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MINIREVIEW

Analyses of the associations between the genes of 22q11 deletion syndrome and schizophrenia

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Abstract Schizophrenia is a severe, debilitating mental disorder characterized by profound disturbances of cognition, emotion and social functioning. The lifetime morbid risk is surprisingly uniform at slightly less than 1% across different populations and different cultures. The evidence of genetic risk factors is our strongest clue to the cause of schizophrenia. Linkage and association analyses have identified genes associated with the development of schizophrenia. However, most of the alleles or haplotypes identified thus far have only a weak association or are reported to be population specific. A deletion of 22q11.2 that causes the most common microdeletion syndrome (22q11DS) with an estimated prevalence of 1:2,500–1:4,000 live births may represent one of the greatest known genetic risk factors for schizophrenia. Schizophrenia is a late manifestation in approximately 30% of patients with 22q11.2 deletion, comparable to the risk to offspring of two parents with schizophrenia. Clinical and neuroimaging assessments indicate that 22q11DS-schizophrenia is a neurodevelopmental model of schizophrenia. Recent studies have provided evidence that haploinsufficiency of *TBX1* is likely to be responsible for many of the physical features associated with the deletion. Most of the genes in the 22q11 deletion region are conserved together on mouse chromosome 16, enabling the generation of mouse models. Similarities in the cardiovascular and other phenotypes between 22q11DS patients and mouse models can provide important insights into roles of genes in neurobehavioral phenotypes. Because more than one gene in the 22q11DS region is likely to contribute to the marked risk for schizophrenia, further extensive studies are necessary. Analyses of 22q11DS will help clarify the molecular pathogenesis of schizophrenia.

Keywords Chromosome 22 · Microdeletion · Haploinsufficiency · Schizophrenia · Prepulse inhibition · Mouse model

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Introduction

Schizophrenia, a devastating mental disorder that affects approximately 1% of the world's population, is a genetically complex disorder. The multifactorial polygenic model has received the most support for the mode of inheritance responsible for the familial distribution of schizophrenia; therefore, a variety of genetic, environmental and stochastic factors are likely involved in the etiology. However, it is also possible that specific genes play a major role in susceptibility to schizophrenia, and efforts to identify such genes have revealed that an overall loss of DISC1 function by either haploinsufficiency or dominant-negative, or both (Ishizuka et al. 2006), or gene(s) involved in 22q11.2 deletion syndrome (22q11DS) substantially increases susceptibility to schizophrenia. Alteration of *DISC1* has been reported in only two families, whereas the

22q11 deletion is detected relatively frequently in schizophrenia patients; a number of studies have shown that 22q11DS-schizophrenia is a true genetic subtype of schizophrenia (Bassett and Chow 1999; Karayiorgou and Gogos 2004). Here I review recent studies of humans and rodents that have clarified the genetic basis for this specific subtype.

22q11DS and psychiatric problems

22q11DS is the most common microdeletion syndrome, with an estimated prevalence of 1:2,500–1:4,000 live births (Tezenas Du Montcel et al. 1996; Oskarsdottir et al. 2004). It is estimated that only 5–10% of 22q11.2 deletions are inherited (Scambler 2000). The deletion of 22q11.2 is associated with a wide variety of birth defects and malformations that occur in various combinations and with widely differing severity. 22q11DS is associated with several diagnostic labels including DiGeorge syndrome (DGS), velocardiofacial (or Shprintzen) syndrome (VCFS), conotruncal anomaly face, Cayler syndrome and Opitz GBBB syndrome.

22q11DS is also associated with learning difficulties, specific cognitive deficits and increased risk of neuropsychiatric disorders (Scambler et al. 1992; Swillen et al. 1997a, b; Henry et al. 2002). Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric problems associated with 22q11DS in children. ADHD, primarily the inattentive subtype, is present in 35–55% of 22q11DS cases (Gothelf et al. 2004a). In addition, approximately 11% of children with 22q11DS are autistic, and these children show greater developmental delay than those without autistic spectrum disorder (Fine et al. 2005). Other common psychiatric problems in children with 22q11DS include affective disorders such as bipolar disorder and depression (Arnold et al. 2001).

In adults with 22q11DS, high rates of obsessive-compulsive disorder (OCD) and schizophrenia have been reported. In one study, diagnostic criteria for OCD were fulfilled in 32.6% of individuals with 22q11DS (Gothelf et al. 2004b). Schizophrenia is a late manifestation in approximately 30% of cases, which is comparable to the risk to offspring of two parents with schizophrenia. Bassett et al. (2005) described a study of 78 adults (age ≥17 years) with 22q11DS who met two or more of seven broad categories of features (dysmorphic facies, hypernasal speech, history of learning difficulties, cardiac defect, thymic hypoplasia, other birth defects and hypocalcemia). Intellectual disability was observed in 92.3% of the adults with 22q11DS (borderline intellect, 51.3%; mild mental retardation, 33.3% and moderate mental retardation, 7.7%). Adjusting for ascertainment source, 25.8% of patients had cardiac anomalies and 22.6% had schizophrenia.

Prevalence of the 22q11.2 deletion in unselected schizophrenia patients

Several studies screened for 22q11.2 deletion in adult patients with schizophrenia. The first study found such a deletion in 2 of 100 patients with schizophrenia (Karayiorgou et al. 1995), and the second study found a deletion in 1 of 326 psychiatric inpatients (Sugama et al. 1999). The patient's full IQ indicated mild retardation with the verbal IQ being higher than the performance IQ. We screened 300 patients meeting the DSM-IIIR criteria for schizophrenia and identified 1 patient with 22q11.2 deletion and mild retardation (Arinami et al. 2001). Additional studies screened for 22q11.2 deletion in a subset of schizophrenia patients. Usiskin et al. (1999) recruited 47 patients with childhood onset schizophrenia and found that 3 carried a deletion of 22q11.2; all patients had premorbid impairment of language, motor and social development. Thus, there is a 20- to 80-fold higher prevalence of the 22q11.2 microdeletion in patients with schizophrenia relative to that of the general population. A deletion of chromosome 22q11.2 may represent one of the greatest known genetic risk factors for schizophrenia.

Psychopathologic characterization of 22q11.2

Although many of physical symptoms in 22q11DS are well understood, far less is known about the apparent changes in brain structure and function, and their relation to the range of cognitive impairments and psychiatric disorders. A study of 33 children and adults with 22q11DS reported a mean full-scale IQ in the borderline range of intellectural functioning (71.2±12.8) (Moss et al. 1999). With regard to psychosocial and behavioral functioning, significantly elevated scores for the ''social problems,'' ''attention problems'' and ''withdrawn'' sub-scales were indicated by the Child Behvior Checklist (Swillen et al. 1997a, b).

Examination of the schizophrenia phenotype in individuals with 22q11DS without metal retardation (IQ ≥70) revealed no significant differences in age at onset, lifetime or cross-sectional core positive and negative schizophrenic symptoms or global functioning

between schizophrenic patients with 22q11DS and those without it. Thus, the core clinical schizophrenia phenotype does not differ significantly between individuals with the 22q11 deletion subtype and those with schizophrenia who do not have the 22q11 deletion subtype (Bassett et al. 2003). Because high rates of congenital dysmorphic features, developmental structural brain abnormalities and cognitive dysfunction in 22q11DS are consistent with a subtype of schizophrenia representing an especially neurodevelopmental form of the illness, the authors concluded that the findings support the utility of 22qDS-schizophrenia as a neurodevelopmental model of schizophrenia as well as support for prospective studies of individuals with 22qDS to help identify precursors of schizophrenia.

Neurocognitive dysfunction has long been considered a core component of schizophrenia (Ragland 2003). The presence of cognitive deficits before and at the onset of schizophrenia supports a neurodevelopmental hypothesis of pathogenesis and indicates that chronic illness and/or treatment do not cause these deficits (Weinberger 1987). Chow et al. (2006) described the neurocognitive profiles of individuals with 22q11DS with and without schizophrenia. The two groups had similar mean estimated IQs and academic achievement; however, the neurocognitive profiles differed significantly. The group with schizophrenia performed significantly more poorly on tests of motor skills, verbal learning and social cognition. Thus, in adults with 22q11DS, the pattern of neurocognitive differences between those with and without schizophrenia appears similar to that between patients with schizophrenia and control subjects. The authors concluded that 22q11DS-schizophrenia is a genetic model for neurodevelopmental investigations of schizophrenia (Bassett et al. 2003; Chow et al. 2006).

Brain morphology in 22q11DS cases

MRI studies of 22q11DS cases revealed decreases (8.5–11%) in total brain volume (Eliez et al. 2000; Kates et al. 2001; Simon et al. 2005) and left parietal and right occipital grey matter volume (Eliez et al. 2000; Kates et al. 2001). Reduced white matter volume in the right cerebellum (Eliez et al. 2000) and bilateral frontal, parietal and temporal regions and the external capsules as well as increased fractional anisotropy in posterior brain regions were also reported (Kates et al. 2001, 2004; van Amelsvoort et al. 2001, 2004; Barnea-Goraly et al. 2003; Simon et al. 2005). Simon et al. (2005) suggested that increased fractional anisotropy in the posterior brain regions may be indicative of corpus callosum displacement due to enlarged cerebral ventricles in individuals with 22q11DS. Campbell et al. (2006) reported a significant reduction in cerebellar grey matter and white matter reductions in the frontal lobe, cerebellum and internal capsule in individuals with 22q11DS. Among individuals with 22q11DS, a significant positive correlation was found between the severity of the schizotypy score and grey matter volume of the temporo-occipital regions and the corpus striatum and between social behavioral difficulties and grey matter volume in the frontostriatal regions. Thus, there is preliminary evidence for specific vulnerability of the frontostriatal and cerebellar-cortical networks in 22q11DS (Campbell et al. 2006).

Linkage and association studies

Several studies have suggested linkage between 22q11 and schizophrenia (Myles-Worsley et al. 1999; Takahashi et al. 2003; Williams et al. 2003). However, in a multicenter sample of 779 pedigrees, no significant evidence for linkage to schizophrenia or for linkage associated with early onset, sex or heterogeneity across sites was observed. The authors interpreted these findings to mean that the population-wide effects of putative 22q schizophrenia susceptibility loci are too weak to detect by means of linkage analysis even in large samples (Mowry et al. 2004). These linkage findings indicate that mutations of genes on 22q11 are unlikely to contribute to familial aggregation of schizophrenia in most families.

Six genes from the region deleted in 22q11DS have been reported as candidate genes for association with schizophrenia (Fig. 1). These genes are *COMT*, *PRODH*, *ZDHHC8, CLDN5*, *DGCR14 and DGCR2*. *COMT* has been studied the most extensively.

COMT encodes catechol-*O*-methyl-transferase, an enzyme that is critical for dopamine catabolism. A common polymorphism in *COMT* creates a valine-to-methionine (Val158/108Met) substitution at codon 108 or 158 (codon 158 of the membrane-bound form; codon 108 of the soluble form). The Val and Met isoforms are high- and low-activity enzymes, respectively (Lachman et al. 1996). Individuals homozygous for the high-activity Val allele have approximately 40% higher enzyme activity in the prefrontal cortex than do individuals homozygous for the Met allele (Chen et al. 2004a), and they perform less well in tests of cognition and working memory (Egan et al. 2001; Malhotra et al. 2002). A similar result was found in

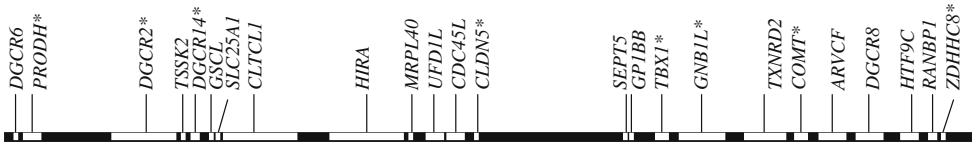

Fig. 1 Gene array of the proximal 1.5-Mb portion of chromosome 22q11.2 deleted in most of patients with 22q11.2 deletion syndrome (positions of chromosome 22, 17.2–18.5 Mb NCBI Build 36.1). *Asterisks* indicate the genes described in the text

22q11DS patients. Met-hemizygous patients perform significantly better on a composite measure of executive function (comprising set-shifting, verbal fluency, attention and working memory) than do Val-hemizygous patients. The authors concluded that a functional genetic polymorphism in the 22q11 region may influence prefrontal cognition in individuals with *COMT* haploinsufficiency (Bearden et al. 2004). However, hemizygosity of the Met allele was shown to be associated with cognitive decline and increased severity of psychosis in patients with 22q11 deletion (Gothelf et al. 2005). Thus, a complex relation exists between COMT activity associated with a specific *COMT* polymorphism and psychopathology and schizophrenia.

Association studies of *COMT* Val/Met and schizophrenia have yielded inconsistent results (Fan et al. 2005; Munafo et al. 2005). Although most studies examined the Val/Met polymorphism, other *COMT* genotypes or haplotypes might have greater effects (Shifman et al. 2002; Bray et al. 2003; Dempster et al. 2006), though the associations have not yet been examined thoroughly.

PRODH encodes proline dehydrogenase (POX), a mitochondrial enzyme involved in proline catabolism and glutamate biosynthesis. POX catalyzes the conversion of L-proline to Δ^1-pyrroline-5-carboxylate, which can be converted to glutamate or γ-aminobutyric acid (GABA). Some patients with 22q11DS showed elevated levels of plasma proline (Goodman et al. 2000; Jacquet et al. 2002). However, the levels of hyperprolinemia are considerably lower than those associated with hyperprolinemia type I (OMI, 239,500), a rare and usually benign condition. Hyperprolinemia was associated with schizoaffective disorder and bipolar patients, but not with schizophrenia (Jacquet et al. 2005). Extensive functional assays for genetic variation of *PRODH* were reported (Hoogendoorn et al. 2004; Bender et al. 2005), and some of the polymorphisms expected to be associated with decreased ROX activity were associated with schizophrenia (Jacquet et al. 2002; Liu et al. 2002). However, subsequent studies have failed to confirm the associations (Rapoport et al. 2005; Jacquet et al. 2005, 2006). Deletion of the entire gene was observed in two siblings with schizophrenia (Jacquet et al. 2002). However, deletion of the entire gene is also found in the general population (Ohtsuki et al. 2004).

ZDHHC8 encodes a putative transmembrane palmitoyl-transferase. Palmitoylation is a post-translational modification with the lipid palmylate that reversibly modifies many neuronal proteins, including neurotransmitters (el-Husseini Ael and Bredt 2002). *ZDHHC8* was suggested as a schizophrenia candidate gene through screening for association with schizophrenia of 72 single-nucleotide polymorphisms (SNPs) distributed across the entire 1.5-Mb region deleted in 22q11DS. Five SNPs were associated with schizophrenia, and among them, 1 SNP (rs175174A/G) localized to intron 4 of *ZDHHC8* had the strongest association. This SNP was associated with the relative abundance of unspliced transcripts. The A allele was associated with schizophrenia in women by the transmission disequilibrium test (TDT) and with higher levels of unspliced transcripts (Mukai et al. 2004). The biologic effects of this allele on the abundance and function of the enzyme are unknown. Other studies have not confirmed the association of rs175174 with schizophrenia (Faul et al. 2005; Glaser et al. 2005; Otani et al. 2005; Saito et al. 2005) or have shown an association of the rs175174G, not the A allele, with schizophrenia (Chen et al. 2004b). The role of *ZDHHC8* in 22q11DS-schizophrenia is unclear.

A weak association of SNPs in *CLDN5*, which encodes claudin-5, a member of the claudin family, with schizophrenia has been reported (Sun et al. 2004; Ye et al. 2005). The claudin proteins are a major component of tight junctions that play crucial roles in responses to changing natural, physiologic and pathologic conditions. The relation between claudin-5 and schizophrenia is not known. Associations of promoter polymorphisms of *DGCR14* were also reported (Wang et al. 2006); however, confirmatory studies have not been reported.

DGCR2 encodes a putative adhesion receptor protein. Associations between *DGCR2* polymorphisms and schizophrenia were reported. In a gene expression analysis, the risk allele of a coding SNP

associated with schizophrenia was found to be associated with a reduced expression of DGCR2. The expression of *DGCR2* was also found to be elevated in the dorsolateral prefrontal cortex of schizophrenic patients relative to matched controls. This increase is likely to be explained by exposure to antipsychotic drugs because significantly elevated levels of DGCR2 transcripts were found in rats exposed to antipsychotic medication (Shifman et al. 2006).

Haploinsufficiency of *TBX1* is associated with 22q11DS and the psychopathology in human

TBX1 that encodes TBX1 protein, a member of the T-box transcription factor family, is located in the 1.5-Mb region deleted in 22q11DS. *TBX1* point mutations were identified in five individuals with classic 22q11DS, but without the common chromosomal deletion (Yagi et al. 2003), suggesting that *TBX1* is a major contributor to 22q11DS. One of these mutations was found to be a loss-of-function mutation (Stoller and Epstein 2005). The contribution of *TBX1* haploinsufficiency to psychiatric disease was suggested by the identification of a family with VCFS in a mother and her two sons. These three patients all had a null mutation of *TBX1*. A diagnosis of Asperger syndrome in one of the sons was made after psychiatric assessment (Paylor et al. 2006).

Mouse models of 22q11DS

Because 22q11DS is caused by hemizygosity of at least 20 genes, the most appropriate animal model would be one with a deletion identical to that in humans. With the exception of *CLTCL1*, the genes deleted in 22q11DS are conserved together on mouse chromosome 16 with only some minor changes in gene order. Lindsay et al. (1999) engineered a chromosome deletion (*Df1*) spanning a segment of the region of mouse chromosome 16 deleted in human 22q11DS. Mice heterozygous for the deleted region (*Df1*/+) developed cardiovascular abnormalities identical to those associated with 22q11DS. In certain genetic backgrounds, *Df1*/+ mice developed mild thymic and parathyroid defects. Thus, in *Df1*/+ mice, as in human patients, the heart and thymic phenotypes are expressed independently (Taddei et al. 2001). These findings suggest that the mouse orthologs of the gene(s) responsible for some of the most common 22q11DS phenotypes are located within *Df1*.

The conotruncal defects of mice hemizygous for a 1.5-Mb deletion corresponding to that on 22q11 can be partially rescued by a human BAC containing the *TBX1* gene, and mice heterozygous for a null mutation in *Tbx1* develop conotruncal defects (Merscher et al. 2001). Thus, *Tbx1* is likely to be responsible for many of the physical features associated with the deletion.

Behavioral abnormalities in mouse models of 22q11DS

Although many psychiatric symptoms cannot be readily studied in rodents, component parts of psychiatric disorders can be effectively studied in mice. Impairments in working memory and sensorimotor gating that are associated with schizophrenia can be tested in mice. The prepulse inhibition (PPI) of the acoustic startle reflex is considered an intermediate phenotypic marker of sensorimotor gating in schizophrenia. The PPI assay has been a major component of the behavioral analyses of mouse models of schizophrenia. Reduced PPI has been reported in patients with 22q11DS (Sobin et al. 2005). However, the specificity of reduced PPI to individual psychiatric disorders is low, because abnormal PPI is associated with schizophrenia, schizotypal personality, OCD, Tourette's syndrome, Asperger syndrome and Huntington's disease (Braff et al. 2001).

Paylor et al. (2006) mapped PPI deficits in a panel of mouse mutants that carry deletions and defined a PPI critical region that comprises four genes. They then used single-gene mutants to identify the causative genes. The PPI assay revealed that either $Tbx1^{+/-}$ or $Gnb1l^{+/-}$ mice had reduced PPI. Thus, normal gene dosage of both *Tbx1* and *Gnb1l* is required for normal sensorimotor gating in mice. Expression of *Tbx1* is limited to the vasculature in brains of full-term mouse embryos and adult mice (Paylor et al. 2006). A role for the microvasculature in the pathophysiology of schizophrenia has been proposed on theoretical grounds because microvascular damage could satisfy both the developmental and degenerative models of schizophrenia (Hanson and Gottesman 2005). *GNB1L* located in 2 kb telomeric to *TBX1* encodes guanine nucleotide-binding protein beta subunit-like protein 1. The phenotypes with which mutations or haploinsufficiency of *GNB1L* are associated have not been reported.

$Tbx1^{+/-}$ mice did not display distinguishable differences in locomotor activity, habituation, nesting or locomotor responses to amphetamine compared with wild-type littermates (Hiroi et al. 2005). Therefore, it is also possible that haploinsufficiency of *Tbx1* does not

cause the behavioral abnormalities associated with 22q11DS with the exception of PPI deficits in mice.

Mouse models of 22q11 duplication

Reciprocal duplication of the chromosome region deleted in 22q11DS has been identified. The phenotypes of individuals with this duplication range from mild to severe, sharing a tendency for velopharyngeal insufficiency with DGS/VCFS, but having other distinctive characteristics as well (Edelmann et al. 1999; Ensenauer et al. 2003; Hassed et al. 2004; Portnoi et al. 2005; Yobb et al. 2005). Such individuals exhibit impulsivity, aggression, oppositional defiant disorder, social immaturity, short attention span, attention deficit disorder and cognitive deficits, although their neuropsychiatric disorders have not been fully characterized. Mice that overexpress an approximately 200-kb region of human 22q11.2 containing *Sept5*, *Gp1bb*, *Tbx1* and *Gnb1l* exhibited spontaneous sensitization of hyperactivity and a lack of habituation. These effects were ameliorated by antipsychotic drugs (Hiroi et al. 2005).

Additional modifier

Although many of the physical features of 22q11DS are likely caused by haploinsufficiency of *TBX1*, its variable expressivity indicates the involvement of additional modifiers. *VEGF* that encodes vascular endothelial growth was reported to be a modifier of cardiovascular birth defects in 22q11DS (Stalmans et al. 2003). The $Vegf^{164}$ isoform caused birth defects in mice, reminiscent of those found in patients with 22q11DS. Knocked-down *vegf* levels enhanced the pharyngeal arch artery defects induced by *tbx1* knockdown in zebrafish. A *VEGF* promoter haplotype was associated with an increased risk for cardiovascular birth defects in individuals with 22q11DS. *FGF8* that encodes fibroblast growth factor 8 was reported as a potential modifier of 22q11DS (Frank et al. 2002). Fibroblast growth factor 8 is a signaling molecule expressed in the ectoderm and endoderm of the developing pharyngeal arches and is known to play an important role in survival and patterning of first arch tissues. The *Fgf8* mutants display the complete array of cardiovascular, glandular and craniofacial phenotypes seen in human deletion 22q11 syndromes.

An interaction between *COMT* and *NOTCH4* genotypes in the treatment response to typical neuroleptics in patients with schizophrenia has been reported (Anttila et al. 2004).

Conclusions and future directions

Microdeletion of 22q11.2 represents one of the greatest known genetic risk factors for schizophrenia. Although it is likely that more than one gene contributes to the marked risk, studies in humans and mice have narrowed the possible causative gene(s). *TBX1* plays a crucial role in the cardiovascular defects and may be involved in some of the behavioral abnormalities and psychiatric disorders associated with 22q11DS. Other genes are also important candidates for behavioral abnormalities and psychiatric disorders associated with 22q11DS. For example, transcriptional and behavioral interactions between *Prodh* and *Comt* in dopamine signaling in the frontal cortex have been reported (Paterlini et al. 2005), and therefore, the complex interactions between genes located in the region must be elucidated.

Comprehensive analyses of genomic variations in 22q11.2 in patients with schizophrenia, particularly those with premorbid impairment of language, motor and social development, are also necessary. Analyses of the expression of specific transcripts and proteins of the genes located in the deleted region in brains of patients with psychiatric disorders will also help narrow the search for causative genes. Expression of mouse orthologs of the genes in the 22q11DS region (Maynard et al. 2003) provides fundamental information for such studies. Furthermore, 22q11DS yields highly variable behavioral and psychiatric phenotypes as well as physical abnormalities, suggesting the involvement of genetic modifiers in expression of a specific phenotype. 22q11DS is associated with ADHD, autism, OCD, bipolar disorders, depression and schizophrenia. Genome-wide analyses of DNA from individuals with 22q11DS may help identify other genes that contribute to the development of these psychiatric disorders. In conclusion, analyses of 22q11DS are contributing to our understanding of the genetics and molecular pathogenesis of schizophrenia.

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