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Review article

Cognitive phenotype and psychiatric disorder in 22q11.2 deletion syndrome: A review

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ABSTRACT

The behavioural phenotype of 22q11.2 deletion syndrome syndrome (22q11DS), one of the most common human multiple anomaly syndromes, frequently includes intellectual disability (ID) together with high risk of diagnosis of psychotic disorders including schizophrenia. Candidate cognitive endophenotypes include problems with retrieval of contextual information from memory and in executive control and focussing of attention. 22q11DS may offer a model of the relationship between ID and risk of psychiatric disorder. This paper reviews research on the relationship between the cognitive phenotype and the development of psychiatric disorders in 22q11DS.

Aspects of cognitive function including verbal I.Q., visual memory, and executive function, are associated with mental health outcome in people with 22q11DS. This relationship may result from a common neurobiological basis for the cognitive difficulties and psychiatric disorders. Some of the cognitive difficulties experienced by people with 22q11DS, especially in attention, memory retrieval, and face processing, may, however, in themselves constitute risk factors for development of hallucinations and paranoid delusions.

Future research into factors leading to psychiatric disorder in people with 22q11DS should include assessment of social and psychological factors including life events, symptoms associated with trauma, attachment, and self-esteem, which together with cognitive risk factors may mediate mental health outcome.

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1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS), is a multiple anomaly syndrome with an estimated prevalence of 1:4000 (Gothelf & Lombroso, 2001; Shprintzen, 2005, 2008), resulting from an autosomal dominant microdeletion on the long (q) arm of chromosome 22 (Prescott & Scambler, 2005). Its phenotypic presentation is extensive and variable (Ryan et al., 1997); the behavioural phenotype involves high rates of behavioural, cognitive, communication and psychiatric disorders commonly including intellectual disability (ID) (De Smedt et al., 2007; Jones, Morley-Canellas, Owen & Murphy, 2001; Murphy, Jones, Griffiths, Thompson & Owen, 1998; Stevens & Murphy, 2005). Approximately 25% of people with 22q11DS develop schizophrenia (Vorstman et al., 2015), and the majority of adults with 22q11DS experience difficulties in adaptive functioning, with I.Q. a significant (but not sole) predictor of adult functioning (Butcher et al., 2012).

Cognitive decline is an important feature of the symptomatology of schizophrenia in the general population, and 22q11DS, having a known genetic aetiology, well-defined cognitive phenotype, and high associated risk of schizophrenia, is widely regarded as a valuable model for understanding the developmental processes leading to schizophrenia in the general population (Vorstman et al., 2015). The syndrome, however, may also provide a model for understanding the elevated (relative to the general population) rate of psychiatric disorder, and particularly psychosis, in the total population of adults with intellectual disabilities (Cooper, Smiley, Morrison, Williamson, & Allan, 2007).

The purpose of this review is to examine the evidence on the relationship between the cognitive and psychiatric phenotypes in 22q11DS, including both research on the empirical relationship between the phenotypes and on possible mechanisms underlying any such relationship. Our aim is to examine the evidence for two possible pathways to psychosis in 22q11DS, which are outlined in simplified form in Fig. 1. If there is a systematic relationship in 22q11DS between aspects of the cognitive phenotype and risk of psychiatric disorder, the relationship may result from the cognitive phenotype and psychiatric risk having shared causes in the neuroanatomical or neurochemical consequences of the deletion. There may, however, be an alternative or complementary pathway in which the cognitive deficits experienced by people with 22q11.2DS, in interaction with factors in their social environment, mediate their increased risk for psychiatric disorder. To the extent that the first pathway is important, explanation of variability in mental health outcome for people with the deletion must be sought primarily in epistatic interactions between genes within the deleted region and elsewhere. If the second pathway also has a role, however, such variability in outcome may be explained by social factors in interaction with cognitive deficits. Evaluating the evidence for each pathway may therefore have some heuristic value for future research in 22q11DS, and additionally suggest the extent to which 22q11DS may offer a model not only for understanding schizophrenia, but also for understanding risk for psychosis in people with other conditions associated with intellectual disability.

We firstly briefly outline the key features of the cognitive phenotype, which has been more extensively reviewed elsewhere (Furniss, Biswas, Gumber & Singh, 2011), and review recent research on cognitive development in childhood. We then review research on psychiatric disorder in 22q11DS, looking both at disorders in childhood and at major psychiatric illness and especially psychosis in adulthood. Thirdly, we briefly examine research which has compared the phenomenology of various psychiatric disorders in 22q11DS and in the general population, a topic relevant to consideration of whether the syndrome offers a potential comprehensive model for those disorders or only a model of certain elements in their symptomatology. We next review research which has examined associations between aspects of the cognitive phenotype of 22q11DS and risk for psychiatric disorder, again with an emphasis on factors associated with psychosis risk. Fifthly, we consider evidence for three potential mechanisms underlying these associations; shared neuroanatomical causes of cognitive deficits and psychiatric disorder, shared causation by disturbance of neurotransmitter function, and a direct influence of the cognitive deficits on risk for psychiatric disorder. Finally, we consider some implications of our review for further research and clinical practice.

2. Cognitive phenotype and cognitive development in 22q11DS

Approximately 75% of young people with 22q11DS have higher Verbal I.Q. (VIQ) than Performance I.Q. (PIQ) (De Smedt et al., 2007), and the cognitive phenotype also comprises better verbal than visuospatial memory, and better performance in reading than mathematics (Furniss et al., 2011; Wong, Riggins, Harvey, Cabaral & Simon, 2014). Mathematical difficulties involve counting, comparison of numbers of objects outside of subitizing ranges, and comparisons of object and numeral

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