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Invited review

Converging levels of analysis on a genomic hotspot for psychosis: Insights from 22q11.2 Deletion Syndrome

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ABSTRACT

Schizophrenia is a devastating neurodevelopmental disorder that, despite extensive research, still poses a considerable challenge to attempts to unravel its heterogeneity, and the complex biochemical mechanisms by which it arises. While the majority of cases are of unknown etiology, accumulating evidence suggests that rare genetic mutations, such as 22q11.2 Deletion Syndrome (22qDS), can play a significant role in predisposition to the illness. Up to 25% of individuals with 22qDS eventually develop schizophrenia; conversely, this deletion is estimated to account for 1–2% of schizophrenia cases overall. This locus of Chromosome 22q11.2 contains genes that encode for proteins and enzymes involved in regulating neurotransmission, neuronal development, myelination, microRNA processing, and post-translational protein modifications. As a consequence of the deletion, affected individuals exhibit cognitive dysfunction, structural and functional brain abnormalities, and neurodevelopmental anomalies that parallel many of the phenotypic characteristics of schizophrenia. As an illustration of the value of rare, highly penetrant genetic subtypes for elucidating pathological mechanisms of complex neuropsychiatric disorders, we provide here an overview of the cellular, network, and systems-level anomalies found in 22qDS, and review the intriguing evidence for this disorder's association with schizophrenia.

This article is part of the Special Issue entitled 'Neurodevelopmental Disorders'.

1. Introduction

Although schizophrenia is a highly heritable neurodevelopmental disorder, the precise biochemical pathways by which it wreaks its devastating effects remains elusive. The complexity and heterogeneity of this illness poses enormous challenges to biomedical discovery. While the majority of cases are of unknown etiology (idiopathic), there is increasing evidence that rare genetic mutations may account for a larger proportion of cases than was previously believed (Sebat et al., 2009; Tam et al., 2009; Walsh et al., 2008). While these findings have fundamentally changed our understanding of the genetic architecture of schizophrenia, they do not address the mechanisms by which structural mutations of genes may contribute to the disease. As such, in-depth investigation of a known genetic cause of psychosis offers a unique window into specific biological pathways leading to its development. 22q11.2 Deletion Syndrome (Velocardiofacial/DiGeorge syndrome; 22qDS) affecting about 1/4000 live births, is one such genetic disorder. This genetic microdeletion syndrome is estimated to account for 1–2% of schizophrenia cases, and currently represents the only known recurrent copy number mutation responsible for introducing new cases of schizophrenia into the population (Karayiorgou and Gogos, 2004). About thirty percent of individuals afflicted by 22qDS are estimated to meet criteria for a psychotic disorder and up to 25% of these individuals are diagnosed with schizophrenia by adulthood (Murphy et al., 1999; Bassett and Chow, 1999). The phenotypic consequences of this deletion event are complex and varied, ranging from facial dysmorphology, congenital heart defects, hypocalcaemia and cleft palate, to cognitive deficits and neurodevelopmental delays (Drew et al., 2011; McDonald-McGinn et al., 2001). Several of the genes within this region are highly expressed in the brain, and known to affect early neuronal migration and cortical development (Maynard et al., 2003). As such, this syndrome provides a unique window into gene-brain-behavior relationships.

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While the majority of individuals diagnosed with this syndrome have a similar 3 Megabase (Mb) deletion, encompassing ≈60 identified genes, an estimated 8–10% of cases have smaller (approximately 1.5 Mb) deletions, a region that includes up to 35 identified genes (Drew et al., 2011; Edelmann et al., 1999) (see Fig. 1). Importantly, the smaller and less common deletion seems to contain all of the genes necessary for development of the syndrome (Carlson et al., 1997), and the increased risk of psychosis (Drew et al., 2011; Karayiorgou et al., 1995). Accordingly, this review will focus on the genes implicated in this 1.5 Mb Critical Region, in the context of a unifying theoretical framework from which to understand the biological mechanisms underlying psychotic symptom development in this syndrome. We first review the developmental trajectory of psychopathology in 22qDS, findings on neurocognitive dysfunction and its ostensible similarities to the cognitive phenotype of schizophrenia, and then discuss the structural and functional neuroanatomic alterations that are characteristic of the disorder. Finally, we highlight recent findings from animal models of the 22q11.2 deletion, which inform our understanding of specific genetic mechanisms relevant to the development of psychosis, via their structural and functional consequences and their overall impact on brain systems involved in motivation, attentional and memory processes.

2. Developmental trajectory of 22qDS-associated psychopathology

While psychotic symptoms usually evolve during adolescence or early adulthood, non-psychotic psychiatric disorders and behavioral abnormalities are present from early childhood in 22qDS, some of which may be premorbid indicators of psychosis susceptibility (Gothelf et al., 2007a). In particular, 14–50% meet autistic spectrum criteria (Antshel et al., 2007; Fine et al., 2005; Niklasson et al., 2001; Vorstman et al., 2006), and attention deficit hyperactivity disorder (ADHD) is diagnosed in 35–55% of children and adolescents with the deletion (Antshel et al., 2005b; Gothelf et al., 2007b; Niklasson et al., 2001). In addition, afflicted individuals exhibit an elevated rate of mood and anxiety disorders (Gothelf et al., 2008; Green et al., 2009). Indeed, in two large cohorts from Israel and Western Europe, Green et al. (2009) found that psychopathology in 22qDS patients appeared to follow a developmental pattern, with high rates of ADHD in early childhood, and substantially increasing rates of mood and psychotic disorder in adolescence and young adulthood. The spectrum of psychopathology associated with this syndrome, spanning a range of DSM-IV diagnostic categories, suggest a model of genetic pleiotropy, in which the same genetic variant can influence multiple phenotypes. Such findings also suggest that schizophrenia and other neuropsychiatric disorders may share overlapping biological pathways (Sebat et al., 2009).

3. Neurocognition

22qDS is characterized by a diverse assortment of neurocognitive deficits, ranging from overall reduced IQ, to abnormal results on assays of more specific endophenotypes such as prepulse inhibition (Kiley-Brabeck and Sobin, 2006; Sobin et al., 2005a, 2005b; Vorstman et al., 2009a; Vorstman et al., 2009b) tasks of spatial and attention-switching (Simon et al., 2005a; Sobin et al., 2006), and time perception (Drew et al., 2011). Although 22qDS patients have lower Full Scale IQ relative to typically developing children, verbal skills tend to be better preserved than non-verbal skills on both IQ and academic achievement measures in children with 22qDS (Bearden et al., 2001b; Moss et al., 1999; Swillen et al., 1999). 22qDS patients show a characteristic neurocognitive profile involving marked deficit in visuo-spatial cognition and memory, with corresponding difficulties with arithmetic (Bearden et al., 2001b; Simon et al., 2005b). A key question is whether intermediate cognitive traits characteristic of idiopathic schizophrenia are also characteristic of 22qDS. While few studies have directly compared these patient groups, two studies to date have directly compared neurocognition in adults with 22qDS with and without psychosis. The most pronounced differences were seen on tests of abstraction, social cognition, spatial working memory, motor skills and verbal learning, with poorer performance in the 22qDS-schizophrenia subjects, supporting the view that the 22qDS subtype of schizophrenia shares general characteristics of cognitive expression with idiopathic schizophrenia (Chow et al., 2006; van Amelsvoort et al., 2004). Moreover, Lajiness-O'Neil (2006) found Wisconsin Card Sort Test performance was significantly inversely correlated with the Thought Problems subscale of the Child Behavior Checklist (CBCL) in 22qDS children, suggesting that executive dysfunction may be an indicator of risk for later-onset psychopathology. This notion is consistent with the literature on youth with a family history of psychosis, which indicates that executive function deficits may be a vulnerability marker for psychosis (Byrne et al., 2003; Davalos et al., 2004; Whyte et al., 2006).

The study of social cognition is also considered to be a high-priority target in current research in schizophrenia (Green et al.,

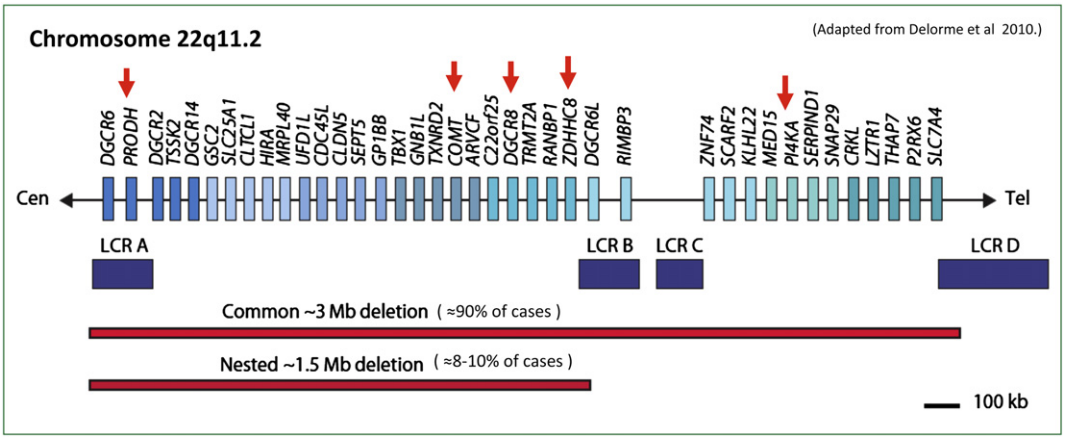

Fig. 1. The *del22q11.2* region on chromosome 22, with genes of interest marked by red arrows. Purple blocks represent low-copy repeats (LCRs) which are believed to mediate the common 3 Mb deletion. The common 3 Mb typically deleted region (TDR), present in over 85% of *22qDS* patients and the 1.5-Mb deletion are shown.