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Social cognitive impairment in 22q11 deletion syndrome: A review

Emily M. Norkett[a], Sarah Hope Lincoln[a,b,*], Joseph Gonzalez-Heydrich[a,b], Eugene J. D'Angelo[a,b]

[a] Department of Psychiatry, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, United States
[b] Department of Psychiatry, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, United States

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ABSTRACT

Individuals with 22q11.2 deletion syndrome (22q11DS) exhibit a broad array of physical and psychiatric features, of which impaired social cognition and poor social functioning are common. This review seeks to (1) characterize the current understanding of impairment across social cognitive domains in the context of 22q11DS, and (2) synthesize the relevant literature on social cognition and psychosis, given that the prevalence of psychosis in 22q11DS is especially high compared to the general population. A total of 16 papers examining social cognition in 22q11DS were identified through a comprehensive literature search conducted using electronic databases such as PubMed and PSYCInfo. Results suggest that individuals with 22q11DS exhibit impaired emotion processing and complex theory of mind relative to their typically developing peers, though some findings were accounted for by neurocognitive and intellectual abilities. Further, no studies have examined the domains of attribution bias or social perception in 22q11DS, highlighting a critical gap in the extant literature. More research is needed to better elucidate the trajectory of how and why social cognitive impairment develops in 22q11DS, and to explore possible relationships to psychiatric comorbidities like psychosis. Treatment implications and future steps are considered.

1. Introduction

The 22q11.2 deletion syndrome (22q11DS) is a neurogenetic condition caused by an autosomal dominant microdeletion of about 50 genes on chromosome 22. Autosomal dominance is a pattern of inheritance where a trait or disorder—the 22q deletion, in this case—is located on a non-sex chromosome, and a single occurrence of the mutation (deletion) is sufficient to cause disease. The 22q11DS is one of the most frequently known microdeletion syndromes, equally affecting males and females, with a prevalence of around 1 in every 4000 births (Oskarsdottir et al., 2004), although other published estimates vary from 1 in 2000 to 1 in 6000 (Botto et al., 2003; Robin and Shprintzen, 2005). The phenotype associated with 22q11DS is highly variable, even within families, involves multiple organ systems, and ranges from life-threatening conditions to only a few characteristics of the syndrome. In addition to physical, metabolic, and endocrine features, individuals with 22q11DS are at increased risk for psychiatric disorders throughout development, especially autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), anxiety and affective disorders, and schizophrenia spectrum disorders and psychosis (Tang et al., 2015). This review focuses on the psychiatric phenotypes of 22q11DS, with specific attention given to the social cognitive domain and its relevance to both 22q11DS and psychosis.

1.1. 22q11DS: Genetics, identification, and phenotypes across development

In the early 1990's, fluorescent in situ hybridization (FISH) studies—in which the technique uses fluorescent probes that bind to specific, complementary parts of chromosomes, thereby "labeling" or detecting those parts—enabled the specific identification of 22q11.2 microdeletions that were found to underlie a heterogeneous group of patients previously diagnosed with what was called DiGeorge or velocardiofacial syndrome. Current detection methods include FISH as well as Multiplex Ligation-dependent Probe Amplification and single nucleotide polymorphism arrays, all of which detect the deletion at a chromosomal level. Most deletions (~90%) are *de novo* (Scambler, 2000), or not inherited from either parent, as a result of non-homologous recombination of chromosomes due to low copy repeats (LCR), or duplicated segments that bracket either ends of the region susceptible to recombination. Four distinct blocks, each comprised of repeats, are located within that region and named LCRs A through D. These blocks define the breakpoints and size of the resultant chromosomal deletion or duplication; the most common deletion of about 50 genes (or 3 million basepairs) extends from LCR A-D and is seen in 70–80% of patients, but smaller, nested deletions can occur between any

* Corresponding author at: Department of Psychiatry, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, United States.

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breakpoints from LCR A to D (McDonald-McGinn and Sullivan, 2011; for graphical representation, see Jonas et al., 2014). This heterogeneity in breakpoint combinations serves as a partial explanation for the extensive phenotypic variation seen in 22q11DS. Even among common deletions, phenotypic variation still occurs, and thus it is thought that environmental exposures and genetic modifiers may also play a key role in expressivity (Guo et al., 2011).

The presence and severity of phenotypic expressions vary across development. As early as the prenatal period, diagnostic clues can be identified via fetal ultrasound or echocardiography and include: congenital heart disease, polyhydramnios (excess amniotic fluid in the amniotic sac), cleft palate, clubfoot, spina bifida, polydactyly, and others (McDonald-McGinn and Sullivan, 2011). Some of the most common indications of 22q11DS in childhood are: conotruncal cardiac anomalies (cardiac outflow tract defects), palatal defects (e.g., cleft palate or cleft lip, Pierre Robin syndrome) and/or delayed speech, immunodeficiency and/or chronic infection, hypocalcaemia, severe feeding difficulties, developmental delays (McDonald-McGinn and Sullivan, 2011), and behavioral differences including overactivity, impulsivity, emotional lability, shyness, and disinhibition (Gerdes et al., 1999). While some studies have reported divergent cognitive trajectories across age (e.g., stable versus deteriorating IQ trajectory; Duijff et al., 2013), other research suggests some cognitive decline for most 22q11DS individuals as they grow into adulthood, a decline that is notably steeper for those who go on to develop psychotic symptoms (Vorstman et al., 2015). In the context of behavioral indicators, a developmental progression has been documented such that those with 22q11DS transition from displaying more externalizing behaviors (e.g., impulsivity, oppositionality) in early childhood to more internalizing behaviors (e.g., withdrawal, anxiety, depression) into adolescence (Swillen et al., 1999). More general social impairment (i.e., difficulty initiating and maintaining social relationships) has been well documented as characteristic of 22q11DS across all ages, for those with and without psychiatric diagnoses.

1.2. 22q11DS: Psychiatric presentation

Psychiatric disorders are among the most common manifestations of 22q11DS (Antshel et al., 2010), but like other components of the syndrome, the cognitive and behavioral phenotypes are widely variable. Diagnoses characteristically prevalent in childhood include ADHD (30–40%), primarily among 6–12 year olds (Schneider et al., 2014), and ASD (10–30%; Antshel et al., 2007; Vorstman et al., 2006), mostly among 13–17 year olds (Schneider et al., 2014). Other common diagnoses include anxiety (30–40%) and mood (20–30%) disorders, which increase in prevalence during adolescence (Jolin et al., 2012). A recent review by Tang and colleagues (2015) offers further insight into the presentation, identification, and management of these comorbidities. As they observed, by adulthood, 20–30% (and some reports of as high as 40%, e.g., Schneider et al., 2014) of adults with 22q11DS are diagnosed with schizophrenia and other psychotic disorders, such that the odds for psychosis in 22q11DS are 20 to 1 relative to the 1% lifetime risk in the general population (Bassett et al., 2000). Thus, the 22q11.2 microdeletion is one of the highest known risk factors for schizophrenia, other than having a first-degree relative with schizophrenia. Given such concerning elevated risk, it is clear why the literature has increasingly focused on understanding the high prevalence of psychosis in 22q11DS populations. Research that identifies what features are shared between the diagnoses and what features are unique to either is critical for elucidating the genetic and neurobiological mechanisms underlying both.

Studies indicate that the schizophrenia phenotype of 22q11DS is essentially indistinguishable from idiopathic schizophrenia on several variables, including age of onset, core positive and negative symptoms, global functioning, and cognitive deficits (Bassett et al., 2003). Moreover, sub-threshold symptoms characteristic of the prodromal period of psychosis also seem to be common in 22q11DS (Tang et al., 2014). As mentioned above, steeper early cognitive decline in 22q11DS is a risk factor for the development of psychosis, in addition to other reported predictors such as executive function, anxiety disorders, and social dysfunction (Antshel et al., 2010; Gothelf et al., 2013; Hooper et al., 2013). While difficulties in social functioning may be caused by psychosocial factors (e.g., anxiety, bullying), they can also be related to deficits in social cognition, or the processes by which individuals perceive, interpret, and engage in social behavior. A breadth of studies has examined social cognition in schizophrenia (Green et al., 2015; Savla et al., 2012) and its at-risk populations (Lee et al., 2015; Thompson et al., 2011); social cognition is strongly linked to functional outcome and, given the accumulating evidence of social cognitive deficits in periods preceding the onset of psychosis, increasingly seen as a viable predictive factor and treatment target.

1.3. Social cognition

Social cognition, the set of mental operations that underlie social interaction (Penn et al., 2008), enables individuals to understand and engage successfully with the social world. The Social Cognition Psychometric Evaluation (SCOPE) project identified four major domains of social cognition: emotion processing, theory of mind, social perception, and attribution bias (Pinkham et al., 2014). Emotion processing involves perceiving and using emotions, primarily through emotion recognition, emotion understanding, and emotion management. Theory of mind (ToM) refers to the process of thinking about the mental states, including goals, thoughts, beliefs, and intentions, of others. Social perception is the ability to decode and interpret social cues from others and social contexts. Attribution bias describes how individuals tend to explain the causes of social interactions and events.

It has been well documented that individuals with 22q11DS have poorer social skills (Kiley-Brabeck and Sobin, 2006) and functioning compared to their typically developing peers (Swillen et al., 1999, 2001; Woodin et al., 2001). Those with 22q11DS also have poorer social and emotional functioning compared to children with other chronic medical conditions, despite having similarly rated levels of physical health (Looman et al., 2010). Examining social cognition in 22q11DS may not only shed light on one possible mechanism underlying the commonly observed social dysfunction, but may also further elucidate the overlap and comorbidity between 22q11DS and psychosis. Because 22q11DS is detectable very early in life, there is significant potential for studies examining typical and atypical social development in children with 22q11DS to compare and differentiate such impairment from other disorders (e.g., Moss et al., 2013). In turn, such comparisons may provide links between social cognition and impairment and specific, underlying genetic perturbations. Moreover, a better understanding of social cognitive deficits and how they develop can serve to inform treatment options, and as a result, improve quality of life and perhaps decrease the observed high rate of conversion to psychosis. The current paper reviews the extant literature on social cognition and 22q11DS.

2. Methods

Electronic databases, including PsycInfo, PubMed, and Medline, as well as bibliographies from relevant publications, were searched and papers eligible for inclusion were identified (Fig. 1). Based on previously identified definitions and domains of social cognition (Pinkham et al., 2014), search terms included: “social cognition,”

E-mail address: slincoln@fas.harvard.edu (S.H. Lincoln).