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Imaging genetics in autism spectrum disorders: Linking genetics and brain imaging in the pursuit of the underlying neurobiological mechanisms

Marc Fakhoury *

Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montreal, Quebec H3C 3J7, Canada

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ABSTRACT

Autism spectrum disorders (ASD) include a wide range of heterogeneous neurodevelopmental conditions that affect an individual in several aspects of social communication and behavior. Recent advances in molecular genetic technologies have dramatically increased our understanding of ASD etiology through the identification of several autism risk genes, most of which serve important functions in synaptic plasticity and protein synthesis. However, despite significant progress in this field of research, the characterization of the neurobiological mechanisms by which common genetic risk variants might operate to give rise to ASD symptomatology has proven to be far more difficult than expected. The imaging genetics approach holds great promise for advancing our understanding of ASD etiology by bridging the gap between genetic variations and their resultant biological effects on the brain. This paper provides a conceptual overview of the contribution of genetics in ASD and discusses key findings from the emerging field of imaging genetics.

Contents

1. Introduction

Autism spectrum disorder (ASD) is a set of heterogeneous neurodevelopmental conditions characterized by early-onset deficits

* Corresponding author.
E-mail address: marc.fakhoury@umontreal.ca.

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in social communication, and the appearance of unusual restricted and repetitive patterns of behavior (American Psychiatric Association, 2013). ASD affects more males than females (Halladay et al., 2015), and is often accompanied by other medical conditions such as epilepsy, gastrointestinal complications, and comorbid psychiatric disorders including episodic mood disorders, bipolar disorder, and anxiety-related disorders (Doshi-Velez et al., 2014). Although the exact cause of ASD is yet to be determined, there is converging lines of evidence from family and twin studies supporting the contribution of genetics in ASD (Ozonoff et al., 2011; Rosenberg et al., 2009). Such evidence also derives from the development of molecular genetic tools including chromosomal microarray analysis (CMA) and whole-exome sequencing (WES), which have led to the identification of a number of different genetic risk variants involved in ASD etiology (Reddy, 2005; Yu et al., 2013; Yuen et al., 2015).

One of the most prevailing observations in the ASD literature is the presence of altered structural and functional connectivity of specific brain circuits in affected individuals. Structural connectivity forms the basis of functional connectivity, yet the latter may still exist between areas without direct structural linkage (Honey et al., 2009). Neuroimaging tools have extensively been used to study the brain structural connectivity, and have allowed for a more accurate assessment of ASD neuroanatomical underpinnings. Studies using these tools have demonstrated the existence of atypical white matter (WM) (Billeci et al., 2012; Schumann et al., 2010; Wolff et al., 2012) and gray matter (GM) volume (Courchesne et al., 2001; Greimel et al., 2013; Palmen et al., 2005) in children with ASD. Unusual brain growth pattern is also observed in children with ASD (Courchesne et al., 2001; Hazlett et al., 2005, 2011), but appears to normalize during late adolescence and adulthood (Aylward et al., 2002; Riedel et al., 2014). In addition to reports indicating the existence of abnormal structural connectivity in ASD, a wide array of neuroimaging studies has observed the presence of disrupted WM integrity and altered functional brain connectivity in prefrontal and parietal regions of individuals with ASD (Koshino et al., 2005; Rausch et al., 2016; Rudie et al., 2013). Together with the significant progress in genetics, these studies point to an involvement of altered neuronal circuits that may contribute to ASD pathogenesis at the genetic level. However, how genetic variations translate into structural and functional alterations within specific brain circuits has remained elusive, until recently.

The imaging genetics approach, which links genetic variations to structural and functional changes in the brain, has recently spurred increased interest in the field of ASD research and has helped decipher the neurobiological basis of several neuropsychiatric disorders. This review highlights findings from genetic studies, and summarizes the progress achieved to date in the developing field of imaging genetics applied to ASD. A better understanding of how genetic variations of specific risk genes lead to alterations in brain function and structure could offer a tremendous potential for improved therapeutic strategies.

2. Genetic underpinnings of ASD

2.1. Heritability and genetic heterogeneity

ASD can be thought as a collection of rare neurodevelopmental disorders with a strong, yet complex genetic component. Early evidence supporting the contribution of genetics in ASD etiology comes from twin studies showing a high concordance rate (>90%) in affected pairs of monozygotic twins (Bailey et al., 1995; Ritvo et al., 1985; Steffenburg et al., 1989). More recent investigations have also demonstrated a high recurrence rate in ASD, with concordance rates of 88% in monozygotic twins, 31% in dizygotic twins, and 18.7% in siblings (Ozonoff et al., 2011; Rosenberg et al., 2009). Of important note is the fact that no twin studies have ever reported a monozygotic concordance rate of 100%, which highly suggests that the heritability of ASD may be contingent on factors other than genetic variations such as environmental risks and gene-environment interplay (Chaste and Leboyer, 2012; Lai et al., 2014).

Notwithstanding the high degree of heritability in monozygotic twins, the genetic etiology of ASD is heterogeneous inasmuch as numerous genes and chromosomal regions have been implicated in this condition. A wide array of molecular genetic studies, including linkage studies, CMA, WES, and genome-wide association studies (GWAS), have been applied to ASD to better understand its genetic basis. Although findings from linkage studies in subsets of families with affected siblings have led to the identification of possible susceptibility loci on multiple chromosomes (Badner and Gershon, 2002; Cantor et al., 2005; Holt et al., 2010), most of the identified regions have failed to reach suggestive linkage in larger sets of families, thus pointing to heterogeneity in ASD (for review, see Freitag, 2007). On the other hand, findings from CMA and other molecular tests have enabled the identification of several cytogenetically visible chromosomal abnormalities and de novo copy number variations (CNVs) in ASD, with an estimated rate of 3–6% (Konstantareas and Homatidis, 1999; Reddy, 2005) and 5–10% (Marshall et al., 2008; Pinto et al., 2010; Sebat et al., 2007) respectively. GWAS and WES have also been used to detect CNVs (Poultney et al., 2013; Yin et al., 2016), and have been extensively employed for pinpointing other genetic variations in ASD such as single nucleotide polymorphisms (SNPs) (Anney et al., 2010; Vreeburg et al., 2009; Weiss et al., 2009; Yu et al., 2013; Yuen et al., 2015). However, despite significant progress in the identification of autism susceptibility loci, to date, no single risk locus has been found to account for >1% of individuals with ASD, thus urging the need for more research.

2.2. Single gene disorders associated with ASD

In contrast to idiopathic autism which has no known genetic cause, syndromic autism is used to describe autistic individuals with an identifiable Mendelian condition or genetic syndrome, and is estimated to account for 10% of ASD cases (Schaaf and Zoghbi, 2011; Yoo, 2015). Metabolic disorders including mitochondrial disorders, phenylketonuria, adenylosuccinate lyase deficiency, and creatine deficiency have all been observed in individuals with ASD and have been estimated to account for 5% of the cases (Schaaf and Zoghbi, 2011). Although these disorders harbor distinct phenotypic features compared to ASD, they have been extensively studied to better understand the molecular and genetic underpinnings of this condition.

Fragile X syndrome (FXS) is one of the earliest single gene syndromes found to be associated with an increased susceptibility to ASD (Willsey and State, 2015). The prevalence of ASD in FXS is estimated to be between 33 and 67%, with males being more affected than females (Clifford et al., 2007; Demark et al., 2003; Harris et al., 2008; Rogers et al., 2001). FXS is caused by the expansion of a trinucleotide repeat sequence in the fragile X mental retardation 1 (FMR1) gene, resulting in a subsequent decrease in the production of the Fragile X Mental Retardation Protein (FMRP) (Wheeler et al., 2014). Downregulation of FMRP significantly affects the modulation of processes inherent for the proper development of the brain, including protein translation, synaptic transmission, and neuronal excitability (Bhakar et al., 2012; Niere et al., 2012), thereby conferring a higher risk of developing ASD. PTEN macrocephaly syndrome is another single-gene disorder associated with increased susceptibility to ASD, and is found in approximately 5–8% of individuals with this condition (McBride et al., 2010; Varga et al., 2009). Compared to individuals with idiopathic ASD, individuals diagnosed with PTEN-ASD display significantly more impairment in WM integrity and severe reductions in processing speed and working memory (Frazier et al., 2015). Studies of PTEN conditional knockout have also shown that deletion of this gene produces autistic-like features including alterations in social behavior and synaptic connectivity (Kwon et al., 2006; Lugo et al., 2014).

Recent data also provided convincing evidence for an increased rate of ASD in individuals diagnosed with Tuberous sclerosis complex (TSC)