Cognitive, Behavioural and Psychiatric Phenotype in 22q11.2 Deletion Syndrome

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Abstract

22q11.2 Deletion syndrome has become an important model for understanding the pathophysiology of neurodevelopmental conditions, particularly schizophrenia which develops in about 20–25% of individuals with a chromosome 22q11.2 microdeletion. From the initial discovery of the syndrome, associated developmental delays made it clear that changes in brain development were a key part of the expression. Once patients were followed through childhood into adult years, further neurobehavioural phenotypes became apparent, including a changing cognitive profile, anxiety disorders and seizure diathesis. The variability of expression is as wide as for the myriad physical features associated with the syndrome, with the addition of evolving phenotype over the developmental trajectory. Notably, variability appears unrelated to length of the associated deletion. Several mouse models of the deletion have been engineered and are beginning to reveal potential molecular mechanisms for the cognitive and behavioural phenotypes observable in animals. Both animal and human studies hold great promise for further discoveries relevant to neurodevelopment and associated cognitive, behavioural and psychiatric disorders.

Keywords

Velocardiofacial syndrome; DiGeorge syndrome; Mental disorders; Neurological; Nervous system diseases; Genetics; Developmental disabilities; Psychiatric diseases; Copy number variation

Introduction

Microdeletion of chromosome 22q11.2 or 22q11.2 deletion syndrome (22q11.2DS) (MIM #188400/#192430) is the most common human deletion syndrome with an estimated prevalence of 1 in 4,000 live births (Goodship et al. 1998). The phenotypic spectrum

encompasses several previously described syndromes including DiGeorge, velocardiofacial and conotruncal anomaly face syndromes as well as some individuals with other conditions such as Cayler cardiofacial syndrome. The phenotypic expression of the 22q11.2DS is known to be highly variable and ranges from a severe life-threatening condition to affected individuals with few associated features (Bassett et al. 2005; Kobrynski and Sullivan 2007; Ryan et al. 1997). Abnormal development of the pharyngeal arches and pharyngeal pouches gives rise to the cardinal physical manifestations of the syndrome: conotruncal anomaly, hypocalcemia due to dysfunctional parathyroid glands, palatal abnormalities and paediatric immunodeficiency that may be secondary to hypo/aplasia of the thymus (Lindsay et al. 2001; Scambler 2000). Each of these classic manifestations shows variable expression and may be absent altogether in an individual patient with the syndrome. Major heart defects are present in about 40% of cases while minor anomalies, e.g., of the aortic arch, may be identified only on cardiac ultrasonography. Overt cleft palate is rare, whereas submucous cleft palate associated with velopharyngeal insufficiency is characteristic of 22q11.2DS. Hypoparathyroidism is usually transient in the neonatal period but late-onset symptomatic hypocalcemia can occur and is common in adults. Severe immune deficiency is very rare but moderate lymphopenia compatible with normal life is a frequent finding. In contrast, the facial features are considered a constant manifestation of the syndrome (Guyot et al. 2001), although the overall facial appearance is not always readily identifiable even to informed clinicians. Other common features of 22q11.2DS cannot be related to abnormal development of the pharyngeal apparatus. Renal anomalies for example may be present in as many as 30% of cases and features related to abnormal central nervous system (CNS) development are almost always present. Developmental delays and learning difficulties are very commonly associated, although severe intellectual disability (termed mental retardation in the DSM diagnostic system) is rare. Recurrent seizures are common, especially those related to hypocalcemia, and epilepsy may be present in about 5% of patients. Psychiatric conditions may be present in children and over 60% of patients develop treatable psychiatric disorders by adulthood (Bassett et al. 2005). This risk is a major concern for families. In particular, due to the high frequency of schizophrenia in 22q11.2DS patients, the 22q11.2 region is considered to be one of the main schizophrenia susceptibility loci in humans (Bassett and Chow 2008; Insel 2010).

Cytogenetic mechanisms of 22q11.2 deletion

The 22q11.2 region is flanked by low copy repeats (LCRs) with greater than 97% identity. As in many other microdeletion syndromes (Kumar 2008), it has been demonstrated that the microdeletion was the consequence of non-allelic homologous recombination resulting from misalignment of LCRs during meiosis (Edelmann et al. 1999) (Fig. 1). This is about equally likely to occur in spermatogenesis or oogenesis (Bassett et al. 2008; Torres-Juan et al. 2007). Up to 90% of recombination events occur between LCRs A and D giving rise to the common 3 Mb deletion (Shaikh et al. 2000). Approximately 8% of patients have a 1.5 Mb deletion, nested within the 3 Mb deletion. Some smaller or atypical deletions have been reported but there is no evidence for specific genotype–phenotype correlations. Up to 93% of cases occur de novo, whereas in the remaining 7% the deletion is found to be inherited from a parent.

Non-allelic homologous recombination events can also give rise to duplications of the same region (Ensenauer et al. 2003). In most cases the duplicated segment is 3 Mb large, corresponding to the commonly deleted segment. The phenotype of patients harbouring a 22q11.2 duplication is highly variable (Portnoi 2009). Many individuals with a 22q11.2 duplication may be identified by array genomic hybridization testing as part of the evaluation of developmental delay or learning difficulties. This ascertainment bias and limited data on adults mean that the full extent of the phenotype, including neurobehavioural features, associated with 22q11.2 duplication is not well established. Nevertheless, it is worth noting that a significant number of patients with a 22q11.2 duplication have conotruncal defects or velopharyngeal insufficiency, suggesting that either a decrease or increase of gene dosage in this region may have similar phenotypic consequences.

The commonly deleted region in 22q11.2DS encompasses approximately 45 genes and the consequences of decreased gene dosage of multiple genes are believed to be involved in phenotypic expression (Meechan et al. 2010). The molecular substrates underlying the different clinical features of 22q11.2 deletion, however are still debated. *TBX1*, encoding for a transcription factor is the major candidate gene for the cardiac and parathyroid phenotype since *Tbx1* haploinsufficiency is responsible for the cardiovascular, and most of the congenital defects observed in mouse models of 22q11.2DS (Jerome and Papaioannou 2001; Lindsay et al. 2001; Merscher et al. 2001). The identification of eight rare point mutations in the *TBX1* gene in families including probands presenting with a 22q11.2DS-like phenotype, but without any detectable deletion of the 22q11.2 region, reinforces this hypothesis (Paylor et al. 2006; Yagi et al. 2003; Zweier et al. 2007). However, there is no evidence that *TBX1* sequence variants on the intact chromosome 22 are modifiers of the cardiac phenotype in 22q11.2DS (Rauch et al. 2004). In addition, mouse models of the 22q11.2 deletion show reduced penetrance and variable expression of the cardiac phenotype. The fact that most embryos but only about 30% of live births show congenital cardiac anomalies is believed to be in part due to compensatory mechanisms and/or redundancy of genes in key pathways during development (Lindsay et al. 1999; Lindsay and Baldini 2001).

The existence of a behavioural phenotype and susceptibility to develop psychiatric disorders in patients with a 22q11.2 deletion offers unique opportunities to identify genes implicated in cognition, behaviour and schizophrenia (Bassett and Chow 2008; Insel 2010; Meechan et al. 2010). Many of the genes in the commonly deleted region are expressed in mouse and human brain (Maynard et al. 2003; Meechan et al. 2009) and in consequence can be considered as candidate genes for the cognitive and behavioural phenotype of 22q11.2DS. However, for most of these, the exact roles in brain developmental and function are unknown. We will focus on several genes for which both animal models and studies in humans, either schizophrenic cohorts or 22q11.2DS patients, have been conducted.

COMT encodes for catechol-*o*-methyltransferase, one of the major mammalian enzymes involved in the metabolic degradation of catecholamines. *COMT* catalyzes the transfer of a methyl group from S-adenosyl-methionine to a hydroxyl group on a catechol nucleus (e.g., dopamine, norepinephrine, or catechol estrogen), particularly in the prefrontal cortex. The level of *COMT* enzyme activity is genetically polymorphic in human red blood cells and liver. This polymorphism is due to a G-to-A transition at codon 158 of the *COMT* gene,

resulting in a valine-to-methionine substitution, with a low-activity allele, 158met and a high-activity allele, 158val. Due to its role in the metabolism of catecholamines, *COMT* has been an initial consideration as a 22q11.2 region candidate gene for psychiatric disorders. *PRODH* encodes for the proline oxidase or proline dehydrogenase 1, an enzyme involved in the degradation of the amino acid proline by catalyzing the conversion of proline to pyrroline-5-carboxylate. Homozygous mutations in the *PRODH* gene leads to hyperprolinemia type 1, a rare neurologic disorder with variable manifestations, the more severe phenotype being associated with very high levels of proline (Raux et al. 2007). *SEPT5*, a member of the septin family, is abundantly expressed in the brain and exerts negative regulatory control over neurotransmitter release by binding to SNARE-protein (Suzuki et al. 2009). *RTN4R*, encoding NOGO receptor 1, regulates axonal growth as well as axon regeneration after injury and has also been considered as a potential susceptibility gene for schizophrenia (Hsu et al. 2007). *ZDHHC8*, encodes for a palmitoyltransferase. The protein encoded by *DGCR8* plays a critical role in the biogenesis of micro-RNAs which are thought to contribute to phenotypic variation of psychiatric and neurodevelopmental disorders (Xu et al. 2010).

Cognitive and behavioural phenotype of 22q11.2 DS

There is a growing knowledge base about the cognitive and behavioural phenotype of 22q11.2DS. As for many genetic syndromes, the earliest descriptions of the syndrome noted developmental delays and cognitive deficits to be amongst the most common aspects of expression of 22q11.2DS. Increasing emphasis in the literature however focuses on the neurobehavioural phenotype. In part this is because, as a group, the associated psychiatric disorders are amongst the most prevalent manifestations of 22q11.2DS (Antshel et al. 2010; Fung et al. 2010). Like all other components of 22q11.2DS, the cognitive and behavioural phenotype is highly variable between individuals with the same underlying deletion 22q11.2. Importantly, similar to findings for the cardiac phenotype, there is no evidence that the length of the 22q11.2 deletion, or the presence or absence of other physical features, contribute significantly to the variability of the cognitive or behavioural phenotype (Bassett et al. 2008; Gerdes et al. 2001). Studies involving large numbers of the minority of individuals with 22q11.2 deletions other than the common 3 Mb deletion would be needed to determine whether the length and/or position of such variants could modify phenotypes and how that differs from the phenotypic variability seen within the 3 Mb deletion group.

The brain is the least developed of major organs at birth. It is therefore not surprising that in 22q11.2DS the phenotypic features that are associated with aberrant central nervous system (CNS) development and function evolve over time. Indeed, Meechan et al. (Meechan et al. 2010) have recently formulated 22q11.2DS as a genetic disorder of neurodevelopment. Early on, e.g., in the prenatal or neonatal periods, few CNS anomalies would be clinically detectable, apart from neonatal hypocalcemic seizures. Rare, clinically important anomalies reported include neuronal migration abnormalities, such as polymicrogyria and periventricular nodular heterotopia identifiable on structural MRI, and, even rarer, neural tube defects (Kiehl et al. 2009; Robin et al. 2006). In contrast, from infancy onward developmental delays are commonly observed (Gerdes et al. 2001; Roizen et al. 2007; Swillen et al. 1999). These include motor delays, often with hypotonia, which may be

improved with early infant stimulation and physiotherapy (Gerdes et al. 2001; Swillen et al. 1999). Developmental delays of speech and language are perhaps even more common and are not necessarily associated with cognitive delays (Gerdes et al. 2001; Swillen et al. 1999). In addition to surgical correction of palatal anomalies, speech therapy for hypernasality and articulation deficits, early use of augmentative communication (e.g., use of gestures and signs), may help to optimize development and reduce frustration for families.

With respect to learning difficulties, these are common in 22q11.2DS, may be identified at any time from pre-school through secondary school and may affect functioning in adult years. While a minority fall in the average range, the majority of patients with 22q11.2DS have an overall intellectual level that falls in the borderline (IQ 70–84) range (Antshel et al. 2010; Chow et al. 2006; Swillen et al. 1999; Van Amelsvoort et al. 2004). About one-third have mild intellectual disability, while more severe levels of intellectual disability are uncommon (Bassett et al. 2005; Chow et al. 2006; Swillen et al. 2000). The cognitive profile in 22q11.2DS varies within individual over the course of development and is highly variable between individuals. However, there are some replicated trends. In early childhood, some individuals may present with non-verbal learning difficulties, i.e., performance IQ significantly lower than verbal IQ (De Smedt et al. 2009; Jacobson et al. 2010; Swillen et al. 1999). By adolescence however there are no significant differences between mean performance and mean verbal IQ (Antshel et al. 2010; Green et al. 2009). A highly consistent finding is that arithmetic skills are a particular weakness, with reading skills significantly stronger (Bearden et al. 2002; Chow et al. 2006; De Smedt et al. 2009; Swillen et al. 1999). Rote memory appears to be an area of relative strength, given overall intellect (Jacobson et al. 2010). On average, relative weaknesses in adults include the areas of social judgment, motor skills, verbal learning and executive functioning (Chow et al. 2006). Importantly, there is no evidence that those with a lower intellectual level per se have an increased risk for psychiatric illness, including schizophrenia (Chow et al. 2006; Vorstman et al. 2006).

The behavioural expression and profile of diagnosable psychiatric disorders also change over the course of development in 22q11.2DS. In children, attention deficit and anxiety disorders are reported to be relatively common (Niklasson et al. 2009; Antshel et al. 2010), although base rates may also be high in the general population. Autistic spectrum features, though not autism, are also reported to be common (Niklasson et al. 2009; Vorstman et al. 2006), perhaps with a distinctive symptom profile (Bruining et al. 2010). In addition to clinical psychiatric diagnoses, behavioural characteristics reported to be elevated in 22q11.2DS, but that may not be well captured by standard assessment scales, include difficulties socializing, dependency on a caregiver, impulsivity, temper outbursts, perseverative speech and repetitive behaviours (Bassett et al. 2003; Swillen et al. 2000). Importantly, at all ages several factors must be taken into account in assessing behaviour and psychiatric signs and symptoms. These include the individual's developmental and intellectual levels, speech and communication difficulties, as well as other medical conditions and environmental factors such as adequacy of supports and appropriateness of expectations. Another major issue to consider in research reports is the potential of bias related to individuals who enter cohorts for psychiatric and neurobehavioural assessments (Fung et al. 2010).

In adults with 22q11.2DS, in a cohort where psychiatric ascertainment bias was minimized, treatable psychiatric illnesses were found in about 60% of patients, with non-psychotic disorders most commonly associated (Fung et al. 2010). Generalized anxiety disorder occurred at a prevalence two to three times greater than general population expectations. This is consistent with studies of children where, as expected given typical ages at onset, prevalence of generalized anxiety disorder increases over time (Antshel et al. 2010; Green et al. 2009). However, the psychiatric illness of most concern, and that with evidence for the greatest elevation in risk in individuals with a 22q11.2 deletion, is schizophrenia. The best evidence is that between 20 and 25% of individuals, i.e., about 20 times population expectations, will develop schizophrenia or related psychotic disorders such as schizoaffective disorder (Fung et al. 2010). Studies where ascertainment included psychiatric sources have shown even higher prevalence of psychotic disorders (Murphy et al. 1999). Evidence from multiple studies indicates that about 1% of individuals with schizophrenia in the general population have 22q11.2 deletions (Bassett et al. 2010).

Average age at onset and the overall symptom profile appear similar to those of other forms of schizophrenia (Bassett et al. 2003). Also, as for the associated physical illnesses, standard treatments for psychiatric illnesses appear to be as effective in patients with 22q11.2DS as in individuals in the general population with the same psychiatric conditions (Bassett and Chow 2008). The main caveats for treatment in 22q11.2DS are that one must account for the other accompanying physical conditions and predispositions, including endocrine disorders such as thyroid disease and hypocalcemia, increased seizure risk, aberrant neurodevelopment and often multiple medications (Bassett and Chow 2008).

Highly relevant to both clinical and research concerns is the possible identification of factors in individuals with 22q11.2DS that could be early predictors of later psychotic illnesses like schizophrenia. Although there are as yet no replicated early predictors, there are some initial possibilities suggested by prospective and cross-sectional studies. The larger of two prospective studies followed 70 individuals for 3 years on average from late childhood to mid adolescence (mean age 14.7 years) (Antshel et al. 2010). Baseline anxiety scores on parental ratings and non-perseverative errors on the Wisconsin Card Sorting Test were associated with higher parental ratings of possible psychotic symptoms. Overall there was a general decrease in IQ in the cohort but this did not correlate with emergence of possible psychotic symptoms. There were no psychotic illnesses diagnosed in this sample. Another study of 28 individuals reported a diagnosis of a psychotic disorder in nine young subjects (six with schizophrenia or schizoaffective disorder), after an average five year follow-up that was associated with an average 10-point decline in verbal IQ from baseline (Gothelf et al. 2005). There was also greater severity of researcher ratings of psychotic symptoms and parental reports of anxiety or depression at baseline, when compared with the 19 subjects aged 12 to 24 years at Time 2 without a psychotic illness. While in this study, the *COMT* Met allele was said to be associated with psychosis, the larger prospective study found no *COMT* association with psychotic signs (Antshel et al. 2010). Notably, three cross-sectional studies of adults (total $n=213$) have also found no significant association of the *COMT* Met allele with psychotic illness or psychotic symptoms in 22q11.2DS (Bassett et al. 2007; Murphy et al. 1999; Raux et al. 2007). On the other hand, as for general population samples,

performance on frontal lobe-related tasks in 22q11.2DS may be related to this functional *COMT* allele (Bassett et al. 2007).

An initial cross-sectional study of 56 adults with 22q11.2DS showed evidence that individuals with schizophrenia perform significantly worse than those with no psychotic illness on tests of motor skills, verbal learning, and social cognition (Chow et al. 2006). These are similar to the domains showing relative impairment in general population forms of schizophrenia. Another study of adults with 22q11.2DS reported that 13 subjects with schizophrenia performed worse than 15 with no psychosis on individual tests of abstraction, attention, visual-spatial memory and visual recognition (Van Amelsvoort et al. 2004). There is also evidence that brain structure may differ between individuals with 22q11.2DS with schizophrenia and those with no psychotic illness (Chow et al. 2011; Kiehl et al. 2009; Schaer et al. 2009; Van Amelsvoort et al. 2004). The largest study involved 63 adults with 22q11.2DS and found that significant gray matter reductions in the superior temporal gyrus and temporal lobe were associated with expression of schizophrenia (Chow et al. 2011). Interestingly, temporal lobe cortical thinning has been reported in children with 22q11.2DS compared with controls (Bearden et al. 2009). As for cognitive functioning however the age of the individuals studied is key because there are major changes in brain structure over development and with aging. Nonetheless, these findings suggest that, as in the general population of schizophrenia, excessive synaptic elimination in this brain region may be a key component of the pathophysiology of schizophrenia in 22q11.2DS.

There are as yet few studies of the neurobehavioural phenotype of older patients with 22q11.2DS. There are some initial indications that early onset Parkinson's disease may be a late manifestation of the syndrome (Booij et al. 2010; Zaleski et al. 2009). Although further studies are needed to investigate this association, it may be that, as for other syndromes, aberrant neurodevelopment in 22q11.2DS may set the stage for increased risk of neurodegenerative conditions.

The mouse as a model for dissecting the 22q11.2 chromosomal region

The orthologous region of the human 22q11.2 locus is located on mouse chromosome 16. Most of the genes from the commonly deleted region are represented, although the relative organization of the region is different from that in humans (Puech et al. 1997). Several deletion mouse models hemizygous for the proximal deletion region have been engineered (Lindsay et al. 1999; Mukai et al. 2008; Paylor and Lindsay 2006). *Lgdel/+* (Merscher et al. 2001) and *Df(16)A+/-* (Stark et al. 2008) mice harbour a 1.3 Mb hemizygous deletion including 27 genes. *Df1/+* and *Df(16)1/+* mice carry a hemizygous deletion involving 22 genes and 23 genes, respectively. *Smdel/+* mice carry a 550-kb deletion including 16 genes but excluding the *TBX1* gene region and have normal cardiovascular development (Puech et al. 1997). In addition, several mouse models deficient for a single gene from the 22q11.2 deletion region are available.

In addition to the congenital malformative phenotype, mice deleted for the region syntenic to human 22q11.2 region have been noted to also display behavioural abnormalities. Although considerable caution is needed when comparing these to neurobehavioural phenotypes in

humans (Meechan et al. 2010), mouse models are playing an important role in investigating possible CNS effects of the 22q11.2 deletion. The *Df1/+* mouse (Paylor et al. 2001) was reported to have sensorimotor gating anomalies, as demonstrated by impaired pre-pulse inhibition (PPI), a finding described in human schizophrenia and in 22q11.2DS (Sobin et al. 2006). These mice also showed memory and learning impairments. *Lgdel* mice presented similar results for PPI and displayed impaired grip strength and nociception (Long et al. 2006). In contrast, mice heterozygous for a 150 kb portion of the proximal region of the deletion region, excluding all the genes discussed above and below, had increased PPI (Kimber et al. 1999).

Deficits in PPI, learning and memory are thought to result at least in part from hippocampal dysfunction. Studies of transcript levels in the hippocampus of *Df1/+* mice and control mice using microarray technology, showed that only 12 of the 22 genes included in the deletion were differentially expressed in the hippocampus (Jurata et al. 2006; Sivagnanasundaram et al. 2007). Mukai et al. (Mukai et al. 2008) demonstrated that primary hippocampal neurons from *Df(16)A+/-* mice have decreased density of dendritic spines and glutamatergic synapses, and impaired dendritic growth. These deficits were also observed in primary cultures from *Zdhhc8*-deficient mice and could be prevented by introduction of enzymatically active *ZDHHc8* palmitoyltransferase. However, these structural changes were not replicated in *Df1(16)1/+* mice (Earls et al. 2010). Using this model, Earls et al. (Earls et al. 2010) reported deficits in spatial memory associated with increased long term potentiation and enhanced pre-synaptic glutamate release in hippocampal CA3-CA1 pyramidal neurons. They also found that upregulation of the *SERCA2* gene contributed to this dysregulation of pre-synaptic calcium kinetics and synaptic plasticity. Interestingly, these effects were only observable in mature, not young, animals.

Behavioural studies of mice deficient for a single gene from the deleted region have shown that many of these mouse models had deficits in PPI and/or learning, making it difficult to identify a major gene and suggesting that the behavioural phenotype of 22q11.2DS may result from the interaction between several genes (Meechan et al. 2010; Paterlini et al. 2005). PPI was found to be impaired in mice homozygous for *Prodh* deficiency (Gogos et al. 2009). Using several overlapping deletions, Paylor et al. (Paylor et al. 2006) defined a PPI critical region including four genes and showed that both *Tbx1+/-* and *Gnb1l+/-* mice had reduced PPI. In contrast, mice haploinsufficient for *Comt* (Gogos et al. 1998), *Rtn4r* (Hsu et al. 2007) or *Sept5* (Suzuki et al. 2009) had normal PPI. Interestingly, PPI was increased in homozygous *Sept5-/-* mice (Suzuki et al. 2009). Recently, Stark et al. (Stark et al. 2008) identified abnormal microRNA biogenesis in *Df(16)A+/-* mice and demonstrated that this was related to haploinsufficiency of the *Dgcr8* gene. In addition, mice haploinsufficient for *Dgcr8* also had impaired PPI. Due to the potential importance of miRNAs in neural development, the *DGCR8* gene is thought to contribute significantly to the behavioural phenotype of 22q11.2DS.

Consistent with a multiple gene dosage hypothesis, Meechan et al. (Meechan et al. 2010) have provided evidence using the *Lgdel* mouse model for four sets of genes in the 22q11.2 region having successive effects on several mechanisms during neurodevelopment. Beginning with changes in forebrain patterning, other subsets of genes with decreased

dosage modify cortical neurogenesis, then neuronal migration. Changes in genes important to regulation of mitochondrial function can alter neuronal connections, including those involved in synaptogenesis and pruning. The resulting disruptions of cortical circuitry were found most predominantly in cells that correspond to GABAergic interneurons that have been implicated in schizophrenia pathogenesis (Meechan et al. 2010).

Genotype variations of the non-deleted copy of the 22q11.2 Region may explain phenotypic variability of 22q11.2 DS

As clinical variability is not explained by differences in gene content within the deletion, allelic variation(s) in the non-deleted homologous region is considered a possible contributor to phenotypic variability. Regarding the malformative aspects of the syndrome, mutation screening of *TBX1* in 22q11.2DS patients (Rauch et al. 2004; Voelckel et al. 2004) revealed no difference between patients with or without congenital heart defects. Its well-known role in the metabolism of dopamine and functional polymorphism has prompted many studies of the possible role of the *COMT* gene in cognition and susceptibility to psychotic disorders. The results are mixed. For example, hemizygosity for the Met allele in children with 22q11.2DS has been found to be associated with better cognitive functioning in some studies (Bearden et al. 2004; Kates et al. 2006; Shashi et al. 2006; Shashi et al. 2010), and a decline in verbal IQ over time in another study (Gothelf et al. 2005). In 73 adults with 22q11.2DS, Bassett et al. (Bassett et al. 2007) reported that individuals with the Met allele had non-significantly lower cognitive performances when compared to the Val allele group. Other studies have also found no significant effect of this allele on general cognition in 22q11.2DS (Baker et al. 2005; Glaser et al. 2006a; Van Amelsvoort et al. 2008). As noted above, studies of adults with 22q11.2DS have consistently failed to find any association between schizophrenia and this functional *COMT* variant (Bassett et al. 2007; Murphy et al. 1999; Raux et al. 2007). Concerning *PRODH*, Raux et al. (Raux et al. 2007) reported that 22q11.2DS patients with proline levels >550 mmol/l had lower IQ and that hyperprolinemic patients with the *COMT* low activity Met allele may be at risk for developing psychosis and other psychiatric disorders, consistent with possible synergy between the two genes as evidenced by animal studies. Similar phenotypic findings and interactions between the *COMT* genotype and proline levels were also found by Vorstman et al. (Vorstman et al. 2009b) but the association between high proline levels and lower IQ was not replicated. In a study of 79 Caucasian adults with 22q11.2DS, 37 with schizophrenia, Vorstman et al. (Vorstman et al. 2009a) found significant association to the same rs165793-G allele of the *PIK4CA* gene as in a general population sample of schizophrenia (Jungerius et al. 2008). Although a meta-analysis that included an independent study of 20 subjects with 22q11.2DS and psychotic disorders was nominally significant, the results did not confirm a large effect size for this variant (Ikeda et al. 2010).

Evaluation of 22q11.2 genes as candidate susceptibility genes for common psychiatric disorders in the general population

The high incidence of common psychiatric disorders in 22q11.2DS patients suggests that changed dosage of one or more genes in the region might confer susceptibility to these

disorders. Most of the genes from the 22q11.2 deletion region are expressed in fetal and adult brain, thus are candidates for both the psychiatric phenotype of patients with 22q11.2 deletions and susceptibility to psychiatric disorders in the general population (Meechan et al. 2010).

Regarding *COMT*, the many association studies using the functional 158Met/Val polymorphism have given contradictory results, some showing association between schizophrenia and the high-activity Val allele, others with the low-activity Met allele (for review see Prasad et al. 2008). In addition to the effects of genetic heterogeneity, 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 (Costas et al. 2010).

Several studies have found positive association between functional polymorphisms of the *PRODH* gene and schizophrenia (Kempf et al. 2008; Li et al. 2004; Liu et al. 2002), whereas others gave negative results (Abou Jamra et al. 2005; Fan et al. 2003; Glaser et al. 2006a; Glaser et al. 2006b; Ohtsuki et al. 2004; Williams et al. 2003).

Two groups (Funke et al. 2007; Ma et al. 2007) analyzed variations at the *TBX1* locus in two populations of different ethnic backgrounds and found no differences in allele frequencies between patients with psychiatric disorders and controls.

Regarding *ZDHHC8*, two studies reported significant association between specific gene variants and schizophrenia (Liu et al. 2002; Mukai et al. 2004). These results were not confirmed in further studies in the Japanese and European populations (Glaser et al. 2006b; Otani et al. 2005; Saito et al. 2005). Xu et al. (Xu et al. 2010) performed a meta-analysis and found a negative association between *ZDHHC8* polymorphism and schizophrenia.

From the large number of schizophrenia association studies that have been conducted, a single study found a significant association with a functional polymorphism of *UFDIL*, (encoding for the ubiquitin fusion degradation 1 protein, which is expressed in the developing mouse brain) (De Luca et al. 2001), Chen et al. (Chen et al. 2005) found no association between four SNPs of the *ARVCF* gene and schizophrenia but Mas et al. (Mas et al. 2010) recently reported significant association to rs165815, a functional variant in exon 15 of *ARVCF*, in a Caucasian sample from Catalonia.

Summary

Despite limitations in the number of studies to date, effects of ascertainment bias, and the inherent variability of expression and reduced penetrance of the syndrome in both humans and animal models, 22q11.2DS has become an important model for understanding human disease, including complex neurobehavioural phenotypes. In particular, the high risk for schizophrenia imparted by the associated hemizygous 22q11.2 deletion has provided a rare opportunity to help understand this common disease and its neurodevelopmental mechanisms. Future studies will no doubt contribute further to determining the sets of genes that are most responsible for the CNS phenotypes of interest and possibly to identifying early predictors of later onset disorders. Understanding the developmental trajectory of the

associated neurobehavioural phenotypes in 22q11.2DS could also assist with understanding normal human brain development and the molecular genetics underlying this amazing phenomenon.

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Fig. 1.
Mechanism of non-allelic homologous recombination