

The 22q11.2 Deletion Syndrome as a Window into Complex Neuropsychiatric Disorders Over the Lifespan

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Immune Dysfunction in 22q11DS and Idiopathic Neuropsychiatric Disorders

One characteristic component of the 22q11DS phenotype is immunodeficiency, due to impaired T-cell production caused by thymic aplasia (i.e., complete absence of the thymus gland) or hypoplasia. Although complete thymic aplasia characterizes only about 1.5% of 22q11DS patients, the severity of immune deficits present is highly variable (1), and 77% of 22q11DS patients show some evidence of immunocompromise (2; 3). Sullivan *et al.* (3) found no evidence that the severity of immunocompromise was related to other physical phenotypic features of the illness (specifically, cardiac defects, hypocalcemia, or palate anomalies); however, to our knowledge no studies have yet investigated the relationship between immune function and psychopathology in 22q11DS.

Given emerging evidence suggesting that disruption of genes involved in immune function may be relevant to the etiology of both idiopathic autism (4; 5) and psychosis (6-8) this aspect of the 22q11DS phenotype warrants further study. For example, increased serum levels of pro-inflammatory cytokines and chemokines, differential expression of genes involved in inflammatory processes and altered T-cell function have been documented in patients with idiopathic schizophrenia (7). Microglia, the main producers of inflammatory cytokines, show increased activation in schizophrenia patients, which may be relevant to findings of accelerated gray matter loss near the time of illness onset (9). Effects of prenatal maternal infection on subsequent schizophrenia risk have also been extensively documented (e.g., (10)). Genetic variants involved in immunologic function also appear relevant to the etiology of idiopathic schizophrenia, as a recent, very large-scale genome-wide association (GWAS) study highlighted the involvement of the major histocompatibility complex (MHC) in schizophrenia risk (11). Similarly, B- and T-cell dysfunction have also been implicated in idiopathic autism, and viral

infection during pregnancy also elevates risk for the development of autism spectrum disorder (ASD) (4; 5). Although the direct connection between psychiatric illness and immunodeficiency in 22q11DS has not yet been made, the high rate of immunodeficiency associated with the disorder suggests that immune system dysregulation may be relevant to the dramatically increased risk of neuropsychiatric disorder, particularly ASD and psychosis, in patients with 22q11DS.

Psychiatric Symptom Trajectories in 22q11DS

As noted in “Developmental Trajectories of Neuropsychiatric Phenotypes” section of the main text and Figure 2A, psychiatric manifestations of 22q11DS involve social and affective disruptions that cut across traditional diagnostic categories. As such, categorical classification systems may not adequately capture the full range of 22q11DS-associated symptomatology (12). Four domains are of particular interest as their features persist developmentally and may predict later psychiatric morbidity: 1) attention/executive function deficits (13; 14); 2) social-cognitive deficits (15; 16); 3) anxiety and mood dysregulation (13; 17; 18); and 4) subthreshold psychotic symptoms (18; 19). In a longitudinal study, one-third of 22q11DS youth who met criteria for an attention-deficit/hyperactivity disorder (ADHD) diagnosis in childhood no longer met diagnostic criteria at follow-up three years later (13). However, deficits in attention and executive function (assessed dimensionally via parent report and neurocognitive assessments) are pervasive in 22q11DS, are associated with poorer social skills in children with the disorder (20) and also predict prodromal symptoms of psychosis in adolescence (13). In fact, Antshel and colleagues (13) found that parent ratings of childhood odd/eccentric symptoms and number of errors on the Wisconsin Card Sort Test, a classic executive function measure, were the two best predictors of

adolescent prodromal symptoms, with a very low false positive rate. Regarding domain (2), performance on social cognition tasks (i.e. Theory of Mind tasks) has been associated with poorer social competence (21) and impairments in reciprocal social behavior (22) in children with 22q11DS, suggesting that abnormal development of social-cognitive skills has significant implications for real-world functioning. Social cognitive deficits are a fundamental aspect of idiopathic schizophrenia, and performance on Theory of Mind tasks differentiated 22q11DS adults with a schizophrenia diagnosis from those without schizophrenia (23). Furthermore, we recently found that Theory of Mind performance was the best predictor of positive symptoms in adolescents with 22qDS, accounting for 39% of the variance in symptom severity (15). Thus, social cognitive deficits appear pervasive across diagnostic categories in 22q11DS youth.

Symptoms of anxiety are present from early childhood in 22q11DS, with diagnoses of specific phobia and separation anxiety disorder present in almost half of children with the disorder (13). Mood symptoms tend to peak in adolescence and then level off, whereas anxiety symptoms remain prevalent in adults, most commonly evolving into clinical diagnoses of generalized anxiety disorder (24; 25). In one of the very few existing longitudinal studies, Gothelf *et al.* (26) found that subthreshold psychotic symptoms at baseline interacted with COMT genotype and baseline symptoms of anxiety/depression to predict 61% of the variance in psychotic symptom severity at follow-up, suggesting that severity of affective disruption may be predictive of subsequent psychosis risk in 22q11DS. Psychotic symptoms that do not meet criteria for a clinical diagnosis of overt psychotic disorder are present in 28- 57% of adolescents with 22q11DS (27; 28), suggesting that the evolution of psychotic disorders in 22q11DS is a protracted process, manifesting in childhood in the form of subthreshold symptoms of unusual thought content and/or hallucinations, as well as internalizing symptoms (26). The presence of

the 22q11.2 mutation may present a sensitized background, in which increased stress can precipitate the development of fully psychotic symptoms (29). It is not yet known whether early interventions focused on improving social–cognitive functioning and/or stress reduction techniques would reduce risk for subsequent psychopathology; this is a key area for future investigation.

Cognitive Decline as a Risk Factor for Psychosis

Cognitive deterioration in adolescence is a dynamic phenotype that may index psychosis risk in 22q11DS. Two studies have reported that verbal IQ decline over a 3-5 year period was associated with psychotic symptoms at follow-up (26; 30) as well as greater reduction of left cortical gray matter volume over time (26). Moreover, 30% of prospectively followed 22q11DS children display a decrease in IQ over time not only relative to population norms, but also an *absolute* decline in cognitive abilities (31). These findings are consistent with epidemiologic studies of schizophrenia risk in the general population, suggesting that a combination of static and progressive cognitive deficits across early adolescence may characterize individuals at greatest risk for development of psychosis (32).

Sources of Genetic Variability in 22q11DS: Breakpoint Variability

Breakpoint variability may impact gene expression via inclusion or exclusion of specific genes in low copy repeat (LCR) regions. As discussed in the “Epistatic Interactions: *COMT* and *PRODH*” section of the main text, genetic knockout studies in mice show that reduced dosage of specific genes within the locus can substantially impact phenotypes (33; 34). While many of the gene-related sequences within LCRs appear to be either non-functional

pseudogenes or truncated parts of original genes, several functional genes lie within the LCRs in the 22q11.2 locus, including proline dehydrogenase (*PRODH*), *DGCR6*, and *ISG43* (35). Determining where within the LCRs the breakpoints occur may elucidate whether these particular sequences contribute to phenotypic variation; this is a key question requiring further study in large samples.

Notably, while diagnosis of 22q11.2 deletion syndrome is made on the basis of a deletion within the 1.5 Mb DGCR, now that genome-wide microarray technology is increasingly used for clinical diagnosis, atypical deletions within this region may be more frequently identified (36-39). For example, point mutations within specific genes in the 22q11.2 locus such T-box 1 (*TBX1*) have recently been described (40).

Relevance of 22q11.2 Genes to Neural Endophenotypes in the General Population

In the non-22q11DS population, Kempf *et al.* (41) identified functional variants in the *PRODH* gene that were associated with risk for schizophrenia, and then investigated effects of these variants on structural and functional MRI measures. Individuals with the schizophrenia risk haplotype had decreased striatal gray matter volume and increased subcortical-to-frontal functional connectivity during performance on a working memory task, whereas the opposite pattern was found in those with the protective haplotype. These findings suggest that genetic variation in *PRODH* is associated with schizophrenia risk in the general population, and these effects may be mediated via its effects on brain structure and function. Additional findings implicating genes within the 22q11.2 locus in psychosis susceptibility in the general population are detailed in **Table S1**.

Loss versus Gain of Function Mutations: 22q11.2 Duplication Syndrome

The phenotype of 22q11.2 microduplication syndrome has not yet been well characterized, with the first case described in the late 1990s (42). The 22q11.2 microdeletion and duplication are mediated by the same mechanism: nonallelic homologous recombination between LCRs in the region (43). The duplication is estimated to occur at approximately half the rate of the deletion syndrome (44; 45). However, given that phenotypic manifestations are generally less severe than those of the reciprocal deletion (46), its prevalence may currently be under-estimated (43). Interestingly, there are high levels of both phenotypic and genetic variability in this syndrome: although most duplications contain 3 Mb, the duplication ranges from 1.5 to 6 Mb in length. While a significant number of patients with 22q11.2 microduplications have a normal or near normal phenotype, some associated features are also common to the 22q11.2 deletion, including heart defects, velopharyngeal insufficiency, and cognitive deficits, although the mild facial dysmorphic features are distinct from those of 22qDS (46). The neuropsychiatric phenotype includes ADHD, aggressive behaviors, and autism (47-49).

Genotype-phenotype investigations of 22q11.2 duplication syndrome may inform dosage effects related to genes within this locus, and their association with the variable phenotype. For example, recurrent reciprocal microdeletions and microduplications in Chromosome 1q21.1 are associated with features of microcephaly or macrocephaly, respectively (50).

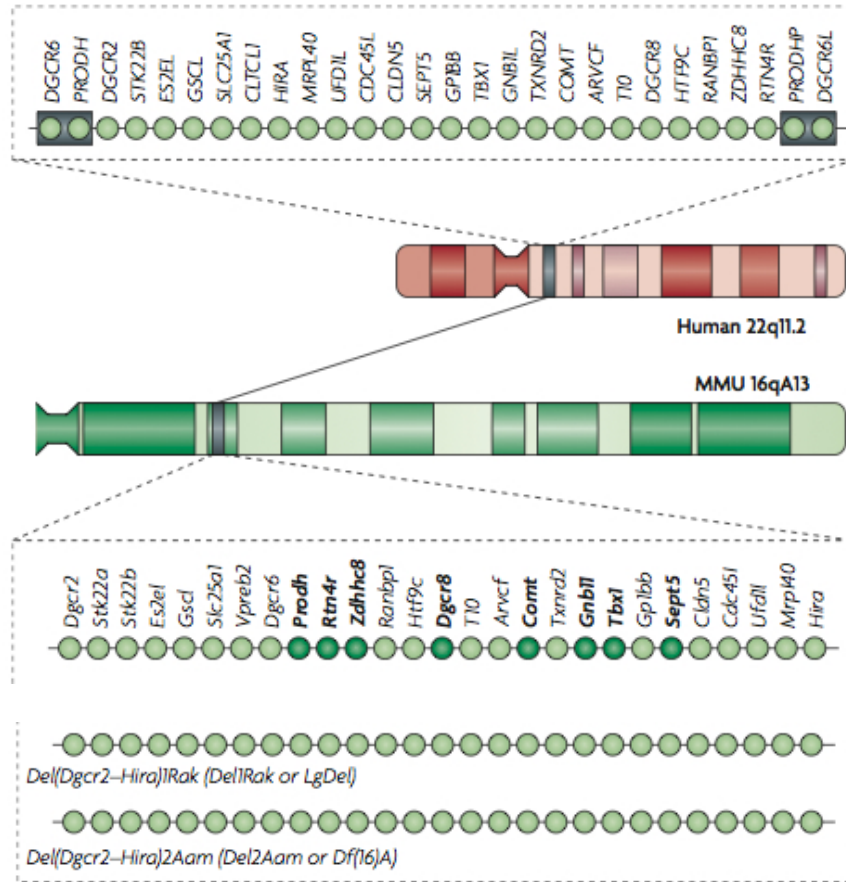


Figure S1. 22q11DS mouse models. As reviewed in Karayiorgou *et al.* (17), various mouse models for the 22q11.2 deletion syndrome have been developed. The two most commonly studied are the *LgDel* and *Df(16)^{+/-}* models. *LgDel* has a hemizygous deletion spanning ~1.3 Mb and contains all but one of the human orthologous genes in the 1.5 Mb deletion region (also referred to as the *Del(Dgcr2-Hira)1Rak* mouse or *Del1Rak* (51)). The *Df(16)^{+/-}* mouse has a hemizygous deletion syntenic to the human 1.5 Mb deletion, and is also referred to as the *Del(Dgcr2-Hira)2Aam* mouse (52). Single gene deletions within the 22q11.2 locus (e.g., *Prodh*, *Tbx1*, *Sept5*) are also utilized to probe the consequences of under-expression of specific genes within the locus (53). Mouse models have thus helped to clarify the contribution of specific genes versus oligogenic effects. Reprinted with permission from Karayiorgou *et al.* (2010).

Table S1. Summary of evidence for the involvement of various sources of genetic variability on endophenotypic traits and behavior, organized by gene within the 22q11.2 locus*

Source of Genetic Variability	Gene(s) in 22q11.2 Region	Effects on Brain Structure and Function in 22q11DS	Effects on Psychiatric Phenotype in 22q11DS	Findings in Idiopathic Psychiatric Illness	Findings in Mouse Models
Haploinsufficiency/ Allelic Variation	<i>COMT</i>	SNP rs4680 low-activity (Met) allele associated with decreased frontal lobe volume in adults (53) and more robust decrease in PFC volume and verbal IQ over time in adolescents (54); Met genotype also associated with better executive functioning in children (55; 56)	SNP rs4680 low-activity allele (Met) a risk factor for development of psychotic symptoms in youth (54); however, SNP rs4680 genotype was not associated with schizophrenia risk in adults (57); Low-activity allele (Met) associated with ADHD and (to a lesser extent) OCD (58)	SNP rs4680 high-activity allele (Val) is more often transmitted to probands with schizophrenia (59); however, (60) found no association of SNP rs4680 variants with schizophrenia; Relationship between this variant and ADHD diagnosis, although direction of association is mixed (61; 62); SNP rs4680 low-activity allele (Met) associated with diagnosis of OCD (63)	<i>Comt</i> deficiency resulted in region-specific changes in DA levels, particularly in PFC (64)
	<i>PRODH</i>	Inverse correlation between plasma proline level and IQ (65)	rs372055'T' allele carriers (22qDS subjects) had significantly higher BPRS scores than developmental disability controls (54)	Screened 6 SNPs: <i>PRODH</i> *1945 T->C, <i>PRODH</i> *1852 G->A showed significant association with schizophrenia (66)	Overexpression of <i>Prodh</i> led to increased PPI (67)
	<i>PIK4CA</i>		Screened 3 SNPs; significant association with SNP rs165793-G and schizophrenia (68; 69); No relationship between SNP rs165793-G and schizophrenia (70)	Significant association with SNP rs165793-G and schizophrenia (69)	

Source of Genetic Variability	Gene(s) in 22q11.2 Region	Effects on Brain Structure and Function in 22q11DS	Effects on Psychiatric Phenotype in 22q11DS	Findings in Idiopathic Psychiatric Illness	Findings in Mouse Models
	<i>GNB1L</i>			SNPs rs5746832 and rs2269726 showed significant association with psychosis (71)	<i>Gnb1l</i> -deficient mice show PPI deficits (71)
	<i>DGCR2</i>			DGCR2 protein expression elevated in DLPFC of schizophrenia patients; risk allele of a coding SNP associated with schizophrenia was associated with reduced expression of DGCR2 (73)	
	<i>TBX1</i>			Inactivating mutations lead to increased risk of autism (72)	<i>Tbx1</i> -deficient mice show PPI deficits (72); Homozygous <i>Tbx1</i> mutants, the distribution of neural-crest-derived cells was disrupted, and the migration pathways of cranial nerves (IX & X) were abnormal (74)
	<i>ZDHHC8</i>			ZDHHC8 rs175174 GG-genotype carriers had gray matter reduction in frontal lobe and increased gray matter posterior volume compared to A-allele carriers (75); SNP rs175174 (A/G) showed significant association with schizophrenia (76)	<i>Zdhhc8</i> -deficient mice show decreased density of dendritic spines and glutamatergic synapses (77)

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microRNA Disruption	<i>DGCR8</i>	Family-based association study of schizophrenia in 22q11DS identified statistically significant enrichment (12/72; 17%) of genes that are potential targets of miRNAs decreased in <i>DGCR8</i> haploinsufficient mice (78)			Decrease in miRNA biogenesis in PFC and hippocampus; reduced dendritic complexity and impaired PPI (52); Increased LTP in mature mice (79); Abnormalities in dendritic spines and structural alterations in the hippocampus (80); Reduced cell proliferation and neurogenesis in adult hippocampus & impaired hippocampal-dependent learning, which could be rescued by IGF2 (81)
Epistasis	<i>COMT/PRODH</i>	Significant interaction between <i>COMT</i> genotype and proline level, with significantly decreased SPEM performance in children with high plasma proline levels and the low-activity <i>COMT</i> (Met) allele (82); Interaction between high plasma protein levels and <i>COMT</i> genotype on visual processing deficits (83)	Hyperprolinemic 22q11DS subjects with SNP rs4680 low-activity allele (Met) allele at increased risk for psychosis (OR = 2.8) (65)	Increased WM density in left IFL in patients with <i>COMT</i> high-activity (Val) allele and with one or two mutated <i>PRODH</i> alleles (84)	Epistatic interaction between <i>Prodh</i> and <i>Comt</i> at the level of transcription and behavior; <i>Prodh</i> -deficient mice show increased neurotransmitter release at glutamatergic synapses, upregulation of <i>Comt</i> mRNA in the PFC, associative learning deficits and increased sensitivity to psychomimetic drugs (85)

ADHD, attention-deficit/hyperactivity disorder; BPRS, Brief Psychiatric Rating Scale; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; IFL, inferior frontal lobe; LTP, long term potentiation; miRNA, microRNA; OCD, obsessive-compulsive disorder; OR, odds ratio; PFC, prefrontal cortex; PPI, prepulse inhibition; SNP, single nucleotide polymorphism; SPEM, smooth pursuit eye movement; WM, white matter.

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