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The 22q11.2 microdeletion: Fifteen years of insights into the genetic and neural complexity of psychiatric disorders

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ABSTRACT

Over the last fifteen years it has become established that 22q11.2 deletion syndrome (22q11DS) is a true genetic risk factor for schizophrenia. Carriers of deletions in chromosome 22q11.2 develop schizophrenia at rate of 25–30% and such deletions account for as many as 1–2% of cases of sporadic schizophrenia in the general population. Access to a relatively homogeneous population of individuals that suffer from schizophrenia as the result of a shared etiological factor and the potential to generate etiologically valid mouse models provides an immense opportunity to better understand the pathobiology of this disease. In this review we survey the clinical literature associated with the 22q11.2 microdeletions with a focus on neuroanatomical changes. Then, we highlight results from work modeling this structural mutation in animals. The key biological pathways disrupted by the mutation are discussed and how these changes impact the structure and function of neural circuits is described.

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1. Introduction

One approach to understanding how schizophrenia is caused in general is to focus on specific cases where the disease is caused by a known factor. Although rare, there are now a number of instances where the primary genetic causative factor appears to have been identified (Karayiorgou et al., 1995; Millar et al., 2000; Xu et al., 2009). Here, we discuss the example of genomic microdeletions in the chromosomal region 22q11.2 that may account for as many as 1–2% of cases of schizophrenia (Karayiorgou et al., 2010) and is, to date, the only confirmed recurrent structural mutation responsible for the introduction of sporadic cases of schizophrenia.

The identification, fifteen years ago, of 22q11.2 microdeletions as a causative factor for schizophrenia was the first demonstration that deletions, or duplications, of chromosomal regions may play an important role in schizophrenia etiology in many cases of the disease (Karayiorgou et al., 1995). Such mutations, known as copy number variations (CNVs), result in altered gene dosage and a rapidly expanding literature shows a high prevalence of such mutations in schizophrenia patients (International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Xu et al., 2008, 2009; Walsh et al., 2008). By allowing the generation of etiological valid animal models, identification of highly penetrant mutations such as these offer unprecedented opportunities to determine the key neural changes that can lead to psychotic illness (Arguello and Gogos, 2006). Here we argue that the 22q11.2 deletion can act as prototype for this type of investigation. That is to say, the rigorous definition of the pathway from mutation to disease phenotype in models of this mutation will provide invaluable insights into the etiology and pathophysiology of schizophrenia as a whole.

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2. 22q11.2 Deletion syndrome

Chromosomal microdeletions at region q11.2 of human chromosome 22 occur at a frequency of around 1 in every 4000 live births, making it the most common known interstitial deletion in humans (Scambler, 2000). Substantial stretches of low copy repeats in this region make it particularly susceptible to deletions during meiosis (Edelmann et al., 1999; Kurahashi et al., 2000; Bittel et al., 2009) and it is of note that duplications at this locus are also relatively common (Portnoï, 2009). The majority of the 22q11.2 microdeletions (~90%) are 3 megabases (Mb) in size (containing approximately 60 known genes, see Tables 1 and 2), while ~8% are 1.5 Mb in size (containing approximately 28 known genes, see Table 1) (Edelmann et al., 1999; Shaikh et al., 2000), and the remainder are atypical deletions (containing only a small number of genes) (Urban et al., 2006). It has been argued that the 1.5 Mb deletions contain all key genes responsible for the syndrome (Carlson et al., 1997) and, in particular, for the increased risk of psychiatric illness (Karayiorgou et al., 1995).

22q11.2 microdeletions cause a complex syndrome that is typically categorized as DiGeorge syndrome or velo-cardio-facial (VCF) syndrome (Scambler, 2000) or 22q11.2 deletion syndrome (22q11.2DS). The first two terms refer, respectively, to the physician who originally delineated the condition in the mid-1960s (Dodson et al., 1969) and to the types of symptoms that normally lead to clinical presentation (velo refers to the palate of the mouth, cleft palates being a common manifestation) (Shprintzen et al., 1978). In this review we will refer specifically to 22q11.2DS to specify a syndrome definitively caused by a mutation at this locus.

The phenotype associated with the 22q11.2 microdeletions is highly variable and involves multiple organ systems, however there is no correlation between the severity of the phenotype and the size of the deletion (Carlson et al., 1997). Phenotypic variability can be caused by breakpoint heterogeneity as well as other genetic, environmental, and stochastic factors. The phenotype includes craniofacial and cardiovascular abnormalities, immunodeficiency, hypocalcaemia, short stature and cognitive impairments (Shprintzen et al., 1978; Ryan et al., 1997; Scambler, 2000; Kobrynski and Sullivan, 2007).

22q11.2 microdeletions account for up to 1–2% of sporadic cases of schizophrenia (Karayiorgou et al., 1995; Xu et al., 2008). Moreover, it has been shown that at adolescence or early adulthood, up to one third of 22q11.2 deletion carriers develop schizophrenia or schizoaffective disorder, which is approximately 25–31 times that of the general population (Pulver et al., 1994; Murphy et al., 1999). This bidirectional association makes the 22q11.2 microdeletion the strongest known risk factor for developing schizophrenia. In addition, since all but the most severe cardiovascular and immune defects associated with 22q11.2DS can now be treated and almost all affected individuals survive into adulthood, long-term medical care and prenatal screening are increasingly being directed toward the recognition and treatment of cognitive and psychiatric phenotypes.

In this review we focus on the now well-established link between 22q11.2 DS and psychotic illnesses, with reference to cognitive dysfunction. We begin with an outline of these psychiatric conditions and cognitive impairments found in 22q11.2 deletion carriers and discuss studies of brain structure and function that have used neuroimaging techniques. Subsequent sections will focus on the complex genetic make-up of this syndrome and how we believe that the creation of mouse models are an essential means of investigation for understanding the syndrome. First we will review behavioral, cell biological and neurophysiological studies in various mouse models of the syndrome, before focusing on what we believe may be the key deleted genes in this region. We also discuss future directions for this work, including the use of induced pluripotent stem cells for creating human neuronal models.

2.1. Psychiatric phenotype of the 22q11.2 deletion syndrome

2.1.1. Susceptibility to schizophrenia

The most prevalent psychiatric disorder in adults with 22q11.2DS is schizophrenia (Karayiorgou et al., 1995; Murphy et al., 1999; Pulver et al., 1994; Xu et al., 2008). Although cases of childhood onset schizophrenia have been described (Usiskin et al., 1999), most carriers develop schizophrenia in early adulthood, as is the case with schizophrenia in general (Shprintzen et al., 1992; Murphy et al., 1999). Overall, the literature suggests that schizophrenia in 22q11.2 deletion carriers is indistinguishable from sporadic forms of the illness (Bassett et al., 1998, 2003). This high association has prompted researchers to look for early psychiatric signs in this 'at risk' population before patients develop a full-blown psychotic disorder. Sub-threshold symptoms indicative of psychosis (*i.e.*, disturbances of social and adaptive functioning prior to the onset of characteristic symptoms of psychosis) were identified in approximately one-third to one-half of children afflicted with 22q11.2DS (Feinstein et al., 2002; Baker and Skuse, 2005; Debbané et al., 2006a). One longitudinal study of patients with 22q11.2DS, following patients from childhood and adolescence to young adulthood, identified similar sub-threshold symptoms as a major risk factor for later development of schizophrenia (Gothelf et al., 2007a).

2.1.2. Cognitive dysfunction

Cognitive dysfunction is common in patients with 22q11.2DS (Chow et al., 2006; De Smedt et al., 2007). Detailed analysis of the domains in which such changes are prevalent is important for pinpointing which neural circuits are likely disrupted by the deletion and additionally to determine which, if any, cognitive changes are specifically associated with development of schizophrenia. Schizophrenia is itself increasingly recognized as a disorder in which cognitive deficits are a core feature.

Most school-aged children who have a 22q11.2 microdeletion fall into the category of 'borderline intellectual functioning' with a Full-Scale IQ (FSIQ) of 71–85, followed by a smaller proportion of children that falls into the 'mild intellectual disability' range (FSIQ 55–70), and a small percentage in the 'low-average intelligence range' (FSIQ > 85) (De Smedt et al., 2007). More severe levels of mental retardation are relatively uncommon (Chow et al., 2006). It is important to emphasize however, that a large number of children with 22q11.2DS present with a cognitive profile that is characterized by a relative sparing of Verbal IQ (VIQ) compared with Performance IQ (PIQ) (Moss et al., 1999; Wang et al., 2000; De Smedt et al., 2007). During school years, reading, spelling, and verbal memory scores are in the low average to superior range (Swillen et al., 1999; Wang et al., 2000; Woodin et al., 2001) and patients consistently score higher on verbal memory than visual-spatial memory (Bearden et al., 2001; Lajiness-O'Neill et al., 2005; Sobin et al., 2005a).

It has been suggested that impairment in attention could be a major contributor to the cognitive profile in 22q11.2DS as attention is required for many nonverbal cognitive functions. For example, studies have suggested that children with 22q11.2DS have difficulty in identifying and interpreting salient spatial and temporal information (Simon et al., 2005a,b; Bish et al., 2007). This suggests that these patients are less able to focus their attention by navigating space, guiding vision, and selecting and integrating goal-relevant information. Counting ability (which requires spatial memory) is also specifically impaired in children with 22q11.2DS. Furthermore, both children and adults with 22q11.2DS demonstrate impairments in 'magnitude comparison' and 'time duration comparison', further pointing to spatial, temporal, and numerical

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