AN OVERVIEW OF CORRELATIONS BETWEEN SCHIZOPHRENIA AND 22Q11.2 DELETION SYNDROME

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Abstract

Objective: 22q11.2 deletion syndrome (22q11DS) is a genetic syndrome associated with a microdeletion of the chromosome 22 band q11 with an estimated prevalence of between 1:2,500 and 1:4,000 live births. Studies of school-age children have shown that individuals with 22q11DS have very high rates of psychiatric morbidity and abnormal behaviors. By late adolescence and early adulthood, up to one-third of patients with 22q11DS develop psychotic disorders resembling above all schizophrenia and schizoaffective disorder. Therefore, 22q11DS is of considerable interest to research concerned with the genetic and epigenetic mechanisms involved in the development of schizophrenic disorder.

Method: A comprehensive literature review based on PubMed/MEDLINE, Cochrane Library, Cinhal and PsycInfo was undertaken.

Results: Schizophrenic disorder associated with 22q11DS largely resembles that found in the general population as regards the core signs and symptoms, treatment response, neurocognitive profile and MRI brain anomalies.

Conclusions: Individuals with 22q11DS are an easy identifiable high-risk group for schizophrenia whose transition rate in early adulthood may be as high as 30%, regardless of environmental factors. This syndrome is thus of considerable interest to researchers and clinicians involved in the early intervention/prevention of schizophrenia.

Key words: 22q11.2 deletion syndrome, schizophrenia

Declaration of interest: none

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1. Introduction

22q11.2 deletion syndrome (22q11DS) first known as velocardiofacial syndrome or Di George syndrome, is a genetic syndrome (Scambler et al. 1992) associated with a microdeletion of the chromosome 22 band q11 with an estimated prevalence of between 13.2/100.000 and 23.3/100.000 (Oskarsdottir 2004). 22q11DS is a complex disorder with multiple abnormalities that affect a large number of tissues and organs, many of which are derived from neural crest cells. The phenotype of this syndrome has more than 180 clinical features (Robin and Shprintzen 2005, Shprintzen 2005). The diagnosis is therefore defined by the deletion of DNA from chromosome 22 at the q11.2 band spanning the region that is regarded as critical.

The physical and neurobehavioral phenotype of the syndrome includes high rates of congenital dysmorphic features (Bassett et al. 1998, Bassett et al. 2001) developmental structural brain abnormalities (Chow et al. 1999), cognitive dysfunction (Swillen et al. 2000) and psychiatric disorders (Gothelf et al. 2008), particularly schizophrenia (Bassett and Chow 1999, Murphy 2005).

The neurocognitive profile of 22q11DS is characterized by general cognitive functioning in the low borderline range, while reading decoding and spelling skills as well as auditory/verbal memory skills

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are areas of relative strength. Differently, visuospatial function, math attainment and executive function are all reported to be impaired (Antshel et al. 2008).

Even though the brain structure in subjects with 22q11DS is not drastically different from typically developing controls, recent quantitative studies have shown a total brain volume decrease of 8.5–11% in children and adolescents with 22q11DS if compared with normal individuals (Eliez et al. 2000, Tan et al. 2009, Karayiorgou et al. 2010). Moreover, the latest imaging techniques (fMRI; DTI) have shown significant differences in brain functioning between subjects with 22q11DS and those without. In Gothelf et al. (2007), the first group display greater longitudinal increase in cranial and cerebellar white matter, superior temporal gyrus, and caudate nucleus volumes. They also have a more robust decrease in amygdala volume.

As regards psychiatric disorders, studies of school-age children have shown that individuals with 22q11DS have very high rates of psychiatric morbidity and abnormal behaviors such as attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (OPD), specific and social phobias, generalized anxiety disorder, obsessive-compulsive disorder and autism spectrum disorder (Feinstein et al. 2002, Gothelf et al. 2004, Antshel et al. 2006).

ADHD is diagnosed in 30-40% of individuals with 22q11DS (Anthshel et al. 2006, Gothelf et al. 2003), whereas anxiety disorders, especially simple phobias and separation anxiety, are present in 30-40% (Antshel et al. 2006; Swillen et al. 1999; Vogels et al. 2002). Autism spectrum disorders can be found in 10-30% (Antshel et al. 2007; Vortsman et al. 2006), while mood disorders, including major depression and bipolar disorder, are present in 20-30% (Antshel et al. 2006, Papolos et al. 1996). However, the incidence of most psychiatric disorders, is no higher among individuals with 22q11DS than in cohorts with other developmental disorders (Feinstein et al. 2002; Antshel et al. 2006). Therefore, none of these disorders, if diagnosed, fulfills the criteria (Feinstein et al. 2002) set forth for a behavioral phenotype that is specifically associated with a syndrome.

By late adolescence and early adulthood, up to one-third of patients with 22q11DS develop psychotic disorders resembling above all schizophrenia and schizoaffective disorder (Murphy et al. 1999, Bassett et al. 2003, Gothelf et al. 2007, Jolin 2012).

Therefore, 22q11DS is of considerable interest to research concerned with the genetic and epigenetic mechanisms involved in the development of schizophrenic disorder.

Our aim is to review current knowledge on the correlations between Schizophrenia and 22q11.2 deletion syndrome. As a first step we shortly describe psychopathological features of schizophrenia in 22q11DS, with a main focus on prodromal symptoms. As second step we summarize current knowledge on potential genetic correlates in 22q11DS.

Finally, we describe neuropsychological correlates of schizophrenia in 22q11DS.

2. Methods

2.1 Search criteria and results

A comprehensive literature search of the PubMed/MEDLINE, Cochrane Library, Cinhal and Psycinfo was carried out predating December 2012.

A search algorithm was based on a combination of the terms: a) schizophrenia, psychotic disorder, prodromal symptoms b) 22q1qDS, 22q11.2 deletion syndrome. Only publications in English or with at least an abstract available in English were included. References of retrieved articles and review were also scanned to identify other possibly relevant studies. 27 articles were finally included in the review. Of these, 9 concerned schizophrenia in 22q11DS; 5 were on prodromal symptoms and Ultra High Risk (UHR) in 22q11DS; 13 based on genetic and neuropsychological correlates in 22q11DS (see **table 1**).

3. Schizophrenia in 22q11DS

The incidence of most psychiatric disorders, including ADHD, generalized anxiety disorder, obsessive compulsive disorder and autism spectrum disorders, is no higher among individuals with 22q11DS than in cohorts with other developmental disorders (Fung et al., 2010; Feinstein et al. 2002, Antshel et al. 2006). Therefore, none of these disorders, if diagnosed, fulfills the criteria set forth for a behavioral phenotype that is specifically associated with a syndrome (Feinstein et al. 2002).

By contrast, individuals with 22q11DS have an increased risk of developing schizophrenia (Philip et al. 2011, Karayiorgou et al. 1995, Xu et al. 2008). Usually first subclinical manifestations occur during adolescence and young adulthood (Armando et al. 2012a): half of the adolescents affected by this syndrome report transient psychotic experiences, while as many as 30% of affected adults are diagnosed with schizophrenia (Philip et al. 2011, Gothelf et al. 2007, Green et al. 2009), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR), a transition rate is comparable to the highest rates observed in ultra-high risk groups (Ruhrmann et al. 2010). This syndrome is therefore one of the highest known risk factors for schizophrenia.

Moreover, the 22q11DS is found in up to one in 50 patients with schizophrenia, with reports ranging from 0.3% to 2% (Karayiorgou et al. 1995, Arinami 2006, Stefansson et 2008), which is significantly higher than the estimated figure of 1 in every 5,000 live births in the general population (Botto et al. 2003). The occurrence of this deletion is even higher in patients with childhood-onset schizophrenia (5.7%) (Sporn et al. 2004) and in patients with schizophrenia and additional major manifestations of 22q11DS (from 20% in patients with 1 manifestation to 53% in patients with 2 manifestations) (Stefansson et al., 2008 Bassett et al. 1998).

Schizophrenic disorder associated with 22q11DS largely resembles that found in the general population as regards the core signs and symptoms, treatment response, neurocognitive profile and MRI brain anomalies (Karayiorgou et al. 2010). When Bassett et al. (Bassetet al. 2003) compared 16 adults with 22q11DS and 46 adults with schizophrenia without evidence of 22q11DS, they did not detect any significant differences in age at onset, in lifetime or cross-sectional core positive and negative schizophrenic symptoms, or in global functioning. The same authors (Bassett et al. 1998) had previously reported similar results when they studied a sample of 10 subjects with schizophrenia and 22q11DS. Focusing on psychotic symptoms in 22q11DS patients, Debbané (Debbané et al. 2006) reported a higher prevalence of auditory hallucination (9/12), delusion (7/12) specially referential type (4/12) and grandiose type.

4. Prodromal symptoms and ultra-high risk state in 22q11DS

Few studies conducted on early signs and symptoms that are predictive of schizophrenia in patients with 22q11DS have explored patterns of psychotic and prodromal symptoms in young people with the 22q11DS. These studies have found that the incidence of major depressive disorder, attention-deficit/hyperactivity disorder, simple phobias, enuresis and impaired social adaptive skills is higher in adolescents with 22q11DS than in normal subjects (Gothelf et al. 2007, Antshel et al. 2006, Debbané et al. 2006, Antshel et al. 2010).

Stoddard (Stoddard et al. 2010) investigated the presence of positive symptoms and attenuate positive symptoms (APS) in a sample of 20 22q11DS adolescents and young adults (age 12-22) using the Structured Interview for Prodromal Syndromes (SIPS). Psychotic phenomena resulted very prevalent in these individual: 45% had moderate to severe positive symptoms and meet criteria for APS. Recently Schneider and colleagues (Schneider et al. 2012) obtained similar results: 40,4% of the sample experienced at least one moderate to severe positive symptoms, negative symptoms were 83%.

To our knowledge, only two studies have prospectively explored specific prodromal symptoms that are predictive of schizophrenia onset. In the first study (Gothelf et al. 2007), 32.1% of the sample developed a schizophrenic disorder during follow-up. The development of psychotic symptoms between the age of 12 years and the age of 18 years was best predicted by the presence of psychotic symptoms at the time of the baseline study (i.e. at the age of 12 years) and by the anxiety and depression scores. Baseline sub-threshold psychotic symptoms combined with both the COMT genotype and the baseline symptoms of anxiety or depression predicted 61% of the variance in the severity of psychosis at the follow-up evaluation. A low IQ at the baseline was a further predictor of high follow-up psychosis rating-scale scores. ADHD was not found to be a predictor of psychotic outcomes.

In the second study (Antshel et al. 2010), a total of 70 children with 22q11DS, 27 siblings of children with 22q11DS and 25 community controls were followed from childhood into mid-adolescence to investigate the predictive value of prodromal symptoms of psychosis in adolescents with 22q11DS. Major depressive disorder, oppositional defiant disorder and generalized anxiety disorder diagnoses were higher in the 22q11DS sample. With very low false positive rates, the best predictor of adolescent prodromal psychotic symptoms were parent ratings of childhood odd/eccentric symptoms and child performance in an executive functioning test. (see **table 1**).

Recently, our research group (Armando et al. 2012b) conducted a study on a sample of 30 Ultra-high Risk for a psychotic onset (UHR) individuals with 22q11DS (UHR+22q11DS) and 81 individuals at UHR without 22q11DS comparing positive, negative and depressive symptoms, level of general functioning and IQ. A significant group difference in negative symptoms was found, while no significant differences were found for positive, global and total symptoms. The UHR+22q11DS group showed a lower level of general functioning. Interestingly, the clinical profile of the UHR+22q11DS group was clearly more homogeneous.

5. Genetic correlates of cognitive/schizophrenia-related abnormalities in 22q11DS

Chromosome 22q11.2 deletion, velocardiofacial and Di George are all clinical syndromes caused by the homozygous deletion of chromosome 22 at the q11.2 band. These deletions are believed to include between 35 and 60 known genes that 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. A comprehensive review (Karayiorgou et al. 2010) and several studies (Bassett and Chow 2008, Insel 2010, Meechan et al. 2010, Delio et al. 2013) on this topic has recently been published. It is not yet known which of the 35-60 hemideleted genes are responsible for the psychiatric disorders of 22q11DS. However, we will discuss as an example a promising gene that is deleted in all individuals with 22q11DS, the catechol-O-methyl transferase (COMT) gene. COMT regulates the cortical dopamine catabolism and plays a critical role in executive functions (Yavich et al. 2007, Papaleo et al. 2008, Armando et al. 2012c, Scheggia et al. 2012). Moreover, the pathophysiology of schizophrenia is strongly dependent on dysregulation of dopamine levels, particularly in the prefrontal cortex (PFC) (Winterer and Weinberger 2004, Sambataro et al. 2009). Therefore, the COMT gene represents an attractive candidate for the cognitive and psychiatric disturbances found in patients suffering from 22q11DS. However, if reduced COMT enzyme activity were the only cause of these disturbances, all individuals with 22q11DS, and not only 30%, would have these cognitive/psychiatric phenotypes. Moreover, increased COMT enzyme activity results in cognitive deficits and might constitute a weak risk factor for schizophrenia. Indeed, reduced COMT enzyme activity in healthy humans and rodents has been found to improve executive functions (Tunbridge et al. 2006, Papaleo et al. 2008, Sambataro et al. 2009, Scheggia et al. 2012, Papaleo et al. 2012). In contrast, subjects with 22q11DS that carry only one copy of the COMT gene may be exposed to unusually high brain dopamine levels from an early age if they also carry COMT polymorphisms and/or haplotypes that per se result in reduced COMT enzyme activity. This hypothesis is supported by studies showing that functional COMT polymorphisms and haplotypes interact with 22q11DS in the morphology of the brain and in the susceptibility to illnesses such as ADHD and OCD (Kates et al. 2006, Michaelovsky et al. 2008, van Amelsvoort et al. 2008). However, the data available regarding the effects of COMT polymorphisms and haplotypes in 22q11DS in measures of neurocognitive performance and schizophrenia are not yet clear. It was suggested that cognitive/schizophrenia-like abnormalities in 22q11DS may originate from a genetic interaction of COMT with other genetic loci. Indeed, 22qDS cognitive/schizophrenia abnormalities might share the characteristics of a contiguous gene syndrome. For example, the PRODH and COMT genes are both present in the 22q11.2 locus, and PRODH-deficient mice exhibit cognitive and schizophrenia-like phenotypes only when COMT is pharmacologically blocked, thereby demonstrating the ability of COMT and PRODH to interact and compensate for one another (Paterlini et al. 2005). However, if the hemideletion of both PRODH and COMT were the only cause of cognitive/schizophrenia-like symptoms in 22q11DS, every subject with this deletion would present these

Table 1. *Genetic, neuropsychological and psychopathological correlations between 22q11DS and Schizophrenia*

Reference	Study design	Sample size	Sample age	Correlates of schizophrenia in 22q11DS
Schizophrenia in 22q11DS				
Xu et al. (2008)	Case-control	1,077	No limits	Increased risk of developing schizophrenia
Green et al. (2009)	Cohort	172	5-54	Higher rates of schizophrenia in patients with 22q11DS
Stefansson et al. (2008)	Case-control	11,236	No limits	Higher rates of 22q11DS in patients with schizophrenia
Sporn et al. (2004)	Longitudinal	75	<13	Higher rates of 22q11DS in patients with schizophrenia
Bassett et al. (2003)	Case-control	62	<50	Higher rates of 22q11DS in patients with schizophrenia
Baker et al. (2005)	Case-control	50	13-21	Age of onset, positive/negative symptoms, reduced functioning
Carroll et al. (2008)	Case-control	45	>18	Cognitive impairment
Devrim et al. (2008)	Case-control	64	No limits	Cognitive impairment
Ruhrmann et al. (2010)	Prospective	245	> 18	Biological and environmental mechanism underlying psychosis
Prodromal symptoms				
Gothelf et al. (2007)	Case-control (5- year)	51	Children	Sub-threshold psychotic, depressive and anxiety symptoms
Feinstein et al. (2002)	Case-control	57	6-19	Specific phobia, ADHD and oppositional defiant disorder
Antshel et al. (2006)	Between-group	154	6-15	ADHD, major depressive disorder and simple phobias
Antshel et al. (2010)	Case-control (3- year)	70	Children	Odd/eccentric symptoms
Armando et al. (2012c)	Between-group	30	16,5	Features of prodromal symptoms in 22q11DS
Genetics and Neuropsychology				
Debbané et al. (2008)	Case-control	52	12-17	Source monitoring deficits
Gothelf et al. (2005)	Longitudinal	24	Children	Decrease in verbal IQ
Debbane´ et al. (2006)	Cross-sectional	43	6-19	Decrease in verbal IQ
Sobin et al. (2005)	Cross-sectional	40	5-12	Deficits in prepulse inhibition
Moss et al. (1999)	Cross-sectional	33	6-27	Short-term and working memory deficits
Wang et al. (2000)	Cross-sectional	36	5-12	Short-term and working memory deficits
Lajiness-O'Neill et al. (2005)	Case-control	42	5-19	Deficits in free recall
Kates et al. (2006)	Case-control	47	Children	Smaller volume in pre-frontal cortex and amygdala
Sambataro et al. (2009)	Cross-sectional	75	21-90	COMTval(158)met modulates age-related change in executive function
Gothelf et al. (2011)	Longitudinal	19	>17	Morphometric spatial patterns predicted psychotic symptom
Dujiff et al. (2012)	Longitudinal	69	>5.5	Marked decline in cognitive abilities.
Flahault et al. (2012)	Longitudinal	31	6-22	Associations between hippocampal head volume and psychotic symptom
De Koning et al. (2012)	Cohort	28	> 18	Deficit in prepulse inhibition

abnormalities. As suggested by Paterlini and colleagues (2005), alternatively, additional genes might be involved. It is consequently likely that cognitive/schizophrenia abnormalities associated with 22q11DS might result from an alternative epistatic interaction with other genes in the genome. Indeed, according to this hypothesis, a protective allele (i.e. which reduces COMT activity) might become an allele at risk in a different epistatic context (e.g. through synergistic mechanisms) (see **table 1**).

6. Neuropsychological correlates of schizophrenia in 22q11DS

22q11DS is associated with a distinctive cognitive phenotype. 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 (Swillen et al. 1999, Van Amelsvoort et al. 2004, Chow et al. 2006, Antshel et al. 2010, Duijff 2012). About one-third have mild intellectual disability, while more severe levels of intellectual disability are uncommon (Swillen et al. 2000, Bassett et al. 2005, Chow et al. 2006). 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 (Swillen et al. 1999, De Smedt et al. 2009, Jacobson et al. 2010). By adolescence however there are no significant differences between mean performance and mean verbal IQ (Green et al. 2009, Antshel et al. 2010). A highly consistent finding is that arithmetic skills are a particular weakness, with reading skills significantly stronger (Swillen et al. 1999, Bearden et al. 2002, Chow et al. 2006, De Smedt et al. 2009). 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).

Results of two longitudinal studies, respectively in adolescents and in patients with 22q11.2 deletion syndrome in late childhood/adolescence suggesting that at least some of these individuals show a gradual decline in cognitive development as they grow into adulthood (Gothelf et al. 2005, Antshel et al. 2010). The high prevalence of schizophrenia in this syndrome suggests that a decrease in IQ scores may be viewed as the first manifestation of disorder.

Indeed, research into cognitive development in schizophrenia in the general population indicates

that cognitive decline occurs in late adolescence (Woodberry et al. 2008) but some studies also suggest that academic or cognitive deficits can be found as early as in the first grade of school (Monte et al. 2008). These findings are in keeping with the neurodevelopmental model of schizophrenia. Furthermore, Debbané et al. (2006) reported that the children with psychotic symptoms had significantly lower verbal IQ (VIQ) scores than those without such symptoms.

Gothelf et al. (2005, 2007, 2011) and Antshel et al. (2010) reported that a decline in VIQ in adolescence may be associated with an increased risk of psychotic symptoms during follow-up.

A number of other studies have highlighted the cognitive similarities between adolescents with 22q11DS and those at high risk for schizophrenia

(Erlenmeyer-Kimling et al. 2000, Sobin et al. 2005, Lencz et al. 2006, Duijff et al. 2012, Flahault et al. 2012).

Reduced executive function capacities seem to reflect a genetic risk for schizophrenia, while an executive function deficit seems to be strongly related to a high risk for schizophrenia in people with 22q11DS. Moreover, deficits in prepulse inhibition, a form of response inhibition, have been documented both in schizophrenia and in children with 22q11DS (Braff et al. 2001, Turetsky et al. 2007, De Koning et al. 2012).

Prepulse inhibition (PPI) is a measure of reduction of the acoustic startle response when a weak nonstartling stimulus (prepulse) is presented before a startling stimulus (Braff et al. 1978). PPI is seen as a measure of sensorimotor gating (Braff et al. 1978), and reduced PPI I has consistently been found in mice with long-range deletions that model the deletion in 22q11DS, suggesting that the deleted region plays an important role in the modulation of PPI (Paylor et al. 2001, Paylor et al 2006, Stark et al. 2008, Drew et al. 2011).

PPI has been investigated in individuals with 22q11DS, showing disrupted PPI compared with age-matched controls (Sobin et al. 2005a, Sobin et al. 2005b, Vorstman et al. 2009, De Koning 2012)

There is also evidence suggesting that deficits in verbal memory, spatial working memory and attention are indicators of genetic susceptibility to schizophrenia (Erlenmeyer-Kimling et al. 2000, Lencz et al. 2006). In addition, short-term and working memory deficits, especially in the non-verbal domain, have been described as phenotypic characteristics in 22q11DS by several research groups (Moss et al. 1999, Wang et al. 2000).

From a more biological perspective, executive functions have been shown to be related to COMT activity and to dopamine catabolism in prefrontal cortex (PFC) (Yavich et al. 2007, Papaleo et al. 2008, Weickert et al. 2008, Armando et al. 2012b). These brain regions are implicated in the processing of long-term episodic memory. It is noteworthy that deficits in learning and memory are among the most robust correlates of schizophrenia. Indeed, findings yielded by different estimation procedures point to a deficit in recollection and increased reliance on familiarity when recognition memory judgments are made in chronic schizophrenia (van Erp et al. 2000, Lefèbvre et al. 2010). Although these specific areas of memory processing have not yet been studied in 22q11DS, deficits in free recall, which primarily involves the recollection process, have been documented in people with 22q11DS (Lajiness-O'Neill et al. 2005).

Another type of episodic memory processing associated with executive functioning that is impaired both in patients with schizophrenia and in adolescents with 22q11DS is source monitoring. Indeed, the latest findings on source monitoring deficits in schizophrenia suggest that the process of attributing a source to internally generated material (such as thoughts, memories or voluntary actions) is prone to confuse internal and external sources (Franck et al. 2000). Source monitoring deficits have also been reported in adolescents with 22q11DS (Debbané et al. 2008), thereby reflecting a possible genetic risk for schizophrenia in this population (see **table 1**).

In summary, patients with 22q11DS and those with schizophrenia without 22q11DS display similar impairments in a range of cognitive functions, with patients with 22q11DS exhibiting a significant impairment in executive functions, working memory and temporal processing (Baker et al. 2005, Carroll et al. 2008, Devrim-Ucok et al. 2008).

However, as no studies have, to our knowledge, yet directly compared the cognitive phenotype of schizophrenia with 22q11DS patients with that of schizophrenia patients without 22q11DS, further investigation is warranted to shed light on this specific issue.

7. Conclusions and future goals

Individuals with 22q11DS are an easy identifiable high-risk group for schizophrenia whose transition rate in early adulthood may be as high as 30%, regardless of environmental factors.

This syndrome is thus of considerable interest to researchers and clinicians involved in the early intervention/prevention of schizophrenia for at least two reasons:

1) The study of early intervention strategies in this specific ultra-high risk group (UHR) may lead to a better understanding of what therapeutic interventions most effectively reduce/delay the transition rates to psychosis. Moreover, since 22q11DS individuals represent the UHR group with the highest transition-to-psychosis rates, early intervention in the subgroup of children with sub-threshold signs of psychosis and internalizing symptoms (particularly anxiety symptoms) may reduce the risk of the development of psychotic disorders in adolescence.

2) Further longitudinal studies designed to compare the clinical, neuropsychological, genetic and neuroimaging profiles of clinical UHR groups with those of 22q11DS+UHR may significantly improve knowledge regarding the specific etiopathogenetic mechanisms involved in schizophrenia, on the one hand, and the detection of early signs and symptoms that are highly predictive of future psychotic onset, on the other.

Last but not least, a synergism between preclinical and clinical studies may be achieved by cross-feeding experiments that will lead to the early detection of 22q11DS individuals who are at high risk of developing not only specific cognitive deficits and schizophrenia-related symptoms, but schizophrenia itself. Indeed, as recently highlighted in a *Nature* special issue on schizophrenia, direct translational studies that closely combine human and animal genetic studies are critically needed in order to develop preventive strategies and new therapeutic approaches for this debilitating neurodevelopmental disorder.

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