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Review

Autism genetics

Antonio M. Persico[a,b,c,*], Valerio Napolioni[a,b]

[a] Child and Adolescent Neuropsychiatry Unit, University "Campus Bio-Medico", Rome, Italy
[b] Department of Experimental Neurosciences, IRCCS "Fondazione Santa Lucia", Rome, Italy
[c] Mafalda Luce Center for Pervasive Developmental Disorders, Milan, Italy

HIGHLIGHTS

- Autism spectrum disorder has strong, complex and heterogeneous genetic underpinnings.
- The phenotypic expression of these genetic components is also highly variable.
- All autism genes are also involved in intellectual disability, and several in other disorders like schizophrenia.
- Autism genetics includes syndromic forms, CNVs or point mutations, mitochondrial forms and polygenic autisms.
- Genome-wide association studies and whole-exome sequencing have recently provided valuable contributions to the field.

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ABSTRACT

Autism spectrum disorder (ASD) is a severe neuropsychiatric disease with strong genetic underpinnings. However, genetic contributions to autism are extremely heterogeneous, with many different loci underlying the disease to a different extent in different individuals. Moreover, the phenotypic expression (*i.e.*, "penetrance") of these genetic components is also highly variable, ranging from fully penetrant point mutations to polygenic forms with multiple gene–gene and gene–environment interactions. Furthermore, many genes involved in ASD are also involved in intellectual disability, further underscoring their lack of specificity in phenotypic expression. We shall hereby review current knowledge on the genetic basis of ASD, spanning genetic/genomic syndromes associated with autism, monogenic forms due to copy number variants (CNVs) or rare point mutations, mitochondrial forms, and polygenic autisms. Finally, the recent contributions of genome-wide association and whole exome sequencing studies will be highlighted.

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* Corresponding author at: Child and Adolescent Neuropsychiatry Unit, Lab. of Molecular Psychiatry & Neurogenetics, University "Campus Bio-Medico", Via Alvaro del Portillo 21, I-00128 Rome, Italy. Tel.: +39 06 225419155; fax: +39 06 501703333.
E-mail address: a.persico@unicampus.it (A.M. Persico).

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1. Introduction

Since the first description of autism in 1943 by Leo Kanner, who defined "enclosure in one's self" as the distinctive trait shared by a cohort of eleven children [1], extraordinary advances have been achieved in understanding the physiopathology underlying this complex disorder. Autism, the prototypic pervasive developmental disorder (PDD), is characterized by onset prior to 3 years of age and by a triad of behavioral signs and symptoms, including (a) hampered verbal and non-verbal communication, (b) lack of reciprocal social interaction and responsiveness, and (c) restricted, stereotypical, and ritualized patterns of interests and behavior [2,3]. Autism spectrum disorder (ASD) is a broader diagnostic category, encompassing autistic disorder as well as the less severe Asperger Disorder (AD) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). ASD will be the single diagnostic category adopted by DSM-V, although DSM-V criteria may not consistently detect AD and PDD-NOS as part of ASD [4]. Finally, the "broad autism phenotype" includes individuals with some signs and symptoms of autism, not meeting full criteria for ASD [5]. Collectively, these diagnostic categories and their change over time clearly speak to the difficulty in categorizing deficits in social cognition which are dimensional and quantitative in real life, rather than categorical [6].

ASD is characterized by striking clinical heterogeneity, seemingly underlied by an equally impressive degree of etiological heterogeneity. Researchers have so far aimed to address this great heterogeneity following two complementary strategies, the analysis of endophenotypes and genetic studies. Endophenotypes are familial and heritable quantitative traits associated with a complex disease and able to identify subgroups of patients possibly sharing homogeneous pathophysiological underpinnings [7]. The best established endophenotypes in autism research have been reviewed elsewhere [8]. On the other hand, autism has conclusively been recognized as the neuropsychiatric disorder with the greatest genetic component, due to monozygotic twin concordance rate as high as 73–95%, extraordinary heritability (>90%, as estimated by twin studies), and a noticeable sibling recurrence risk (5–6% for full-blown autistic disorder, approximately 15–25% for broad ASD) [9]. These heritability estimates, obtained mainly in the UK and in Northern Europe in the early 1990s, were recently confuted by a twin study undertaken on a California twin sample, compatible with a larger proportion of variance explained by shared environmental factors as opposed to genetic heritability (55% *vs.* 37% for strict autism, respectively) [10]. Conceivably, the relative weight of genetic and environmental factors may be region-specific and could be changing over time, as less severe forms of the disease are increasingly diagnosed within the spectrum. However, the related increase in sibling recurrence risk, estimated by recent baby sibling studies at 18.7% (26.2% for males and 9.1% for females) [11], and the presence of mild autistic traits in many first-degree relatives of patients with autism [5] still indicate a strong genetic component in ASD. Linkage and association studies have identified numerous susceptibility genes, located on various chromosomes, especially 2q, 7q, 15q and on the X chromosome. The clinical heterogeneity of ASD is thus believed to at least partly reflect the complexity of its genetic underpinnings, whose general underlying mechanisms include different modes of inheritance and gene–environment interactions. Here we will review the genetics of ASD moving from monogenic forms to the most recent contributions provided by genome-wide association and whole-exome sequencing studies.

2. Monogenic autisms

Autism can be part of a known genetic syndrome. This instance occurs in approximately 10% of all ASD cases, it is typically associated with malformations and/or dysmorphic features ("syndromic" autism) and, unlike "idiopathic" or "primary" ASD, it shows an equal male:female sex ratio [12–14].

Well-known genetic or genomic disorders can encompass autistic features in their clinical presentation, such as fragile X syndrome, tuberous sclerosis, neurofibromatosis, untreated phenylketonuria, Angelman, Cornelia de Lange and Down syndrome. These disorders can stem from: (a) genomic DNA mutations, triplet repeat expansions, or rare chromosomal abnormalities visible by high-resolution karyotyping. (Table 1); (b) rare *de novo* and some inherited copy number variants (CNVs) identifiable with various genome analysis platforms, including array comparative genomic hybridization (aCGH), single nucleotide polymorphism (SNP) genotyping platforms, and next-generation sequencing (Table 2). Notably, the clinical manifestations of syndromic autism can be highly heterogeneous, even in the presence of the same well-characterized mutation or genomic rearrangement, likely due to differences in genetic background and epigenetic influences.

In addition to these forms, several new monogenic forms of autism have been recently discovered (see Sections 2.3–2.6 below). These rare conditions, each accounting for less than 1% of the general ASD population, stem from genetic/genomic anomalies not present in large pools of control chromosomes. These findings suggested that many autisms may represent a group of syndromes due to rare, if not even private mutations or CNVs [15]. However, causal mutations and chromosomal rearrangements should ideally appear *de novo*, but they are more often segregating in the family, which again underscores their variable degree of penetrance and the heterogeneous expression of the genotype into a behavioural phenotype.

2.1. Main genetic syndromes associated with autism: Fragile X syndrome (FXS) and tuberous sclerosis (TS)

Autism and intellectual disability are commonly found both in Fragile X syndrome and in tuberous sclerosis [16,17]. Both syndromes share, as their underlying pathophysiological mechanism, abnormal mRNA translation leading to increased protein synthesis, which has been linked to both intellectual disability and autism [17,18]. Indeed, mutations in genes encoding proteins involved in the molecular machinery regulating synaptic protein synthesis (*FMR1*, *TSC1/2*, *EIF4E* and *PTEN*) are strongly associated with autism [18,19]. Abnormally increased levels of plasticity-related proteins available to active synapses in neurons may affect synaptic connectivity, compromising network performance and producing cognitive impairment [19].

Fragile X syndrome is caused by the unstable expansion of a CGG repeat (>200 repeats) in the *FMR1* gene, located in Xq27.3, producing abnormal methylation, *FMR1* transcription silencing and decreased FMRP protein levels in the brain [20]. FXS accounts for about one-half of cases of X-linked mental retardation and it is the