ	146 (47%) patients with a deficit (negative) syndrome subtype	MLPA (DiGeorge kit)	NA	Hoogendoorn et al. [52]

22qDS—22q11.2 deletion syndrome; FISH—fluorescence in situ hybridization; MLPA—multiplex ligation-dependent probe amplification; MR—mental retardation; ms—microsatellite; NA—not applicable; NI—no information; SNP—single nucleotide polymorphism; SZ—schizophrenia.

Table 2. Nonoverlapping samples ($n \geq 4$) of 22qDS (FISH confirmed) with schizophrenia or SA

Schizophrenia and schizoaffective disorder							Sample ascertainment			
N	SA (%)	Diagnostic criteria	Median age at onset, *y* (range)	MR (%)	Negative symptoms	Response to antipsychotic treatment	Country	Details	Length of 22q11.2 deletion	References
4	1 of 4 (25%)	*DSM-III-R*	20.5 (15–26)	NI	NI	NI	US	Age > 15 y; study of 22qDS from a craniofacial clinic ($n = 14$)	NI	Pulver et al. [8]
4	0	*DSM-IV*	12 (11–12)	0	Less severe than other COS	Good	US	COS ($n = 75$) screened for 22q11.2 deletions	4 common 3 Mb	Sporn et al. [10]
4	0	*DSM-IV*	20.5 (9–24)	2 of 4 (50%)	Prominent	Poor	Israel	Psychiatric sources	3 common 3 Mb, 1 short proximal	Gothelf et al. [11]
6	NI (≥ 33%)	*DSM-IV*	NI	NI	NI	NI	US	From cohort ($n = 28$) referred with 22qDS (age 7–20 y observed to age 12–24 y); baseline anxiety disorders in 60.7%	NI	Gothelf et al. [13,21]
13	1 of 13 (8%)	*DSM-IV*	26 (16–41)	6 of 12 (50%)	Less severe	Good (11 of 12)	UK	Mixed (genetics, psychiatric, support group), $n = 48$ adults in a study of 22qDS; > 50% transmitting parents	NI	Murphy et al. [7]
18	0	*DSM-III-R*	16.7 (12–27)	14 of 18 (78%)	NI	NI	France, Belgium, Netherlands	Mixed (genetics, psychiatric, support group); age > 14 y with 22qDS ($n = 92$) in a study of *COMT* and hyperprolinemia	NI	Raux et al. [19]
33	5 of 33 (15%)	*DSM-III-R*, *DSM-IV*	21 (14–31)	15 of 33 (45%)	Similar to other schizophrenia or SA	Mixed, mostly good (unpublished data)	Canada (white)	Mixed (psychiatric, cardiology, genetics); adults with 22qDS ($n = 73$) in a study of *COMT*	32 common 3 Mb, 1 atypical 2 Mb (unpublished data)	Bassett et al. [36]

22qDS—22q11.2 deletion syndrome; COS—childhood-onset (age at onset < 13 y) schizophrenia; FISH—fluorescence in situ hybridization; Mb—million bases; MR—mental retardation; NI—no information; SA—schizoaffective disorder.

response in 22qDS-schizophrenia. We follow clinical practice guidelines for schizophrenia and have found that most of the 45 patients with 22qDS-schizophrenia or schizoaffective disorder we have seen in our program respond reasonably well to standard antipsychotic medications (Bassett and Chow, unpublished observations). Neurologic side effects are a significant issue (Bassett and Chow, unpublished observations), as would be expected in this group of patients with neurodevelopmental and learning difficulties. For example, patients with 22qDS appear to be at a 10-fold increased risk of suffering seizures of any type compared with expectations for patients on antipsychotic medications [16]. Thus, anticonvulsant treatment is often needed. Also, diagnosis and adequate treatment of endocrinologic disorders, including hypocalcemia and thyroid diseases, that can mimic psychiatric symptoms and medication side effects are essential [2••]. A small subgroup of patients have treatment nonresponsiveness and/or side effects to such an extent that electroconvulsive therapy is required; with adjunctive antipsychotic medications, this is generally effective (Bassett and Chow, unpublished observations).

Case reports of experimental treatments, such as metyrosine, in patients with 22qDS and psychotic disorders are difficult to interpret because patients often receive concurrent treatment with antipsychotic medications, and no long-term or controlled studies have been conducted. Also, some clinicians have observed clinical deterioration in patients with 22qDS-prescribed metyrosine (unpublished observations). Metyrosine is a tyrosine hydroxylase inhibitor that theoretically may decrease brain dopamine and have sedative effects. Properly designed controlled clinical trials of patients with 22qDS-schizophrenia are needed to document antipsychotic treatment response and adverse effects. In true nonresponders, in whom comorbid medical conditions have been detected and adequately treated, similarly well-designed trials would be needed to test experimental treatments.

Neurocognition

The main difference between 22qDS and general population forms of schizophrenia lies in the overall lower IQ that is characteristic of 22qDS. Most patients with 22qDS have an IQ in the borderline range (70–84), and some studies report mean IQ is similar whether patients have schizophrenia or no psychotic illness [17,18]. Another study, in which 69% of patients exhibited mental retardation (including 27% with IQ < 55), found lower IQ in patients with 22qDS and psychotic illnesses compared with those with no psychosis [19]. Although ascertainment bias affects rates, in general, about 40% of patients with 22qDS have mild mental retardation; more severe levels of mental retardation are uncommon [18].

Two studies have indicated that the cognitive profile of 22qDS-schizophrenia resembles that of other forms of schizophrenia [17,18]. One study showed that 27 adults with 22qDS-schizophrenia performed significantly more poorly on tests of motor skills, verbal learning, and social cognition than 29 adults with 22qDS but no psychosis [18]. Other tests (abstraction, visuospatial memory, visuospatial perception) also showed nominally worse performance in the schizophrenia group. Individuals with schizophrenia, on average, completed fewer years of schooling and, similar to 22qDS in general, had relative preservation of reading and spelling compared with arithmetic skills [18]. Another study using a different test battery reported that 13 adults with 22qDS and schizophrenia performed worse than 15 with no psychosis on individual tests of abstraction, attention, visuospatial memory, and visual recognition [17]. Both studies indicated that patient-to-patient variability in neurocognitive impairments may be a core feature of schizophrenic illness in 22qDS, as it is in the general population.

Brain imaging

Structural brain abnormalities in 22qDS-schizophrenia appear to be similar to those found in general population samples of schizophrenia, although only two studies to date have compared small samples of individuals with 22qDS with and without schizophrenia [20,21]. Findings include smaller overall brain volume [20], midline defects such as cavum septum pellucidum [22], and white matter hyperintensities on MRI [20,22]. As in general schizophrenia populations, some evidence suggests that increased ventricular and sulcal cerebrospinal fluid and decreased temporal gray matter volumes are associated with schizophrenia in 22qDS [20,23]. A young sample showed no differences in brain volumes between 7 psychotic and 12 nonpsychotic patients with 22qDS; however, the latter (mean age 18 years) remain at risk for developing schizophrenia [21]. Qualitative MRI findings for 68 adults with 22qDS revealed evidence of neuronal migration abnormalities in 2 (8%) of 26 patients with schizophrenia—polymicrogyria in one and right cerebellar disorganization in the other—whereas none was found in 42 nonpsychotic individuals [24].

Neuropathology

A recent study reported findings in three adults with schizophrenia in the first postmortem brain tissue study of 22qDS [24]. The most dramatic finding was a neuronal migration abnormality in one case, including bilateral periventricular nodular heterotopia in the frontal lobes, large numbers of ectopic neurons scattered throughout the frontal white matter, and evidence of extensive hippocampal and minor cerebellar migration defects [24]. The other two cases showed no evidence of migration abnormalities, but both had extensive astrocytic gliosis and focal collections of macrophages in the cerebral white matter—suggestive of cerebrovascular events—including the site of a T2-hyperintensity focus visible on MRI [24]. Also, one case showed a small region of corpus callosum

thinning, and the other showed severe cerebrovascular hypertensive-type changes [24]. These initial neuropathologic results suggest that early developmental brain changes (eg, neuronal migration abnormalities affecting connectivity) and, later, vascular pathology may play a role in the pathogenesis of the neuropsychiatric phenotype of 22qDS, including white matter imaging abnormalities and schizophrenia.

Molecular Genetics

Complexity of the 22q11.2 deletion region

The most common (3-Mb) 22q11.2 deletion region contains more than 45 genes (http://www.genome.ucsc.edu). Hemizygous loss of at least 30 of these genes is seen in most individuals with 22qDS [25••]. However, specific causes of the high prevalence of schizophrenia in 22qDS remain to be identified.

No studies have yet taken into account the 22q11.2 region's marked structural variability and numerous repeat sequences. For example, genes *PRODH*, *TBX1*, *GNB1L*, *COMT*, *ARVCF*, *DGCR8*, *RANBP1*, *ZDHHC8*, and *PIK4CA* are in regions of segmental duplication or copy number variation (http://projects.tcag.ca/variation/). This could affect interpretation of single nucleotide polymorphism (SNP) or other marker results and could also contribute to inconsistency of molecular genetic findings.

Length of 22q11.2 deletion

No single 22q11.2 deletion region is both necessary and sufficient for expressing the major features of 22qDS [26]. Hemizygosity of various lengths involving overlapping and nonoverlapping segments within the 22q11.2 region is sufficient; there is no "critical" region [26]. The relatively few studies reporting on the extent of 22q11.2 deletions in 22qDS and schizophrenia are consistent with this (Table 2). A typical 3-Mb hemizygous 22q11.2 deletion is most commonly associated with schizophrenia [4]. However, deletions of various extents have been reported, and no region of 22q11.2 hemizygosity is shared by all individuals with 22qDS and schizophrenia [4] (Table 2). For example, 22 adults with schizophrenia in one study had 22q11.2 deletions that included most of the telomeric half of the 3-Mb common deletion. Proximally, the deletion did not include the *PRODH* gene in three individuals [4]. In contrast, the telomeric 22q11.2 deletion region was not included in case reports of other deletions with schizophrenia [4]. Thus, no evidence indicates that the length or position of the 22q11.2 deletion predicts schizophrenia expression in 22qDS.

Linkage and association studies

The 22q11.2 region and general population samples of schizophrenia

Although no linkage study has shown genome-wide significance, meta-analyses implicate a broad region of the long arm of chromosome 22 in general schizophrenia susceptibility [27,28]. One study found suggestive genome-wide linkage of schizoaffective disorder to 22q11 (logarithm of the odds = 1.96) [29]. Arinami [30••] reviewed molecular genetic studies in humans with 22q11.2 deletions and murine models of 22qDS relevant to schizophrenia up to mid-2006. He concluded that there was no evidence to support mutations of genes in the 22q11.2 region contributing to familial forms of schizophrenia in most families in the general population. This review also included association studies that assessed 22q11.2 candidate genes in general population samples of schizophrenia. For each of six genes (*COMT*, *PRODH*, *ZDHHC8*, *CLDN5*, *DGCR14*, and *DGCR2*), the association results were summarized as inconclusive or inconsistent [30••]. Studies published since mid-2006 generally are in line with these conclusions [31,32]. One study reported that *TBX1*, which has been shown to play an important role in congenital heart defects in 22qDS, may also play a role in behavior [33]. However, a general population sample of schizophrenia showed no association to *TBX1* [34]. Three SNPs in the *PIK4CA* gene showed significant association (odds ratio 1.54; 95% CI, 1.28–1.86) to schizophrenia in a Dutch case-control study of 138 genes corrected for multiple testing [35]. All studies need replication.

Association of 22q11.2 genetic variants and schizophrenia in 22qDS

Few studies have investigated candidate genes for schizophrenia susceptibility in patients with 22qDS. A study of the *COMT* functional $Val^{158/108}Met$ allele in 73 white adults with 22qDS found that the lower-activity Met allele was not significantly more prevalent than the Val allele in 33 patients with schizophrenia [36], which was consistent with other studies with fewer affected patients [7,19]. Met *COMT* hemizygosity is present in about one half of patients with 22qDS (with and without psychotic illness) [36]. Several studies have found no significant differences between Met and Val allele carriers in positive and negative symptom severity [7,36,37]. The results suggest that the *COMT* functional allele is not a major factor in schizophrenia expression in 22qDS, similar to findings for schizophrenia in the general population. However, another study of 22qDS in which most patients had mental retardation reported that when combined with hyperprolinemia, the Met *COMT* allele was associated with a broad definition of psychotic conditions comprising schizophrenia (n = 18) and other disorders (n = 15), including autism and schizotypal personality, compared with 59 nonpsychotic patients with 22qDS [19].

In contrast to core symptoms of schizophrenia, *COMT* Met allele hemizygosity was associated with more severe excitement symptoms (including impulsivity, uncooperativeness, and hostility) and worse performance on frontal cognitive tests, even after accounting for schizophrenic illness effects [36]. These results

suggest that hemizygosity of the *COMT* functional allele may exert a modest effect on some measures of frontal brain functioning in 22qDS, implicating elevated levels of tonic dopamine activation in these aspects of expression, although not in risk for psychosis itself.

Possible Risk and Predictive Factors for Schizophrenia Expression in 22qDS

In addition to cross-sectional studies, the high prevalence of schizophrenia in adults with 22qDS provides an opportunity for prospective studies to determine factors that could predict who may develop schizophrenia. One group has studied a cohort of 28 individuals with 22qDS at two points in time: at baseline referral for assessment at age 7 to 20 (mean 13) years and on average 5 years later, at age 12 to 24 (mean 18) years [13]. Most had a nonpsychotic disorder at baseline (eg, 60.7% had an anxiety disorder). Nine (32.1%) met criteria for a psychotic illness at time 2, including six with schizophrenia or schizoaffective disorder [13]. In contrast to the three cross-sectional studies summarized in the previous section, which had a total sample of 213 mostly adults with 22qDS and found no significant association of the *COMT* Met allele with psychotic illness [7,19,36], this allele was reported to be associated with the nine patients with psychotic illness in this young cohort [13]. The cohort study also reported that diagnosing a psychotic disorder at follow-up was associated with an average 10-point decline in verbal IQ from baseline and greater severity of parental reports of anxiety or depression and researcher ratings of psychotic symptoms at baseline.

As noted, no differences were observed in brain volumes between the 7 psychotic and 12 nonpsychotic patients with 22qDS studied prospectively with MRI scans and compared with normal controls [21]. There was also no evidence of the accelerated decrease in cortical gray matter volume commonly reported in other samples at high risk for schizophrenia. The decrease in volume (pruning) of the superior temporal gyrus gray matter usually seen in normal adolescent development was not observed in 22qDS, possibly due to delayed maturation [21]. The significance of the results from this cohort study is limited by the small sample size, possible ascertainment bias of patients referred for a psychiatric study, factors selected for investigation, and the young age of nonpsychotic patients at follow-up. These early findings will need to be replicated in larger samples using broader ascertainment strategies. The patients also need to be observed for a longer time, and more potential risk factors must be studied.

Possible Pathogenetic Pathways to Schizophrenia

Notably, 22q11.2 hemizygosity does not predict the actual mechanism of phenotypic expression, which would include several possibilities, none of which has been proven for 22qDS-schizophrenia. For example, haploinsufficiency refers to lower expression of a gene product that is inadequate for normal functioning when an otherwise-normal gene is present in only a single copy. However, for many genes, compensatory mechanisms can ensure sufficient protein expression even with only one copy of a gene (eg, with hemizygosity). Also, some genes may be expressed in ratios lower than the expected 0.5 ratio or have expression levels that are highly variable between individuals. Contiguous genes imply that genes that are physically close to each other in a chromosomal region act together to express certain phenotypic traits. Loss of heterozygosity would be the applicable term if a deletion combined with a mutational event within the normal allele on the intact chromosome and rendered the cell hemizygous for a deleterious allele.

Despite the current lack of definitive knowledge, accumulating evidence supports the likelihood that variants and/or hemizygosity of several genes within the 22q11.2 region may be necessary for expression of major 22qDS phenotypes and that variants of genes from other areas of the genome can modify the effects of 22q11.2 hemizygosity [25••,26,38]. Murine models have revealed substantially different sensitivity to gene dosage in different tissues and at different times, underlying the importance of the developmental context within which gene dosage reduction occurs [39]. Using a murine model of the 22q11.2 deletion, Meechan et al. [40] showed that expression levels of at least nine genes are reduced in embryonic tissue and developing and adult brain tissue. The authors proposed a role for subtle but pervasive pathology of cortical circuits in 22qDS due to this decreased expression of multiple genes in a quantitatively stable cell population contributing to schizophrenia vulnerability in 22qDS [40]. Another group using a murine model recently selected differentially expressed genes in hippocampal tissue for validation studies [41]. Eight genes from the deletion region and 15 (56%) of 27 other genes were validated as true changes [41]. Another study showed that phenotypic variability itself may be related to mRNA dosage [39].

Meechan et al. [25••] recently published a comprehensive review of 22qDS pathogenesis and how gene dosage effects may be involved. This review goes through each of three possibilities with respect to major phenotypic expression: 1) a single gene causing all phenotypes; 2) independent action of several contiguous genes at distinct sites, including the brain; or 3) combinational effects of multiple genes (ie, the cooperative nature of diminished gene dosage and synergy between subsets of genes expressed at distinct times) [25••]. This review makes a case for the role of several subsets of genes in brain development: 1) those with unifying transcriptional control, 2) cell cycle genes, 3) mitochondrial genes, and 4) those with expression restricted to the adult brain. These subsets of genes could affect neuronal cell migration, synaptogenesis, and/or neurogenesis—all plausible mechanisms in schizophrenia.

Conclusions

22qDS is an identifiable genetic subtype of schizophrenia affecting about 1 in 100 patients. However, the relatively small numbers of individuals with 22qDS and schizophrenia reported indicate that the syndrome continues to be underrecognized. More continuing education for clinicians about 22qDS and its commonly associated features is needed. How patients with 22qDS are ascertained is an issue that can potentially bias results in all studies. Despite these limitations, we are beginning to learn more about the clinical and molecular features of 22qDS-schizophrenia. Most clinical neuropsychiatric features appear broadly similar to those observed in general schizophrenia population samples, yet little is known about the molecular genetics or pathogenesis of 22qDS-schizophrenia. Neither length of the deletion nor the functional allele of *COMT* appears to be a major factor in risk for schizophrenia expression. Murine models suggest multiple gene dosage effects may play a role, although this remains to be proven. Further prospective and larger cohort studies across the lifespan will begin to address the many remaining questions. Nevertheless, the results to date support 22qDS as an important subtype of schizophrenia and a valuable model for studying neurodevelopmental mechanisms involved in the illness.

Acknowledgments

The authors wish to thank the patients, their families, centers across Canada that make research studies of 22qDS possible, and Gladys Wong for assistance in preparation of the manuscript.

Disclosures

This research was supported by grants from the Canadian Institutes of Health Research, W. Garfield Weston Foundation, the National Alliance for Research on Schizophrenia and Depression, and Canada Research Chair in Schizophrenia Genetics to Dr. Bassett. No further potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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This chapter provides updated genetic counseling guidelines for 22qDS-schizophrenia and places this genetic subtype in the context of other forms of schizophrenia.

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This article provides clinical practice guidelines for adults with 22qDS and a comprehensive table listing 43 common features of 22qDS.

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