

# 22q11 deletion syndrome: a review of the neuropsychiatric features and their neurobiological basis

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**Abstract:** The 22q11.2 deletion syndrome (22q11DS) is caused by an autosomal dominant microdeletion of chromosome 22 at the long arm (q) 11.2 band. The 22q11DS is among the most clinically variable syndromes, with more than 180 features related with the deletion, and is associated with an increased risk of psychiatric disorders, accounting for up to 1%–2% of schizophrenia cases. In recent years, several genes located on chromosome 22q11 have been linked to schizophrenia, including those encoding catechol-O-methyltransferase and proline dehydrogenase, and the interaction between these and other candidate genes in the deleted region is an important area of research. It has been suggested that haploinsufficiency of some genes within the 22q11.2 region may contribute to the characteristic psychiatric phenotype and cognitive functioning of schizophrenia. Moreover, an extensive literature on neuroimaging shows reductions of the volumes of both gray and white matter, and these findings suggest that this reduction may be predictive of increased risk of prodromal psychotic symptoms in 22q11DS patients. Experimental and standardized cognitive assessments alongside neuroimaging may be important to identify one or more endophenotypes of schizophrenia, as well as a predictive prodrome that can be preventively treated during childhood and adolescence. In this review, we summarize recent data about the 22q11DS, in particular those addressing the neuropsychiatric and cognitive phenotypes associated with the deletion, underlining the recent advances in the studies about the genetic architecture of the syndrome.

**Keywords:** 22q11 deletion syndrome, microdeletion, neuropsychiatric disorders, cognitive impairments

## Introduction

The 22q11.2 deletion syndrome (22q11DS) is one of the most common multiple anomaly syndromes, caused by an autosomal dominant microdeletion of chromosome 22 at the long arm (q) 11.2 band, one of the most frequent known interstitial deletions identified in humans. The microdeletion occurs at a population frequency of around 1:4,000 live births,<sup>1</sup> although published estimates vary from approximately 1:2,000 to 1:6,000 live births;<sup>2,3</sup> it represents one of the most common known recurrent copy number variants (CNVs).

Common physical manifestations of the disorders include mild dysmorphic facial features, congenital cardiovascular anomalies, palatal defects with velopharyngeal insufficiency, submucous cleft palate and hypernasal speech, thymic hypoplasia with immunodeficiency, hypocalcemia, and a broad spectrum of neuropsychiatric disorders. To date, it is well known that in most cases, 22q11DS is caused by a hemizygous deletion of 3 million base pairs of DNA encompassing approximately 40 known genes,

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while 8% have smaller nested deletions of 1.5 million base pairs spanning 34 known genes.<sup>4,5</sup>

## History of the syndrome

The first documentation of the syndrome, in that time named velocardiofacial syndrome (VCFS), was in 1978,<sup>6</sup> and it focused exclusively on the clinical importance of a pattern of congenital malformations in 12 patients; there were no data relating to the chromosomal and genetic profile of these patients.

The 22q11DS is among the most clinically variable syndromes, with more than 180 features associated with the deletion. Throughout its history, 22q11DS has been called by many names, including not only the already mentioned VCFS<sup>7,8</sup> or Shprintzen syndrome, but also Sedlačková syndrome,<sup>9,10</sup> DiGeorge syndrome,<sup>11</sup> conotruncal anomaly face syndrome, Cayler syndrome,<sup>12,13</sup> and CATCH 22 (cardiac abnormality, abnormal face, T-cell deficits, cleft palate, and hypocalcemia);<sup>14</sup> this last eponym was proposed in order to unify the rapidly expanding number of conditions that were found to be caused by the 22q11.2 deletion, but it was rejected<sup>15</sup> because of the association with Joseph Heller's homonymous black humor novel, representing a no-win situation, something that is obviously inappropriate for the 22q11DS that can often be treated very effectively.

This diversity of names reflects the variable phenotype that results from 22q11.2 deletions. In fact, the phenotype associated with this microdeletion is highly variable and involves multiple organ systems.<sup>5</sup> It was widely demonstrated that phenotypic variability can be caused by breakpoint heterogeneity as well as other genetic, environmental, and stochastic factors. Studies have shown that this variability is not only dependent on genotype: to date, no consistent correlations have been detected between deletion extent and phenotype despite the increasing attention on the correlation between CNVs and the susceptibility to cognitive disorders and schizophrenia.<sup>16</sup> Furthermore, there are many published examples of affected relatives that demonstrate that the clinical presentation can be widely different even within a single family. Studies of monozygotic twins with 22q11.2 deletion have demonstrated that identical deletions do not ensure identical phenotypes.<sup>17,18</sup> In light of such evidence, it is possible to affirm that genotype alone cannot entirely predict the outcome of 22q11.2 deletions, as for schizophrenia and other complex genetic disorders.<sup>19</sup>

At this time, fluorescence in situ hybridization (FISH) is the diagnostic procedure most commonly used to identify the deletion on the basis of clinical suspicion. This procedure

involves the use of DNA probes to determine if a specific region of the genome is present in two copies in a chromosome preparation obtained from peripheral blood, denatured in order to allow the hybridization of a probe specific to the site in question (in this case, the 22q11.2 region). FISH for a 22q11.2 deletion is essentially accurate 100% of the time.<sup>3</sup>

As described above, in addition to the physical features of the 22q11DS, this syndrome is associated with high rates of psychiatric disorder across the lifespan.<sup>20</sup> In the spectrum of the multiple anomalies related to the syndrome, the behavioral and developmental disorders have aroused much attention from the scientific community since the first report of psychiatric disorders in 1992.<sup>21</sup> This report coincided with the identification of the deletion from 22q11.2, and this coincidence suddenly drew substantial research interest to identify the gene that resided in the deleted region that would influence psychiatric phenotypes.<sup>8,16</sup> In recent years, several genes located on chromosome 22q11 have been linked to schizophrenia, including *catechol-O-methyltransferase (COMT)*<sup>22–24</sup> and *proline dehydrogenase (PRODH)*.<sup>25–27</sup> Other functional candidate genes from within this region include those encoding *G protein, beta polypeptide 1-like (GNB1L)*, *phosphatidylinositol 4-kinase, catalytic, alpha (PIK4CA)*, and *armadillo repeat gene deleted in velocardiofacial syndrome (ARVCF)*. The deletion is thought to disrupt the expression of multiple genes involved in maturation and development of neurons and neuronal circuits and neurotransmission. In a study by van Beveren et al,<sup>28</sup> decreased expression of several genes (among which *COMT*, and genes encoding *ubiquitin fusion degradation protein 1-like (UFD1L)*, *PC2 glutamine/Q-rich-associated protein (PCQAP)*, and *GNB1L*) previously linked to schizophrenia has been identified, as well as involvement of signaling pathways relevant to schizophrenia, of which neurotrophin/tyrosine protein kinase receptors and neuregulin signaling seems to be especially notable. It is important to note that this study was performed by whole-genome gene expression of peripheral blood mononuclear cells of a small sample of patients, and the use of this kind of peripheral cell sampling to investigate brain molecular biological processes could be considered a limitation of the study.

It has been suggested that haploinsufficiency of some genes within the 22q11.2 region may contribute to the characteristic psychiatric phenotype and cognitive functioning of schizophrenia.<sup>29</sup> In particular, the Val-108/158-Met *COMT* polymorphism has received empirical attention as a possible risk factor for psychosis.<sup>30</sup> The biologic basis of mental illness in 22q11DS is not clear yet, but it is clear that the syndrome

presents an excellent model for understanding psychiatric disorders, especially psychosis, in humans.

The rate of psychosis in 22q11DS is more than 20 times greater than in the general population,<sup>31,32</sup> so it is almost possible to affirm that a genomic factor (or genomic factors) in the deleted region exerts some control over brain development or function.

The most commonly reported psychiatric disorders are attention deficit/hyperactivity disorder (ADHD),<sup>33,34</sup> anxiety<sup>20,35,36</sup> autism spectrum disorders,<sup>37</sup> mood disorders including major depression and bipolar disorder,<sup>38,39</sup> and psychotic disorders.<sup>40–42</sup> There has also been substantial research focusing on brain structure and function in 22q11DS.<sup>43–45</sup> Reductions in both grey and white matter volumes have been documented with anomalous characteristics of the corpus callosum, the amygdala, the caudate nucleus, and temporoparietal regions of the brain, and neuroimaging studies on cerebral development in 22q11DS have shown deviant maturational courses characterized by local reductions in brain volume, both gray and white matter density and cortical gyrification and thickness.<sup>46–48</sup>

## Genetic outlines

Since 1981,<sup>49</sup> an autosomal dominant mode of inheritance for the 22q11DS has been established, and in 1992 Scambler et al<sup>8</sup> pointed out that the genetic cause of the syndrome was the interstitial microdeletion of chromosome 22 band 11.2. However, the large majority of cases are by de novo mutation: fewer than 10% of individuals with 22q11DS inherited the deletion from an affected parent (most frequently mothers with mild neuropsychiatric phenotypes),<sup>50</sup> and neither parent is affected in over 90% of cases.<sup>51</sup> These data indicate that the 22q11.2 region is quite mutable and susceptible to rearrangement during meiosis, considering also that the penetrance is 100% with highly variable expression.

This vulnerability of the 11.2 region on chromosome 22 had already been confirmed since the early 1990s by Halford et al<sup>52</sup> and Edelman et al.<sup>53,54</sup> These studies illustrated that the most common deletions observed within the region of 22q11.2 occur between sets of repeated elements known as low copy repeats (LCRs), which are genomic elements of approximately 200 kb in length and share high homology with each other; on chromosome 22 at the q11.2 band there are four series of LCRs (A–D) flanking the deletion region.<sup>55</sup> Because these LCRs share high homology with each other, it appears that during gametogenesis, in the homologous recombination process within the 22q11.2 region, the LCRs

can align inappropriately, leading to a deletion on one recombinant chromosome and a duplication on the other.

Most recombination events occur between LCRs A and D, giving rise to the common 3 Mb deletion. Approximately 8% of patients have a 1.5 Mb deletion, nested within the 3 Mb deletion.<sup>20,54,56</sup> It has been argued that the 1.5 Mb deletions contain all key genes responsible for the syndrome and, in particular, for the increased risk of psychiatric illness.<sup>5,57</sup>

The proximal breakpoints region includes the genes located in the 1.5 Mb critical region of 22q11DS that are, among others, encoding frames *PRODH*, *COMT*, *TBX1* (T-box1), *ZDHHC8* (zinc finger, a member of the *DHHC* family of palmitoyl transferases [PAT]), *DGCR* (DiGeorge syndrome critical region protein), and *UFDIL* (ubiquitin fusion degradation 1-like; with two other proteins it forms a complex involved in both the degradation of ubiquitinated proteins and in mitosis). *ARGDV* (armadillo repeat gene deleted in velocardiofacial syndrome) is a member of the catenin family that encodes a protein with an N-terminal coiled-coil domain and an armadillo repeat sequence in the midregion, that in a protein complex can facilitate interactions between proteins and a predicted nuclear-targeting sequence, which suggests a nuclear function.

The distal breakpoints include the genes located in the 3 Mb deletion region but outside of the 1.5 Mb critical region. The most investigated are *PI4KA* (*phosphatidylinositol 4-kinase, catalytic, alpha polypeptide*), which encodes for a kinase that is involved in the biosynthesis of phosphatidylinositol 4,5-bisphosphate, and *SNAP29* (*synaptosomal-associated protein [29 kDa]*), a member of the *SNAP25* gene family that encodes a protein involved in cellular membrane trafficking and is localized in intracellular membrane structures and also in the plasma membrane, but a significant fraction of it is found free in the cytoplasm.<sup>58,59</sup>

As aforementioned, the phenotype of the 22q11DS is highly variable and can affect multiple organs and tissue, but the severity is unrelated to the size of the deletion. However, data suggest that genes within the 1.5 Mb region are crucial for the etiology of the syndrome. It is possible that a small number of genes contribute most of the phenotypic effects, and one or few loci may have a greater phenotypic impact; however, at some level, some form of synergistic interaction between these elements is occurring to substantially increase disease risk. The variability of the cognitive and psychiatric phenotypes of the syndrome may also depend on the presence of additional trans- or cis-acting genetic modifiers.<sup>5,28,58</sup>

Although several genes have been identified as possible susceptibility genes in individuals with 22q11DS and in

mouse models resembling 22q11DS, there has not been a single candidate gene that has arisen as the only cause of the deletion syndrome. Several candidate genes have attracted attention because of the phenotype that results from their deletion in mouse models. Likewise, studies of human 22q11DS patients have revealed significant genetic variability, and the different array of deletions observed in the patient population does not implicate a single gene as the unique cause. Studies of 22q11DS mouse models have suggested that large numbers of genes in the deleted region are differentially expressed during brain development, and they are candidates for the behavioral phenotype observed in 22q11DS individuals.<sup>60</sup> The evidence from these studies suggest that multiple genes in the deleted region may increase the risk of psychiatric disorders in individuals with 22q11DS and, in the following sections, we will consider four of the most studied candidate genes.

First, we considered the *COMT* gene, which codes for an enzyme essential in the catabolic clearance of dopamine. *COMT* is critically involved in cognitive disturbances, and it has often been suggested as a sensitive factor in the development of psychiatric disorders. Next, it will be important to consider the *PRODH* gene, encoding for the proline dehydrogenase enzyme, which is involved in the degradation of proline, an agonist of glutamatergic receptors and potentiator of excitatory neurotransmission. The *TBX1* gene, will then be discussed; it is a member of the T-box gene family of transcription factors, with an essential role in organogenesis in both vertebrate and invertebrate embryos. Several studies in mice have found *TBX1* to be the critical cause of the defects found in the 22q11DS phenotype, predominantly the derivatives of the fourth branchial arch artery. Lastly, we considered the *ZDHHC8* gene, which encodes for a PAT enzyme. In fact, dysregulation of palmitoylation could contribute to synaptic dysfunction and thus lead to cognitive symptoms in schizophrenia.

## COMT

The *COMT* gene is located on chromosome 22q11.2, in the 1.5 Mb microdeletion region and encodes for a postsynaptic enzyme implicated in dopamine degradation,<sup>61</sup> especially in the prefrontal cortex (PFC), where wide neuronal expression is found, particularly within layers II, III, and IV of the PFC.<sup>5,62,63</sup> Here, COMT catalyzes the transfer of a methyl group from S-adenosylmethionine to a hydroxyl group on a catechol nucleus (such as dopamine, norepinephrine, or catechol estrogen).<sup>64</sup>

The level of COMT enzyme activity is genetically polymorphic in human red blood cells and liver.

This polymorphism is due to a guanine to adenine transition at codon 158 of the *COMT* gene, resulting in a valine–methionine substitution, with a low-activity allele 158-Met and a high-activity allele 158-Val. These isoforms were shown to influence cortical dopamine levels and cognitive performance in both humans and transgenic mouse models: the *COMT* functional polymorphism at position 158 leads to a 30% reduction in enzymatic activity and subsequent accumulation of dopamine within PFC.<sup>65,66</sup> *COMT* was considered as a 22q11.2 region candidate gene for psychiatric disorders because of its role in the metabolism of catecholamines.

Despite the many independent studies which confirmed a role for *COMT* polymorphisms in affecting cognitive performance, other studies have failed to replicate these findings, leaving the influence of the Val158Met *COMT* polymorphism's impact upon the flexibility of cognition in question.<sup>67,68</sup> A large prospective study by Antshel et al<sup>4</sup> found no *COMT* association with psychotic signs, and similar results were presented by Gothelf et al<sup>69</sup> and van Amelsvoort et al.<sup>70</sup> On the other hand, as for general population samples, performance on frontal lobe-related tasks in 22q11DS may be related to this functional *COMT* allele.<sup>71</sup> These discordant results may be due to the complex regulation of dopamine activity in the prefrontal cortex, where activity is impaired in both states of dopaminergic hyperfunction or hypofunction.<sup>72</sup>

*COMT* polymorphisms seem to be involved in psychotic disorders and in the symptomatology of the schizophrenia-spectrum disorders. Several lines of evidence have implicated the *COMT* gene as a candidate for schizophrenia susceptibility, not only because it encodes a key dopamine catabolic enzyme, but also because it maps to the velocardiofacial syndrome region of chromosome 22q11.2, which is one of the highest known risk factors for schizophrenia.<sup>73</sup>

## PRODH

The *PRODH* gene, found at the far centromeric end of the 22q11.2 critical region, encodes for the proline dehydrogenase enzyme, which is involved in the degradation of proline, an agonist of glutamatergic receptors and potentiator of excitatory neurotransmission.<sup>74,75</sup>

Patients have either a homozygous deletion or a deletion on one allele with a hypomorphic missense mutation on the other one; about half of all 22q11DS patients show elevated proline levels.<sup>76,77</sup> Hyperprolinemia is defined by 2–10-fold increased serum levels of proline, and there are two inherited forms of hyperprolinemia, called type 1 and type 2. Type 1 hyperprolinemia arises from deletion of the

*PRODH* gene and presents a highly variable phenotype, in most cases associated with mental retardation and epilepsy. Type 2 hyperprolinemia is caused by mutations in the *aldehyde dehydrogenase 4 family, member A1* gene that encodes  $\Delta$ -1-pyrroline-5-carboxylate dehydrogenase, an enzyme that catalyzes the nicotinamide adenine dinucleotide-dependent oxidation of glutamate semialdehyde to glutamate, which is the final step of proline catabolism. Type 2 hyperprolinemia patients have low intelligence quotient (IQ), seizures, and in some subjects, mild mental retardation.<sup>78–80</sup>

Research on murine *PRODH* knockouts has shown that these mice have deficits in sensorimotor gating and decreased biosynthesis of glutamate, GABA, and aspartate, and these effects were more pronounced in the frontal cortex. These studies suggested that increased proline levels resulting from decreased proline metabolism can adversely impact tonic neurotransmitter concentrations and may have a bearing on epilepsy, mental retardation, and psychosis, perhaps by adversely modifying neural connections and excitatory neuronal activity.<sup>27,81</sup> In animal models, Lisman et al<sup>82</sup> indicated a relationship between the dysfunctional glutamatergic transmission in the hippocampus and the resulting excess in striatal dopaminergic activity, leading to the glutamate–dopamine theory of psychosis: in those individuals clinically considered at high risk for psychosis this relationship is disrupted, and the severity of disruption is directly correlated with the increased risk of conversion to overt psychosis.<sup>5,83</sup> Thus, there is an epistatic interaction between the two genes, and the effect of the *PRODH* gene is modified by *COMT*. Also, in utilizing *PRODH*-deficient mice, it has been hypothesized that a negative-feedback loop restrains increased local hyperdopaminergic tone, which could explain the upregulation of transcript and protein levels of *COMT* in the PFC.<sup>58,84</sup>

In individuals with 22q11DS, Raux et al<sup>25</sup> showed that cognitive performance was inversely correlated with plasma proline levels, and further, hyperprolinemic 22q11DS patients carrying the *COMT Met* (low-activity) allele had a 2.8-fold increased risk for psychosis. Interestingly, it is believed that decreased inhibition in the hippocampus, perhaps due to N-methyl-D-aspartate receptor hypofunction, may result in increased glutamatergic inputs onto the striatum and an increase in limbic dopaminergic neurotransmission, which can then precipitate psychotic symptoms.<sup>83</sup>

## **TBX1**

*TBX1* is a member of the T-box family of binding domain transcription factors, and it maps within the deleted region

of chromosome 22 in 22q11DS (1.5 Mb critical region of 22q11DS). This gene family, characterized by a highly conserved DNA binding motif (T-box) and by an unusual mode of DNA recognition, has essential roles in organogenesis and pattern formation in both vertebrate and invertebrate embryos.<sup>85</sup>

Mice haploinsufficient for *TBX1* have phenotypes that recapitulate major features of the syndrome, notably abnormal growth and remodeling of the pharyngeal arch arteries. Knockout mice for this gene have persistent truncus arteriosus, hypoplastic pharynx, lack thymus and parathyroid glands, and have ear, jaw, and vertebral anomalies.<sup>86</sup> The embryological basis of these abnormalities is the unsuccessful development of the pharyngeal arches and arch arteries 2–6, and of the pharyngeal pouches 2–4. The severity and extent of the embryological lesion further confirm the importance of *TBX1* during the early stages of the development of the entire pharyngeal apparatus, as the segmentation of the pharyngeal endoderm.<sup>87,88</sup> No other gene so markedly and specifically affects pharyngeal morphogenesis. Moreover, homozygous null mutations of *TBX1* have more severe defects including failure of outflow tract septation and absence of the caudal pharyngeal arches.

*TBX1* is a transcriptional activator, and loss of this activity has been linked also to alterations in the expression of various genes involved in cardiovascular morphogenesis, confirming that the haploinsufficiency of this gene is largely responsible for the physical malformations in 22q11DS. Cardiovascular malformations in these patients are highly variable, and some studies highlight the potential role of the DNA variations in the *TBX1* locus on the remaining allele of 22q11.2.<sup>89</sup> The identification of eight rare point mutations in the *TBX1* gene in families including probands presenting with a 22q11DS-like phenotype, but without any detectable deletion of the 22q11.2 region, reinforces this hypothesis.<sup>86,90</sup> However, there is no evidence that *TBX1* sequence variants on the intact chromosome 22 are modifiers of the cardiac phenotype in 22q11DS.<sup>91</sup> In addition, mouse models of the 22q11.2 deletion show reduced penetrance and variable expression of the cardiac phenotype. Most embryos but only about 30% of live births show congenital cardiac anomalies, and it is believed that is in part due to compensatory mechanisms and/or redundancy of genes in key pathways during development.<sup>92,93</sup>

Data show that *TBX1* haploinsufficiency is responsible for cardiovascular, craniofacial, thymic, and parathyroid defects in mouse models of 22q11.2 microdeletion.<sup>94</sup>

A role for the microvasculature in the pathophysiology of schizophrenia has been proposed on theoretical grounds

because microvascular damage could satisfy developmental and degenerative models of schizophrenia.<sup>95</sup> In fact, numerous clinical studies have reported cerebral blood flow abnormalities and increased prevalence of minor physical abnormalities in schizophrenia patients, and also the role of hypoxia and other perinatal problems correlate with increased prevalence of schizophrenia in these individuals.

## ZDHHC8

The *ZDHHC8* gene encodes a PAT enzyme, which adds a palmitoyl chemical group to proteins to anchor them to cell membranes. Palmitoylation is a reversible process that involves the covalent attachment of a palmitate group to proteins via thioester bonds at cysteine residues. It plays an important role in regulating nervous system development, dendritic morphology, spine density, synaptic proteins, and glutamatergic neurotransmission.<sup>96,97</sup> Many neuronal proteins are palmitoylated, and this reversible modification affects their hydrophobicity and so their interaction with cell membranes. This observation underlines the strategic involvement of palmitoylation in neural signaling, and thus as a hemizygous deficiency of *ZDHHC8* can significantly affect the development and neural function.<sup>98</sup>

Several studies showed that PAT is localized in the Golgi apparatus and vesicular compartment of neurons where the protein palmitoylation is its central function.<sup>99</sup> Maynard et al<sup>100</sup> suggested that PAT is localized in the mitochondria, where if normal functions of mitochondrial proteins are disrupted by diminished dosage and altered activity, synaptic changes implicated in the pathogenesis of schizophrenia and other psychiatric disorders may occur. Thus, altered dosage of this 22q11 gene could cause developmental or functional consequences, including altered synaptic development or function that could contribute to increased vulnerability for psychopathology in 22q11DS.<sup>98,101,102</sup> Furthermore, key proteins implicated in schizophrenia, including glutamic acid decarboxylase 65 (GAD-65) and postsynaptic density protein 95 (also known as PSD-95, that in humans is encoded by DLG4 [discs, large homolog 4]), are known to be regulated dynamically through palmitoylation.<sup>97,98,103</sup> Also these data confirm the role of palmitoylation: when a dysregulation occurs it could contribute to synaptic dysfunction and cognitive symptoms in schizophrenia.

## Psychiatric phenotype of 22q11DS

Patients with 22q11DS have cognitive and behavioral impairments and a high risk to develop schizophrenia: the rate of psychosis 22q11DS is more than 20 times greater than in the general population.<sup>31,32</sup>

Increasing emphasis in the literature focuses on the neurobehavioral phenotype, essentially because psychiatric disorders are amongst the most prevalent manifestations of 22q11DS.<sup>4,5,35</sup> Like all other components of 22q11DS, the cognitive and behavioral phenotype is highly variable between individuals with the same underlying deletion 22q11.2.<sup>20</sup>

## Cognitive impairments and neuropsychiatric disorders

22q11DS is associated with a distinctive cognitive phenotype.<sup>104,105</sup> The majority of the patients with 22q11DS have an overall intellectual level that falls in the borderline IQ range of 70–84.<sup>106,107</sup> About one-third have mild intellectual disability, while more severe levels of intellectual disability are uncommon.<sup>108,109</sup> It is important to note that there is no data about the correlation between a lower intellectual level and increased risk for psychiatric illness, including schizophrenia.<sup>110</sup> Instead, there are several cross-sectional studies that have found a negative correlation between age and IQ scores in 22q11DS,<sup>111–113</sup> suggesting in these patients the possibility of a gradual decline in cognitive development as they grow into adulthood.<sup>114</sup>

Reading, spelling, and phonological processing skills as well as rote auditory/verbal memory are relatively spared in 22q11DS.<sup>115,116</sup> Conversely, math learning disabilities,<sup>117,118</sup> visuospatial deficits,<sup>119</sup> attention deficits<sup>39,120,121</sup> and executive function deficits in domains such as cognitive flexibility, response inhibition, and nonverbal working memory have been reported to be an area of weakness in the 22q11DS cognitive profile.<sup>122,123</sup>

The most commonly reported neuropsychiatric disorders during childhood are attention deficit disorder (present in 30%–40% of individuals with 22q11DS)<sup>34</sup> and autism spectrum disorders (10%–30%),<sup>39</sup> but anxiety disorders, especially simple phobias and separation anxiety, (present in 30%–40%) and mood disorders including major depression and bipolar disorder (present in 20%–30%)<sup>33,39</sup> are also common and increase in prevalence during adolescence.<sup>124</sup> Obsessive compulsive disorder has also been reported.<sup>125</sup> By adulthood, 20%–30% of adults with 22q11DS meet criteria for a diagnosis of schizophrenia,<sup>40–42</sup> giving an odds ratio for schizophrenia in 22q11DS of around 20:1 relative to the general population.<sup>32,39</sup>

## Psychotic disorders and susceptibility to schizophrenia

Clearly, the most worrying feature of the 22q11DS behavioral profile is the elevated risk for schizophrenia and psychosis that is not associated with any other neurogenetic syndrome.<sup>58</sup> Identifying shared and unique features for 22q11DS and

schizophrenia is critical for the understanding of genetic and neural mechanisms underlying both disorders. For these reasons, 22q11DS is considered a human model to study and explore early diagnoses strategies and intervention on schizophrenia-related disturbances.

The 22q11.2 microdeletions account for up to 1%–2% of schizophrenia cases<sup>35,39</sup> and are the only confirmed recurrent CNV responsible for introducing new cases of schizophrenia into the population. Recent studies, both in humans and animal models, shed light on the growing evidence of a widespread role of this genomic variation in determining susceptibility to schizophrenia.<sup>126–129</sup>

The first observation that supported the importance of rare recurrent mutations in schizophrenia vulnerability dates back to 1995,<sup>130</sup> as a reproducible observation of rare and highly penetrant de novo structural mutations at the 22q11.2 locus in sporadic (nonfamilial) cases of schizophrenia. Rare structural mutations, both inherited and de novo, have a substantial etiological role and account for a considerable portion of sporadic and familial cases of the disease. Interestingly, de novo mutations, such as the 22q11.2 microdeletions, can at least in part explain how schizophrenia persists in the population despite the low fecundity of affected individuals.<sup>131,132</sup> The 22q11.2 microdeletion is therefore one of the highest known risk factors for schizophrenia, in addition to being the monozygotic twin of a schizophrenic patient and/or sibling or child of an affected individual.

There are no major clinical differences in the core schizophrenia phenotype between individuals with schizophrenia who have the 22q11.2 deletion and those who have not;<sup>21,39,133</sup> it is important to note that prevalence of schizophrenia in those patients with a learning disability is only about 3%, so there is no correlation between the presence of psychosis and the degree of intellectual impairment, and the mean IQ of individuals with 22q11DS and schizophrenia was in the nonlearning disability range.

In late adolescence and early adulthood, up to one-third of all individuals carrying the 22q11.2 deletion develop schizophrenia or schizoaffective disorder.<sup>58,110</sup> Twenty to 30% of adults experience an intensification of psychotic symptoms leading to a diagnosis of schizophrenia, but it is not known whether psychotic symptoms persist at a subthreshold level in the majority of 22q11DS adults who do not develop schizophrenia. It is logical that early psychotic phenomena may predict later psychotic illness including schizophrenia, and there is some evidence for this continuity.<sup>39,69,134</sup> However, there is no evidence at present that psychotic experiences in 22q11DS are pervasive across diagnoses, contributing to disturbances of mood and anxiety and social interactions.<sup>39,69</sup>

Several studies<sup>109,135–137</sup> have identified patterns of psychotic, prodromal and associated symptoms in young people with 22q11.2 deletion syndrome. Studies of school-age children have confirmed that individuals with 22q11DS have high rates of psychiatric and behavior disorders, such as ADHD, generalized anxiety disorder, and obsessive compulsive disorder.<sup>108,125,138</sup> However, their incidence in 22q11DS is no higher than in other developmental disorders, suggesting that they are not indicative of a behavioral phenotype specifically associated with this syndrome.<sup>108</sup>

A prospective study by Gothelf et al<sup>69</sup> found that the development of psychotic symptoms in children studied at age 12 and in follow-up at age 18 was best predicted by the presence of psychotic symptoms at the time of the baseline study and in part by anxiety and depression scores; lower IQ at baseline was also a further predictor. ADHD was not a predictor of psychotic outcomes.<sup>34,39</sup> By contrast, schizophrenia is specifically associated with 22q11DS.<sup>133,137</sup> Half of the adolescents with 22q11DS report transient psychotic experiences, while up to one-third of affected adults are diagnosed with schizophrenia.<sup>112</sup> Moreover, 22q11DS is found in up to one in 50 patients with schizophrenia, with reports ranging from 0.3%–2%.<sup>58,130</sup> The occurrence of 22q11DS is even higher in patients with childhood-onset schizophrenia (5.7%).<sup>139</sup>

Moreover, progressive pathology in medial temporal and frontal lobe areas has been associated with emergent psychotic symptomatology in 22q11DS adolescents,<sup>140–142</sup> and temporal lobe abnormalities are more pronounced in 22q11DS adults with schizophrenia. In particular, Chow et al<sup>143</sup> linked gray matter volumetric deficits in the superior temporal gyrus to a specific genetic etiology of schizophrenia.

Similarly, in an integrative study of the neuropsychological and brain structural findings in children with 22q11DS, Shashi et al<sup>144</sup> have demonstrated reductions in gray matter within the cerebellum, the posterior cortices, the cingulate, and the anterior and middle cingulate gyrus (areas corresponding to the dorsolateral prefrontal cortex); gray matter volumes within the dorsolateral prefrontal cortex, the cingulate, and the cerebellum were positively correlated with performance in the domains of sustained attention, executive function, and verbal memory in addition to intelligence, strengthening the concept that these brain regions are important mediators of neurocognition. These findings enhance our understanding of neurocognition during adolescence and the development of schizophrenia in later life.

It is important to note that Gothelf et al<sup>145</sup> in a longitudinal study on developmental trajectories of brain structures in 22q11DS adolescents have found a greater longitudinal increase in cranial and cerebellar white matter,

superior temporal gyrus, caudate nucleus volumes, and a robust decrease in amygdala volume. These findings were associated with a significant decline in verbal IQ scores in those patients that developed psychotic disorders and were linked with more robust reduction of left cortical grey matter volume.

Increased combined prodromal symptoms were associated with longitudinal decreases in the volumes of cranial gray and white matter, prefrontal cortex, mesial temporal lobe, and cerebellum. Interestingly, only decreases in temporal lobe gray matter volumes and verbal IQ predicted specifically to positive prodromal symptoms of psychosis. So, early decrements in temporal lobe gray matter may be predictive of increased risk of prodromal psychotic symptoms in youth with VCFS.

## Conclusion

22q11.2 deletion is associated with an increased risk of psychiatric disorders, and data show that several susceptibility genes may be located within the deleted region. Future studies will further examine the contribution of genes such as *COMT*, *PRODH*, and *TBX1* and the interaction between these and other candidate genes in the deleted region. Even if one or a few genes may have a greater impact, it is the cumulative effect of the imbalance of several genes in the deletion that determines the overall phenotype, and the presence of additional genetic and environmental modifiers may also contribute to the variability of the cognitive and psychiatric phenotypes of the syndrome.

Moreover, an extensive literature on neuroimaging shows reductions of the volumes of both gray and white matter, with abnormalities in corpus callosum, amygdala, caudate nucleus, and the temporoparietal brain region. These findings suggest this reduction may be predictive of increased risk of prodromal psychotic symptoms in 22q11DS patients. The relationship among brain structure, function, connectivity, and cognitive impairments in 22q11DS patients, both children and adults, is an important area of future research and will be essential to compare anomalies in mouse models and humans. This shows that experimental and standardized cognitive assessments alongside neuroimaging may be important to identify one or more endophenotypes of schizophrenia as well as predictive prodrome that can be preventively treated during childhood and adolescence.

Understanding the developmental trajectory of the associated neurobehavioral phenotypes in 22q11DS could also assist with understanding normal human brain development and the molecular genetics underlying this syndrome.

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## Disclosure

The authors report no conflicts of interest in this work.

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