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

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Abstract

Evidence is rapidly accumulating that rare, recurrent copy number variants (CNVs) represent large effect risk factors for neuropsychiatric disorders. 22q11.2 Deletion Syndrome (22q11DS; Velo-Cardio-Facial Syndrome (VCFS) or DiGeorge Syndrome) is the most common known contiguous gene deletion syndrome, and is associated with diverse neuropsychiatric disorders across the lifespan. One of the most intriguing aspects of the syndrome is the variability in clinical and cognitive presentation: children with 22q11DS have high prevalence of autism spectrum (ASD), attention deficit, and anxiety disorders, as well as psychotic-like features, and up to 30% of adolescents and adults develop schizophrenia-like psychosis. Recently, cases of early-onset Parkinson's Disease in adults have been reported, collectively suggesting a role for disrupted dopaminergic neurotransmission in the observed neuropsychiatric phenotypes. There is also some evidence that 22q11DS-associated ASD and schizophrenia represent two unrelated phenotypic manifestations, consistent with a neuropsychiatric pleiotropy model. This genetic lesion thus provides a unique model for the discovery of specific genomic risk and (potentially) protective factors for neuropsychiatric disease. Here we provide an overview of neuropsychiatric findings to date, which highlight the value of this syndrome in mapping the developmental trajectory of dimensional phenotypes that traverse multiple diagnostic categories. Potential sources of genetic variability that may contribute to the disorder's heterogeneous presentation are reviewed. Because of its known genetic etiology, animal models can readily be developed that recapitulate specific aspects of the syndrome. Future research directions involve translational models and potential for drug screenable targets in the context of this human model system.

Keywords

Velocardiofacial/Di George Syndrome; schizophrenia; copy number variant; pleiotropy; neurodevelopment; dopamine

I. Introduction

22q11.2 Deletion Syndrome (22q11DS; OMIM #192430), also known as Velocardiofacial or DiGeorge Syndrome, is a neurogenetic disorder resulting from a hemizygous microdeletion of approximately 1.5 – 3 megabases (Mb) on the long arm of chromosome 22.

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With an estimated prevalence of 1/4000 live births, it represents one of the most common known recurrent copy number variants (CNVs). Its physical manifestations frequently include cleft palate, hypocalcemia, cardiac defects, and immune dysfunction (1; 2). 22q11DS is also associated with strikingly elevated risk for neuropsychiatric illness, particularly psychosis (3; 4); 25–30% of individuals with this syndrome develop schizophrenia or affective psychosis, making 22q11DS one of the greatest known risk factors for psychotic illness identified to date. Microdeletions of 22q11.2 account for up to 1–2% of schizophrenia cases and represent the only known recurrent CNV responsible for introducing new cases of schizophrenia in the population (5; 6). Moreover, non-psychotic psychiatric disorders and behavioral abnormalities are present from early childhood in 22q11DS (7; 8). This phenotypic variability implies that there may be distinct biological mechanisms that underlie the development of these psychiatric conditions. Several of the genes encoded in the deleted region are highly expressed in the brain, and known to affect early neuronal migration and cortical development (6; 9). As such, this syndrome provides a unique opportunity to connect genes to brain to behavior.

While about 85% of patients have approximately the same 3 Mb microdeletion, containing about 60 known genes (Figure 1), variability in the deletion size and breakpoint locations, as well as the characteristics of the intact chromosome (1; 6), may play an important role in the observed phenotypic variability in individuals with 22q11DS.

Here we first review current literature on neuropsychiatric phenotypes across the lifespan in 22q11DS, and potential sources of genetic variability that may contribute to the heterogeneous presentation of the disorder. Next, we describe candidate endophenotypes relevant to neuropsychiatric risk, which can be assayed in both humans and animal models, helping us to bridge the gap between genetic and phenotypic variation. Finally, we suggest key directions for future research, involving new computational modeling methods and *in vitro* disease models, which show great promise for elucidating the molecular mechanisms underlying variable neuropsychiatric phenotypes of 22q11DS. Detailed coverage of medical comorbidities of 22q11DS and genetic association findings relevant to this locus in idiopathic neuropsychiatric disorders are outside the scope of this review, but are reviewed in detail elsewhere (10–12; also see Supplemental Material).

II. The Neuropsychiatric Phenotype of 22q11DS

The most specific neuropsychiatric phenotype associated with 22q11DS is schizophrenia, as this is the only psychiatric condition that appears to be found at much higher frequency among 22q11.2 microdeletion carriers relative to other neurogenetic and developmental disorders associated with intellectual disability (5; 6). Nevertheless, $\frac{1}{3}$ to $\frac{1}{2}$ of children with the deletion are diagnosed with attention-deficit/hyperactivity disorder (ADHD), anxiety disorders (most commonly specific and social phobia), mood disorder, and autism spectrum disorders [ASDs; (1; 2; 7; 8; 13; 14); see Figure 2A]. Indeed, at any given age at least 60% of individuals with 22q11DS meet diagnostic criteria for at least one psychiatric diagnosis, regardless of ascertainment method (3; 4; 14). Notably, psychopathology in 22q11DS encompasses emotional, behavioral and social disruptions in domains that cut across traditional diagnostic categories. For example, affective dysregulation, assessed dimensionally, may be part of a ‘core neuropsychiatric phenotype’ of 22q11DS (5; 6; 14).

Some investigators have proposed that psychiatric diagnoses other than psychosis in 22q11DS represent nonspecific expressions of factors that affect brain development and function (6–8; 15); however, these distinct phenotypic manifestations may also represent genetic pleiotropy, in which the same genetic alteration can result in multiple physiological effects and phenotypic expressions. For instance, Vorstman et al. (8) found that, among

patients diagnosed with schizophrenia in adulthood, only 8% had a probable ASD diagnosis in childhood, suggesting that ASD and schizophrenia may be distinct, pleiotropic manifestations of a 22q11.2 deletion. This phenomenon of distinct neuropsychiatric phenotypes is common to many CNVs that appear relevant to the etiology of idiopathic schizophrenia and autism (10–12; 15). It should be noted, however, that this study was conducted cross-sectionally, and thus the diagnosis of ‘probable ASD’ during childhood was made retrospectively (8). Prospective longitudinal studies are needed to confirm the intriguing possibility that 22q11DS-associated ASD and schizophrenia represent examples of true neuropsychiatric pleiotropy.

Ila. Developmental Trajectories of Neuropsychiatric Phenotypes

Although attention deficits (dimensionally assessed) characterize the vast majority of children with 22q11DS, clinical diagnoses of ADHD are not particularly stable over time (14). Nevertheless, a four-year longitudinal study (16) recently found that persistence of ADHD into adolescence in 22q11DS is predicted by childhood variables previously documented in the non-22q11DS ADHD literature, including higher rates of familial ADHD and history of childhood depression. These findings suggest that genetic background (i.e. family history) may also play a role in the variable neuropsychiatric phenotypes of 22q11DS.

The largest study of lifetime psychiatric diagnoses to date in 22q11DS (N=172; ages 5–54 years) combined data from 22q11DS cohorts from Israel and Switzerland (5), and found remarkably similar prevalence and developmental trends across countries. ADHD and anxiety disorders were the most common diagnoses during childhood (although notably, this study did not report on rates of ASDs), whereas rates of psychosis and mood disorders increased dramatically during adolescence and young adulthood. Additionally, while the average age at onset of overt psychotic disorder in 22q11DS is 19 to 26 years (13), earlier manifestations of psychotic-like symptoms characterize almost 1/3 of 22q11DS adolescents (17; 18), and 17% of pre-adolescent children (Figure 2B), suggesting a continuum of psychotic symptom severity in 22q11DS. Moreover, the socio-behavioral correlates of psychotic symptoms in 22q11DS youth - increased social withdrawal, reduced adaptability, and higher anxiety/depression - appeared strikingly similar to those reported in prospective studies of familial risk for schizophrenia (19). Additionally, consistent with epidemiologic studies in the general population (20), cognitive deterioration in adolescence is a dynamic phenotype that may be a potent predictor of psychosis in 22q11DS (21; 22, see Supplemental Material).

Collectively, these findings implicate early social and cognitive abnormalities as risk factors for subsequent development of overt psychotic disorder in 22q11DS; however, longer-term longitudinal follow-up studies are required to better understand the clinical significance and persistence of early psychotic symptoms in 22q11DS youth.

Most children with 22q11DS now survive into adulthood, but little is known about adult functioning. A recent study found significant functional impairment in over 75% of adults with 22q11DS (23). Variability in adaptive functioning was mediated primarily by cognitive abilities and the presence of psychotic disorder. Identification of remediable factors associated with better functioning is a key question for future research.

Finally, one notable and understudied aspect of the 22q11DS phenotype in older adults is that of early-onset Parkinson’s Disease. This phenotype has now been described in multiple case reports (24; 25), suggesting that dopaminergic disruption in 22q11DS may be relevant to the expression of both psychosis and Parkinson’s Disease over the lifespan.

Collectively, these findings illustrate the substantial heterogeneity in the 22q11DS neuropsychiatric phenotype, which may be linked, at least in part, to underlying sources of genetic variability. The spectrum of associated psychopathology suggests a model of genetic pleiotropy, and additionally implies that schizophrenia and other neuropsychiatric disorders may share overlapping biological pathways (15; 26).

III. Sources of Genetic Variability

An initial approach to characterizing genetic variability in 22q11DS was to investigate the effect of the two most common deletion lengths, 1.5Mb and 3Mb, on clinical phenotypes. Early studies did not find evidence for effects of deletion size on severity of syndromic features (27; 28), and it has been argued that the 1.5Mb region contains all of the key genes responsible for the development of the syndrome and associated psychiatric risk (28; 29). However, more recent studies using high-resolution tiling arrays have noted considerably more variation in deletion breakpoints than previously observed (26), suggesting that more precise mapping may yield new insights regarding phenotypic differences between patients with seemingly similar microdeletions.

Close to 90% of cases of 22q11DS arise from *de novo* mutations, whereas approximately 10% of cases are inherited in an autosomal dominant fashion (26; 29). In *de novo* cases, the microdeletion occurs due to mispairing of low copy repeats (LCRs) during meiosis (1; 30). LCRs, or segmental duplications, are found throughout the genome; the 22q11 region contains several large (60- to 600-kb) clusters of such LCRs (26; 31). These regions tend to predict genomic instability, and often cause breakages implicated in various genetic disorders, via non-allelic homologous recombination (see Table 1).

Although the precise mechanisms are currently unknown, four possible genetic mechanisms which may play a role in the clinical heterogeneity of 22q11DS are: 1) breakpoint heterogeneity, which may impact gene expression via inclusion or exclusion of specific genes in LCR regions (see Figure 1 and Supplemental Material); 2) Allelic variation within the intact 22q11.2 chromosome, which may have substantial effects on amino acid translation as there is no compensating normal allele, potentially resulting in downstream effects on behavior (32); 3) Epistatic interactions (i.e., the phenomenon whereby one gene modifies the effects of another) within the intact chromosome (33); 4) Hemizygosity of microRNA (miRNA) genes. miRNAs are short, non-coding ribonucleic acid (RNA) molecules found in eukaryotic cells, and are an essential part of the cellular machinery for regulating gene expression and transcription. Hemizygosity of miRNA genes in the DiGeorge Critical Region (DGCR)- specifically, *Dgcr8*, *mir-185* and *mir-649*- results in insufficiency of mature miRNAs, which can dramatically affect the target gene protein function (34; 35).

Additionally, findings are mixed regarding the contribution of parent of origin for the 22q11.2 deletion to phenotypic variability. One study reported that 11 of 12 *de novo* cases with psychosis had a maternal origin of the deletion (5). While other studies have found quantitative endophenotypes – gray matter volume and language abilities - linked to maternal origin of the deletion (36; 37), another research group found no evidence for an effect of parental origin of the deletion on schizophrenia risk (38).

Recessive mutations in the intact chromosome, which may be unmasked by hemizygous deletion at 22q11.2, present another potential source of genetic variability. This mechanism has been shown to contribute to a variety of genetic disorders (39–41), although to our knowledge has not yet been investigated in 22q11DS

Finally, epigenetic effects refer to inherited changes in phenotype or gene expression resulting from mechanisms other than alterations in the underlying DNA sequence, such as DNA methylation (42; 43). Epigenetic effects are not well understood in 22q11DS and may be an important source of phenotypic variability requiring further study in large samples, and in animal models.

IV. Endophenotypes in Mice and Men

Analysis of quantitative traits that lie intermediate between these levels of analysis, such as changes in molecular and cellular properties, brain structure and function, and cognition, may better elucidate the pathophysiologic mechanisms linking structural genetic variation to distal psychiatric phenotypes. Such “deep phenotyping” approaches in the context of a known genetic model such as 22q11DS allow us to map a relatively homogeneous biological pathway to the development of complex neuropsychiatric disorders.

Notably, the mouse genome contains a region on chromosome 16 that is homologous to the 22q11.2 region in humans, and thus genetic techniques for selective deletion and/or over-expression of genes within the syntenic region in mice allow us to pinpoint genes contributing to specific behavioral phenotypes (see Supplemental Material). Below we provide examples across multiple levels of analysis, based on both human and animal studies.

IVa. Structural Neuroanatomy

Humans—Collectively, human studies suggest global brain volumetric reduction in 22q11DS, particularly in the parietal lobes (44; 45), as well as significant thinning of midline brain regions (46). Interestingly, there appears to be a rostro-caudal gradient of volumetric reduction in 22q11DS, with caudal regions such as the occipital lobe and cerebellum showing greater reductions, while the frontal lobe is relatively preserved, at least in children (44; 47) (Figure 3). This gradient is conserved subcortically, where the caudate is more reduced in posterior regions than anterior (48), as is the thalamus (49) and corpus callosum (50; 51). Genetic influences are likely to play a role in this rostro-caudal gradient, particularly genes that encode neurodevelopmental morphogens involved in establishing the anterior-posterior axis (52). With increasing age, there appears to be differential reduction in fronto-temporal regions, which may also be relevant to increased vulnerability to psychosis onset in adolescence in 22q11DS (see Section V).

Mice—Studies in mice suggest that anomalous cortical neurogenesis may underlie structural abnormalities observed in human MRI studies (Figure 3). Hemizygous deletion of the analogous 1.5 Mb region in mice disrupts proliferation of basal progenitors and interneuronal migration in the cerebral cortex (9), and leads to reduced dendritic spine density in the hippocampus (34), suggesting that these phenomena may be partially responsible for observed cortical thinning in human 22q11DS patients. Nevertheless, studies in animal models cannot tell us whether specific neuroanatomic alterations are relevant to variable psychiatric outcomes.

IVb. Physiologic Alterations and Synaptic Plasticity

Humans—Functional neuroimaging (fMRI) studies in humans with 22q11DS offer insights into how aforementioned structural changes manifest in terms of physiologic alterations. These studies have reported abnormal neural activity in tasks involving response inhibition (53) and working memory (54), specifically involving atypical parietal activation. Although differences in behavioral performance could contribute to the observed neurophysiologic

differences, these findings offer preliminary evidence for atypical development of specific neural circuits critical for higher-order cognitive functions in 22q11DS.

Additionally, given that 22q11DS is associated with psychiatric disorders involving cortical dysconnectivity, the emerging field of resting state fMRI can offer important insights into the functional architecture of the resting brain in 22q11DS. Abnormalities in resting-state functional connectivity have been consistently implicated in idiopathic psychiatric illness (55); in particular, poorly synchronized ‘long distance’ connectivity in 22q11DS may serve as a biologically relevant intermediate phenotype for psychosis risk in 22q11DS (56). Functional variants in genes within the 22q11.2 locus have also been associated with schizophrenia risk, as well as relevant structural and functional neural connectivity defects, in the general population (57).

Mice—Intriguingly, studies in the *Df(16)A^{+/-}* mouse model of 22q11DS have shown reduced hippocampal-prefrontal functional connectivity, suggesting a neuronal basis for long range connectivity defects in human 22q11DS patients (see Supplemental Material). Additionally, altered synaptic plasticity, in the form of hippocampal long-term potentiation (LTP; see Table 1), has been found in mouse models of 22q11DS, a mechanism that may underlie task-based functional MRI abnormalities evident in human 22q11DS patients. This abnormal LTP phenotype is thought to result from haploinsufficiency of *Dgcr8*, a gene important for microRNA biogenesis; microRNA restoration rescued abnormal LTP levels in *Dgcr8^{+/-}* mice (Figure 3). Interestingly, levels of SERCA2 were increased in brains of patients with idiopathic schizophrenia, providing a direct link between abnormalities in LTP and psychiatric illness (58).

IVc. Neurocognition and Behavior

Humans—Patients with 22q11DS exhibit a characteristic cognitive profile involving deficits in nonverbal learning, as well as social cognition, although there is substantial variability in IQ (59–61). Consistent with the literature on youth at familial high risk for psychosis (19; 62), executive function deficits also predict risk for subsequent development of psychotic symptoms in 22q11DS (63).

Notably, sensorimotor gating deficits, indexed by impairments in pre-pulse inhibition (PPI; see Table 1) have been consistently identified as an endophenotype of disorders characterized by poor inhibitory control of attention, including ASD and schizophrenia (64). Similarly, PPI was significantly reduced in 22q11DS patients relative to sibling controls, and lower PPI was associated with subsyndromal psychotic-like symptoms (65).

Mice—Through a series of studies, Hiroi and colleagues (66; 67) selectively knocked out or overexpressed various combinations of genes within the 22q11.2 homolog region, in order to successfully pinpoint essential genes involved in PPI. Another study investigated mice carrying a multi-gene deletion (*Df1^{+/-}*) that models 22q11DS, and subsequently used single-gene mutants to identify the causative genes involved in sensorimotor gating defects. Haploinsufficiency of two adjacent genes within the locus, *Tbx1* and *Gnb1l*, was found to cause the PPI phenotype, suggesting that these genes may be key contributors to the psychiatric phenotype of 22q11DS (68). In humans, the relevance of *TBX1* haploinsufficiency to the 22q11DS psychiatric presentation was further supported by the identification of a family in which the clinical manifestations of 22q11DS, including ASD, segregated with an inactivating mutation of *TBX1* (68).

IVd. COMT as a model for multi-level investigation in 22q11DS

Although haploinsufficiency for multiple genes in the 22q11.2 locus may contribute to the clinical phenotype, dopaminergic (DA) dysfunction is implicated in many of the associated neuropsychiatric phenotypes (69; 70). As such, the catechol-*O*-methyltransferase (COMT) gene within the DGCR has been a particular focus of investigation. COMT encodes a postsynaptic enzyme that modulates prefrontal cortical DA clearance (71). An evolutionarily recent, common polymorphism at codon 158 of the COMT gene involves substitution of a methionine (Met) for valine (Val). COMT enzyme activity in postmortem DLPFC is ~40% higher in human subjects with the COMT-Val allele than those with the COMT-Met allele (72). A similar effect on enzyme activity was confirmed in lymphocytes. This SNP has been widely studied in healthy individuals, and has been linked to differences in executive functioning and the development of psychiatric illness (73; 74). A recent meta-analysis indicated a significant effect of COMT genotype on prefrontal cortical function in the general population (75).

Given that COMT is hemizygotously deleted in 22q11DS patients, genetic variation in the intact chromosome may have a more profound effect on phenotypic expression than that observed in non-deleted individuals. As such, many studies have investigated allelic variability in this gene in relation to phenotypic expression at multiple levels (Figure 4). Overall, evidence for the contribution of COMT Val¹⁵⁸Met genotype to neuropsychiatric symptomatology in 22q11DS is mixed. While Gothelf and colleagues (76) found that the COMT Low-activity (Met) variant increased risk for the development of psychotic symptoms in 22q11DS youth, other groups found no effect of COMT genotype on psychosis spectrum phenomena (77) or neuropsychological performance (78) (see -Table S1). Discrepancies may be due to small and heterogeneous samples, highlighting the need for better-powered studies.

Variation in this SNP has more consistently been linked to differences in brain structure and cognition in 22q11DS patients (79–81). Using single photo emission computed tomography (SPECT) and a selective radiolabeled D₂ receptor antagonist, Boot and colleagues found that Met-hemizygous 22q11DS patients had significantly lower mean striatal Binding Potential (BP_{ND}) compared to Val hemizygotes, and presumably, higher levels of synaptic DA, thus providing initial evidence for a functional impact of allelic variation of genes within the 22q11.2 region (82; 83). Mouse models have helped to elucidate the direct effects of COMT depletion. For example, although baseline DA levels appear normal in *Comt*-deficient mice (84), DA clearance from the extracellular space is twofold slower (71), suggesting that COMT hemizygosity may influence DA function primarily under conditions of increased DA release, such as times of increased stress.

IVe. Epistatic Interactions: COMT and PRODH

Epistasis is known to occur in at least one set of genes within the 22q11.2 locus, COMT and PRODH (85). PRODH encodes an enzyme that converts proline to glutamate in mitochondria, dysfunction of which has been linked to the development of psychiatric illness (86). *Prodh*-deficient mice show *Comt* upregulation in prefrontal cortex, perhaps as a feedback mechanism to increase DA transmission; moreover, brain function was most disrupted in mice having both increased proline and decreased *Comt* activity (87). As a result of the interactive role of these two gene products, it is likely that these genes participate in an epistatic relationship at the level of transcription and behavior.

Working memory appears mostly intact in mouse models with hemizygous deletion of specific genes in the 1.5 Mb deletion region (i.e., NoGo receptor, *Comt* (88) and *Prodh* (42)); however, interfering pharmacologically with the epistatic interaction between *Comt* and

Prodh unmasks an underlying dopamine dysfunction and reveals working memory deficits in *Prodh* mutant mice (42). Inhibition of *Comt* has also been shown to exacerbate other behaviors influenced by cortical DA, e.g. sensitivity to amphetamine and PPI (42).

Most 22q11DS patients are haploinsufficient for both *PRODH* and *COMT*, and thus may be unable to compensate for loss of *PRODH* (and subsequent increase in proline levels) by means of *COMT* up-regulation. 22q11DS patients who carry the low-activity *COMT* Met allele are more likely to have elevated serum proline levels and perform poorly on eye tracking tasks (89; 90). These individuals may be less able to overcome dopaminergic dysregulation, thus placing them at greatest risk for psychotic symptom development.

Epistatic interactions between other genes within the intact chromosome, and/or with known transcription factors outside of the microdeletion region such as *FGF1* (33), may also impact gene expression, and thus may offer clues about risk or resilience to various psychopathological phenotypes.

V. Biological Mechanisms of Psychotic Symptom Development

Studies in idiopathic schizophrenia have demonstrated a decline in cognitive abilities and other changes in behavior, as well as changes in brain morphology, which precede the onset of overt psychotic symptomatology (91–93), and thus may have utility as predictive biomarkers. Importantly, individuals with 22q11DS and schizophrenia do not differ from patients with idiopathic schizophrenia in terms of core clinical symptoms, including age at onset and course of illness (94), but may differ with regard to auxiliary features such as medication response; however, there is little empirical evidence for this to date. Further, neurocognitive and neuroanatomic features studied to date in 22q11DS overlap with those observed in idiopathic schizophrenia (94–96), although identified cognitive deficits appear more severe in 22q11DS-associated schizophrenia (97). Although the mechanisms underlying the development of psychotic symptoms in 22q11DS are not well understood at present, a central component of the neuropathology underlying emergence of these symptoms during adolescence is a process of neuronal volume reduction, resulting in reduced cortical connectivity. A key advantage of studying a major mutational model like 22q11DS is that it can be diagnosed *in utero*, allowing for identification of at-risk individuals long before symptom onset; identification of predictive biomarkers early in life may ultimately lead to the development of novel treatment targets.

Va. Environmental influences

While the availability of a well-characterized genetic model presents an ideal opportunity to investigate genetic contributions to psychopathology, the emergence of psychopathology in 22q11DS is likely modulated by environmental factors. Factors such as perinatal infection, urban environment, cannabis use, and stressful life events are all known to increase risk for schizophrenia in the general population (98; 99). 22q11DS presents a highly sensitized background for the development of psychosis, and thus offers a valuable model in which to investigate role of stress in precipitating symptom onset (100), and/or exacerbations over time.

VI. Moving Forward

Collectively, animal studies and candidate gene studies in humans implicate more than one gene within the 22q11.2 locus in the associated neurobehavioral phenotypes, suggesting an oligogenic basis. Evidence for the relevance of some of these genes to neuropsychiatric disorders in non-22q11DS individuals (see Table S1) suggests that common variants within the 22q11.2 locus may contribute to broader disease risk.

Novel methods in functional genomics and systems biology can shed light on how genetic makeup in 22q11DS can translate into varying clinical phenotypes. For instance, next generation sequencing can now pinpoint, at a single base-pair level, the precise locations of deletion breakpoints. Advances in stem cell technology, such as the generation of induced pluripotent stem cells (iPSCs), offer incredible promise for modeling *in vivo* neuronal development. Specifically, fibroblasts and other tissues from human patients with 22q11DS can be reprogrammed and regenerated into neural progenitors and neurons, and investigated for properties of neuronal cytoarchitecture, electrophysiology, and synaptic transmission (57). Research using these *in vitro* models can lead to development of novel therapeutic agents, and could ultimately even prevent psychosis onset in both 22q11DS and in the broader population.

Finally, large-scale, prospective studies are warranted, paralleling those of behaviorally defined clinical high-risk studies (101), in order to determine clinical and neurobiological predictors of psychosis, as well as the role of environmental factors in contributing to psychosis risk. This is the first, critical step in developing targeted interventions that can be applied early in the course of illness, leading to improved outcomes

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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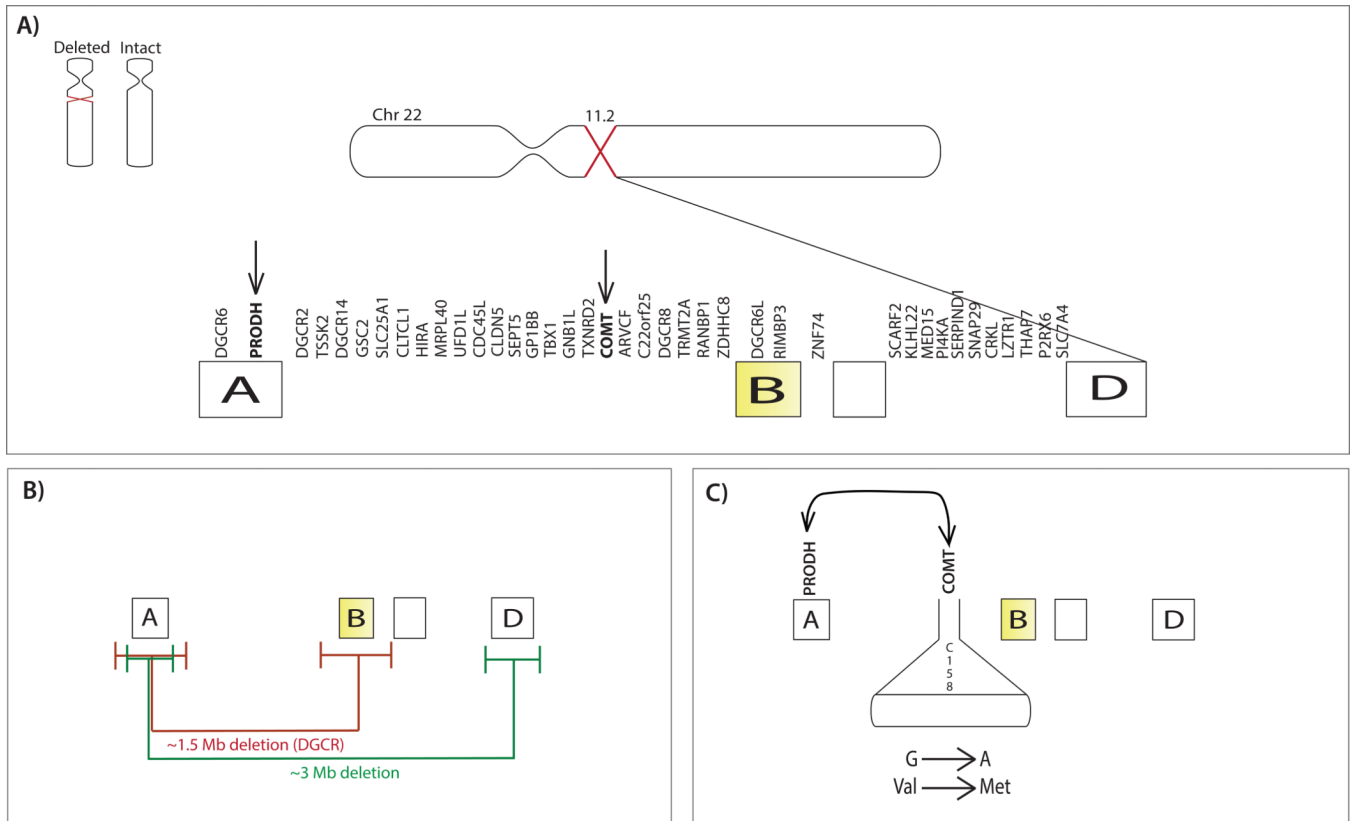


Figure 1. Chromosome 22q and potential sources of genetic variability

(A) Hemizygous 22q11.2 deletion (light purple) and intact chromosome (light pink). To the right, the deleted segment of Chromosome 22 is shown (dark purple). Deletion breakpoints most commonly occur within the four distinct blocks of LCRs that lie in the deletion interval (termed A, B, C, D) (yellow) and deleted genes in the 22q11.2 locus are labeled above the segment (102). The genes *COMT* and *PRODH* are highlighted with arrows to indicate specific examples of genetic variability that are discussed in this review. (B) Breakpoint variability. The deleted segment is illustrated with the two most common deletion lengths, 3Mb (green line) and 1.5Mb deletions (red line), though other atypical deletions have been reported (see Supplemental Material). Error bars denote approximate variance in the deletion breakpoints for the 1.5 and 3Mb deletion lengths. The amount of variability in the deletion breakpoints may differ as a function of deletion size (102). The disorder is defined by a deletion in the DiGeorge critical region (DGCR), i.e. the region of the chromosome located between markers D22S36 and D22S788, which flank LCRs A and B. (C) Allelic variation within the intact chromosome and epistasis. The *COMT* Val¹⁵⁸Met gene variant on the intact chromosome is illustrated as an example of the potential role of allelic variation, involving substitution of a methionine (Met) for valine (Val). As an example of epistasis, *PRODH* and *COMT* are illustrated to show the interactive role of the two gene products. Additional sources of variability include, but are not limited to: unmasking of autosomal recessive mutations via hemizygous deletion, parent of origin effects, and epigenetic effects.

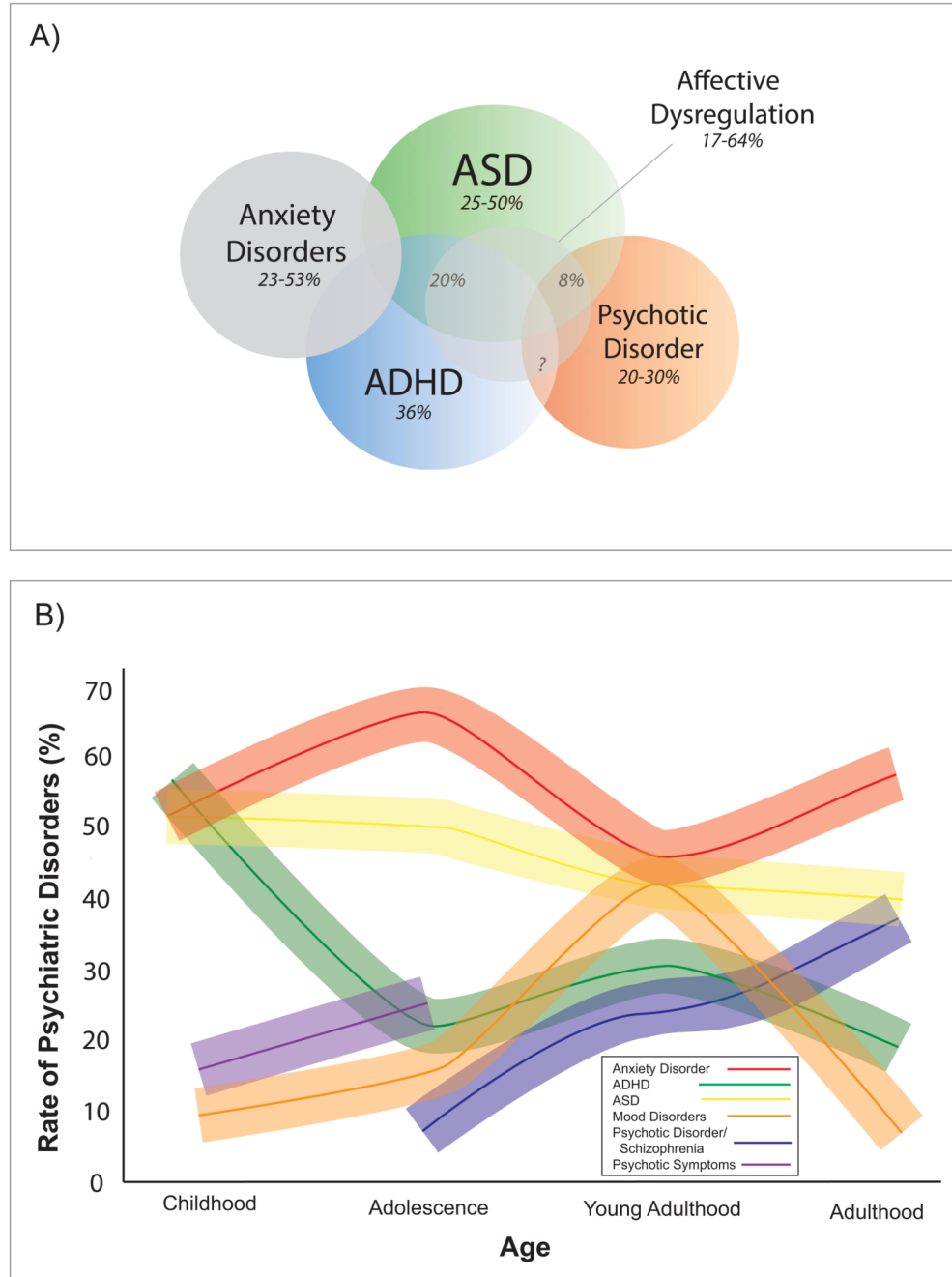


Figure 2. Overlapping and Distinct Neuropsychiatric Phenotypes in 22q11DS
 (A) As a conceptual illustration of the variability of neuropsychiatric phenotypes in 22q11DS, we include autism spectrum disorder (ASD) (18; 103), attention-deficit/hyperactivity disorder (ADHD) (5), anxiety disorders, and psychosis (5), and estimated comorbidity rates across disorders based on existing literature (8; 103). It is important to note that comorbidity rates are not frequently reported in the literature; this is a critical issue for future research. Additionally, affective dysregulation is present in a substantial proportion of 22q11DS patients, regardless of diagnosis. (B) **Developmental trajectories of psychiatric disorders with 22q11DS.** As shown in the figure legend, each colored line

portrays the estimated prevalence of a particular psychiatric disorder in 22q11DS patients throughout the lifespan. Shaded error bars for each line are illustrated to reflect variability across studies. Each percentage point on the line reflects data from published 22q11DS studies reporting on prevalence rates of anxiety disorder (5; 104), ADHD (5), ASD (18), mood disorder (5) psychotic disorder/schizophrenia (5; 77), and psychotic symptoms (17). In cross-sectional studies, rates of mood disorder (particularly depression) appear to peak in late adolescence and then decline, whereas rates of anxiety remain high through adulthood.

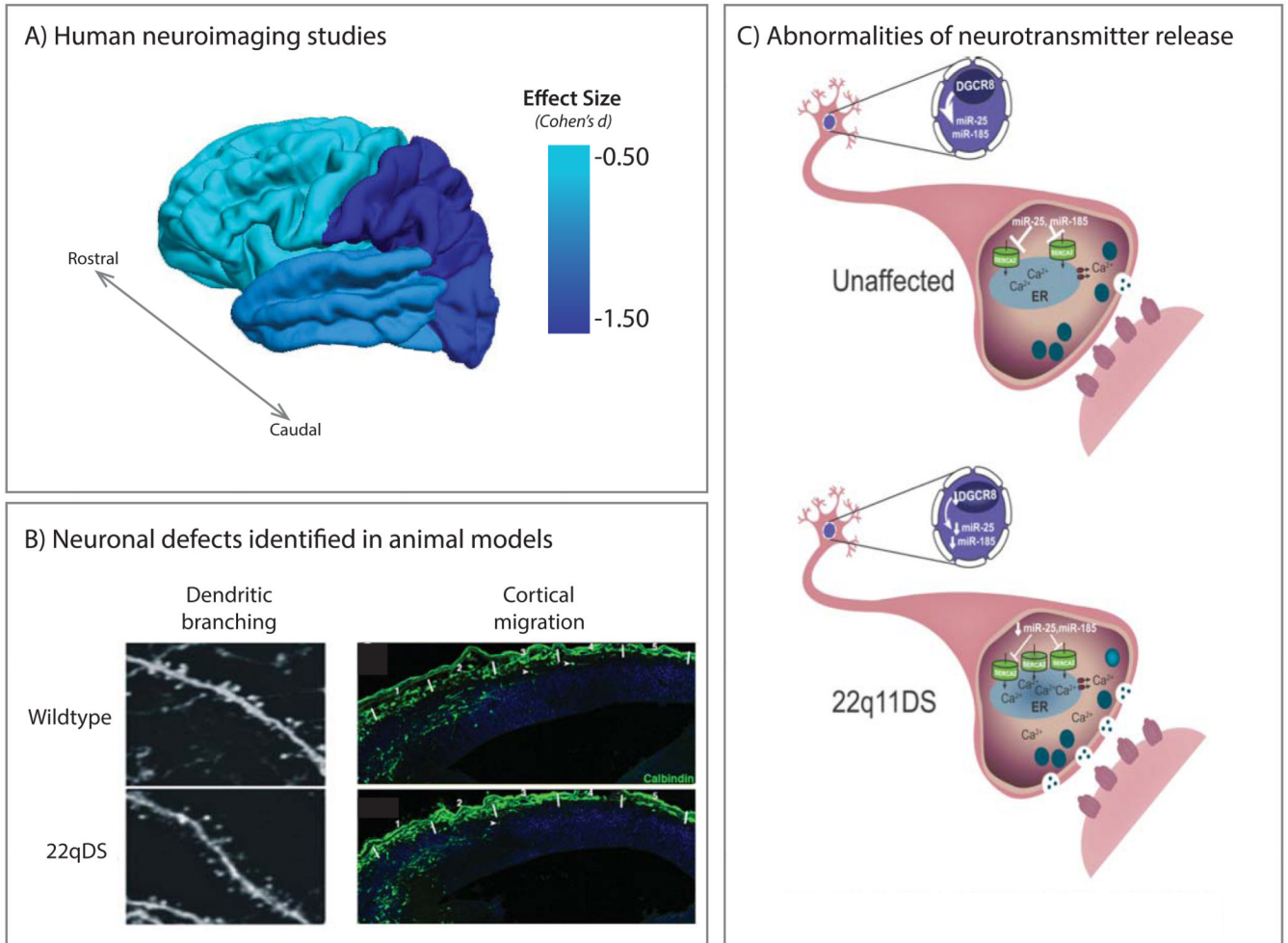


Figure 3. Neuroanatomic Abnormalities in 22q11DS

A) Effect sizes for lobar gray matter reduction in children with 22q11DS relative to typically developing controls, constructed from a meta-analysis of structural MRI studies (45). This effect tends to follow a rostral-caudal gradient. Although not displayed in the figure, effect sizes from subcortical and midline structures are variable, ranging from -0.86 (hippocampus) to -0.20 (amygdala). B) Irregular dendritic branching and abnormal interneuron cortical migration found in 22q11DS murine models (reprinted with permission from Fenelon et al, 2011 (105) and Meechan et al, 2009 (9)). The *Dgcr8* gene, within the 22q11.2 locus, is a key component of the microprocessor complex critical for miRNA production. As shown (left panel), *Dgcr8*^{+/-} mice show reduced width of basal dendrites of pyramidal neurons in the medial prefrontal cortex (mPFC) compared to wildtype. Although basic synaptic transmission is normal in the mPFC of *Dgcr8*^{+/-} mice, short-term synaptic plasticity is impaired, suggesting a neural substrate for cognitive impairment in 22q11DS. Right panel shows abnormal cortical migration of 22q11DS interneurons in the *LgDel* mouse model (9). While the frequency of calbindin-labeled interneurons did not differ between wildtype and *LgDel* mice, there is an aberrant distribution, indicating disrupted interneuron migration, in the cortex of *LgDel* mice. C) Model of sarco(endo)plasmic reticulum Ca²⁺ ATPase (SERCA2)-dependent mechanism of synaptic dysfunction in *Dgcr8*^{+/-} mice, described in Earls et al., 2012 (58). SERCA2 upregulation leads to elevated endoplasmic reticulum Ca²⁺, increasing neurotransmitter release and increased long-term

potentiation (LTP) in an age-dependent manner. MicroRNAs miR-25 and miR-185 are known regulators of SERCA2 and are absent in *Dgcr8*^{+/-} mice; their restoration rescues LTP, suggesting that miRNA-dependent SERCA2 dysregulation may contribute to learning and neuropsychiatric phenotypes in 22q11DS.

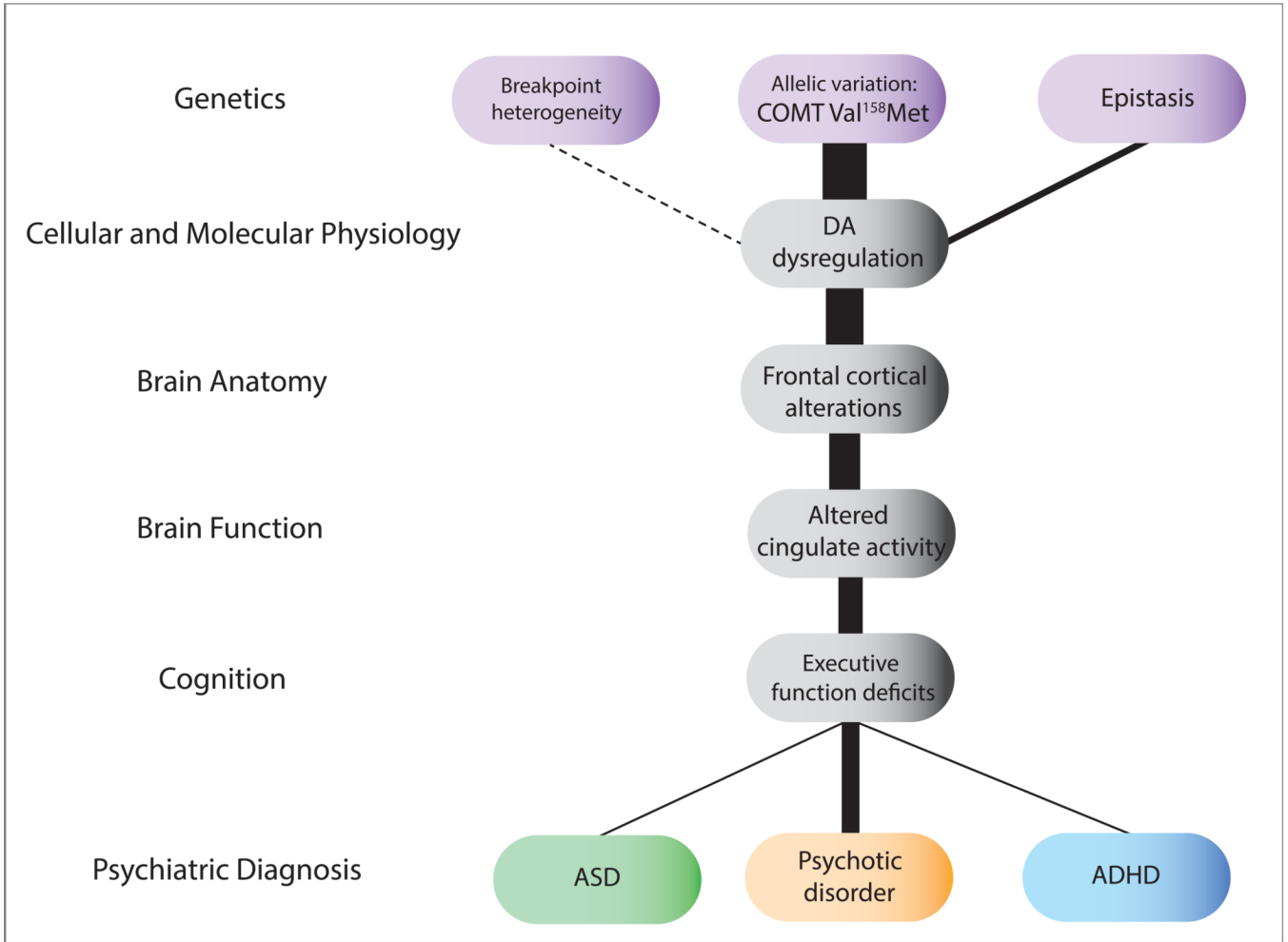


Figure 4. Endophenotypes Relevant to Neuropsychiatric Disorders in 22q11DS

Levels illustrated here indicate how a known genetic etiology can inform pathophysiologic mechanisms relevant to neuropsychiatric phenotypes, using COMT Val158Met genotype as a particular example of how allelic variation in the intact chromosome may contribute to variable phenotypes. Potential sources of genetic variation are indicated in purple, intermediate sources of variability (e.g., endophenotypes) are indicated in gray, and varying phenotypic manifestations are indicated in the bottom row. The line thickness indicates the strength of associations between levels based on existing literature. Increased dopamine (DA) levels were found in patients with 22q11DS, and Met hemizygotes in particular show lower striatal binding potential as compared to Val hemizygotes (82). Studies of structural neuroanatomy have found that Met hemizygotes have smaller frontal lobe volume as compared to Val hemizygotes, which may be associated with inefficient breakdown of DA. One functional neuroimaging study found significantly increased cingulate activity during a Go/NoGo task in Met hemizygotes as compared to Val hemizygotes, implying that the Met subgroup of 22q11DS recruits additional cingulate activation for tasks that require attention and inhibition (53). Several studies have reported significant associations between cognition and COMT genotype such that Met hemizygotes show better executive functioning (79), although not consistently (53; 81) (see Table S1 for details).

Table 1

Glossary

Breakpoint	A specific site of chromosomal breakage associated with a chromosomal abnormality.
Copy number variant (CNV)	A type of genomic variation in which segments of DNA of more than 1,000 base pairs are duplicated or deleted, as genomic risk factor for common complex brain disorders. 22q11.2 microdeletion and duplication are examples of specific CNVs.
Endophenotype	A state-independent biomarker or cognitive marker of an illness (present whether or not the illness is active) that is heritable and present in unaffected relatives of subjects that have the illness (108).
Epistasis	Interactions between genes in which the contribution of one gene to a phenotype depends on the genotype at another locus.
Haploinsufficiency	The situation in which one copy of a gene is incapable of providing sufficient protein production to ensure normal function.
Hemizyosity	A genetic condition where there is only one copy of a gene in an otherwise diploid cell or organism.
Low copy repeats (LCRs)	Highly homologous sequence elements within the eukaryotic genome arising from segmental duplication.
Long-term potentiation (LTP)	A long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously.
Non-allelic homologous recombination (NAHR)	A form of homologous recombination that occurs in two pieces of DNA that have similar sequences, often as a result of the presence of low copy repeats (LCRs). NAHR can occur within the same LCR or in an alternative LCR, and can result in a variety of chromosomal rearrangements, including deletion, duplication, translocation, and inversion. The presence of LCRs and resultant NAHR is believed to play a key role in molecular evolution in primates, as a mechanism involved in rapidly changing gene dosage (which may be advantageous) and even the creation of new genes (30).
Pleiotropy	The phenomenon whereby one gene influences multiple, independent phenotypes.
Prepulse inhibition (PPI)	A quantitative trait, readily measurable in humans and in mice, involving reduced magnitude of the startle reflex that occurs when the subject is presented with a weak stimulus, or prepulse, immediately before the startling stimulus is presented.
Single nucleotide polymorphism (SNP)	Genetic variation in a DNA sequence that occurs when a single nucleotide - A, T, C, or G - in a genome is altered, which can affect function of the gene product.