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Review

Autism genetics

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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.

Contents

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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

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Table 1
Known genetic syndromes associated with autism [187,188].

	Gene/chr. region	Prevalence	Incidence of the syndrome in ASD	Incidence of ASD in the syndrome	Ref.
Fragile X syndrome	*FMR1*	1/3500–1/9000	2.10%	18–33%	[189–191]
Tuberous sclerosis	*TSC1, TSC2*	1–1.7/10,000	1–4% (8–14% if seizures present)	25–60%	[190,192–194]
Neurofibromatosis type 1	*NF1*	1/3000–1/4000	<1.4%	4%	[195]
Untreated phenylketonuria	*PAH*	1/10,000–1/15,000	–	5.70%	[196]
Adenylosuccinate lyase deficiency	*ADSL*	Not known	<1%	80–100%	[187,197]
Smith–Lemli–Opitz syndrome	*DHCR7*	1/10,000–1/60,000	<1%	46–52%	[198]
Cohen syndrome	*COH-1*, unknown	1/105,000	<1%	48%	[199]
Cornelia de Lange syndrome	*NIPBL* *SMC1A* *SMC3* Unknown	1/10,000	<1%	46–67%	[200]
Sotos syndrome	*NSD1*	1/10,000 – 1/50,000	<1%	Not known	[201]
Cole–Hughes macrocephaly	Not known	Not known	<1%	Not known	[202]
Lujan–Fryns syndrome	*UPF3B* *MED12*	Not known	<1%	62.50%	[203]
San Filippo syndromes					
A	*SGSH*				
B	*NAGLU*	0.3–1.6/100,000	<1%	Not known	[204]
C	*HGSNAT*				
D	*GNS*				
ARX syndrome	*ARX*	Not known	<1%	Not known	[205,206]
Ch 2q37 deletion syndrome	2q37.3	Not known	<1%	35%	[207]
Williams–Beuren syndrome	7q11.23 del	1/7500–1/25,000	<1%	7%	[208,209]
Williams–Beuren region duplication syndrome	7q11.23 dup	1/12,500–1/20,000	<1%	35.70%	[210]
15q chromosomal syndromes					
Angelman syndrome	Del/mut in maternal *UBE3A*	1/10,000–1/12,000	≤1%	50–81%	[211–213]
Prader–Willi Syndrome	Del paternal allele at 15q11–q13	1/10,000–1/15,000	Not known	19–36.5%	[214,215]
isodicentric 15q	Dup 15q11–q13, GABRB3	1/30,000	0.5–3%	68.9–81%	[215–217]
Hypomelanosis of Ito	Mosaic del 15q11–q13	1/10,000	<1%	10%	[218]
Smith–Magenis syndrome	17p11.2 del	1/15,000	<1%	93%	[219]
Potocki–Lupsky syndrome	17p11.2 dup	Not known	<1%	90%	[220]
Down syndrome	Trisomy of chr. 21	1/1000	1.7–3.7%	5.6–8%	[190,221,222]
Velocardiofacial/Di George syndrome	22q11.2 del	1/4000	<1%	20–31%	[223,224]
Ch 22q11 duplication syndrome	22q11.2 dup	Not known	<1%	Not known	[225]
Phelan–McDermid syndrome	22q13.3 del	Not known	<1%	50–70%	[75]

second most common cause of mental impairment after trisomy 21 [21]. Autism prevalence in FXS is approximately 30% and PDD-NOS occurs in an additional 30% of cases [22]. Premutation repeat expansions (55–200 CGG repeats) may also give rise to ASD, through a different molecular mechanism involving a direct toxic effect of the expanded CGG repeat *FMR1* mRNA [22]. In premutation carriers, RNA toxicity can also lead later in life to aging effects termed "Fragile X-associated tremor ataxia syndrome", including tremor, ataxia and cognitive decline [22]. ASD in FXS is mainly characterized by deficits in peer interactions and to a lesser extent by impairment in socio-emotional reciprocity, although deficits in theory-of-mind and pragmatic language clearly distinguish FXS with and without ASD [23–25].

Tuberous sclerosis (TS) is an autosomal dominant disease with high penetrance, characterized pathologically by the presence of hamartomas (tumor-like lesions) in multiple organs. Well-known clinical manifestations include epilepsy, learning difficulties, behavioral problems, and skin lesions [26]. TS is due to inactivating mutations in either of two genes, *TSC1* or *TSC2*, located in 9q34 and 16p13.3, respectively. These mutations comprise a variety of nonsense, missense, insertion and deletion mutations, involving nearly all exons of *TSC1* and *TSC2* [26]. Autism is significantly more

Table 2
Syndromic autisms due to recurrent CNVs.

Ch region	Del/Dup	Signs and symptoms
1q21	Del	Autism, attention deficit, hyperactivity, antisocial behaviour, anxiety, epilepsy, mental retardation, developmental delay, depression, hallucinations, schizophrenia; minor dysmorphisms, cardiac defects, cataracts, multiple congenital malformations
	Dup	Autism, attention deficit, hyperactivity, epilepsy, mental retardation, developmental delay, impaired language, learning disability; minor dysmorphisms, multiple congenital malformations
2p15-2p16.1	Del	Autism, developmental delay; microsomy, microcephaly, dysmorphic features
15q13	Del	Autism, attention deficit, hyperactivity, aggression, anxiety, epilepsy, mental retardation, developmental delay, impaired language, schizophrenia; minor dysmorphisms, cardiac defects
	Dup	Autism, anxiety, bipolar disorder, mental retardation, developmental delay, obsessive–compulsive disorder, language delay; minor dysmorphisms, hypotonia, obesity, recurrent ear infections
16p11.2	Del	Autism, Asperger syndrome, attention deficit, hyperactivity, dyslexia, bipolar disorder, anxiety, epilepsy, mental retardation, developmental delay, language impairment, schizophrenia; minor dysmorphisms, hypotonia, multiple congenital malformations
	Dup	Autism, attention deficit, hyperactivity, anxiety, epilepsy, mental retardation, developmental delay, obsessive–compulsive disorder

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frequent among TS patients than in the general population, as its incidence has been estimated at nearly 30% in TS [27]. Individuals with *TSC2* mutations are significantly more likely to display greater severity compared to those with *TSC1* mutations, often including a positive history of infantile spasms, lower intelligent quotient, and autistic disorder [27,28]. Different mutations in the *TSC2* gene have been described in association with severe clinical and epileptic phenotypes, including infantile spasms and Lennox–Gastaut syndrome, West syndrome and cardiac rhabdomyoma, autism, mood and anxiety disorders [27,28].

Given the high phenotypic variability in FXS and TS patients with autism, current research aims at better defining genotype–phenotype correlations, thus providing a solid framework for managing ASD in a clinical genetics setting. Recent studies demonstrated that individuals with ASD and FXS have on average lower IQ and greater deficits in receptive and expressive language compared to patients with FXS alone [24]. Deficits in social interaction and communication tend to persistent over time [29], and may be correlated with decreased cortico-cortical connectivity [30]. Interestingly, *FMR1* mutations may also contribute to the etiology of high-functioning, non-syndromic ASD, particularly in women [31]. In reference to TS, the severity of autistic features is inextricably linked to intelligence and epilepsy [32]. Lastly, a recent study did not report an enrichment of rare *TSC1* and *TSC2* functional variants in a sample of 300 ASD trios, thus excluding mutations in *TSC*1/2 genes as rare causes of non-syndromic autism [33].

Several phenotypes of validated FXS and TS mouse models have been shown to respond to pharmacological treatments affecting protein synthesis [34–38]. Notably, Auerbach et al. [39] showed that these mutations produce opposite effects on long-term depression (LTD) recorded in area CA1 of the hippocampus of *Tsc2*(+/−) and *Fmr1*(−/y) mice, which requires the immediate translation of mRNAs located in the dendrites of hippocampal pyramidal neurons. In particular, *Tsc2*(+/−) and *Fmr1*(−/y) mice display blunted and exaggerated LTD, respectively, which are surprisingly rescued to wild-type (WT) levels in double mutants, as occurs with the memory deficits recorded in both mutant mice using the context discrimination test [39]. Furthermore, LTD can be rescued in *Tsc2*(+/−) and *Fmr1*(−/y) mice by administering agonists and antagonists metabotropic glutamate receptor 5 (mGluR5), respectively. Hence, genetically heterogeneous forms of ASD, resulting in opposite neurophysiological abnormalities, can produce similar behavioral deficits amenable to amelioration by modulating in opposite directions mGluR5 receptors [39]. Converging evidence of a synaptic pathophysiology in autism and of the pivotal role played by group I mGluRs in social cognition is also provided by experiments demonstrating that mGluR5 is the downstream effector of MeCP2 in modulating synaptic scaling [40], and by Neuroligin-3 (*NLGN3*) knockout mice exhibiting disrupted heterosynaptic competition and elevated synaptic mGluR1α levels, both rescued by *NLGN3* expression even in young adults [41]. Collectively these results strongly support a shared synaptic pathophysiology for non-syndromic forms and the genetic syndromes most associated with autism (FXS and TS) [42].

2.2. Copy number variants (CNVs)

Copy number variants (CNVs) are DNA segments ranging in size from 50 base pairs to several megabases among individuals due to deletion, insertion, inversion, duplication or complex recombination [43]. Early studies [44–47] showed an increased frequency of CNVs in ASD population compared to controls (on average 6–10% *vs.* 1–3%, respectively). Notably, these studies found several *de novo* CNVs in autistic children (mainly from simplex families), a result suggesting the existence of genomic instability in a sizable subgroup of cases. However, latter studies failed to replicate the genome-wide differences initially found in CNV frequency between ASD patients and controls [48–50]. This evidence implies that excessive genomic instability does not represent a widespread hallmark of autism, but it may only characterize some ASD families. Recently, it has become evident that CNV location and its functional relevance may play a more important role instead of mean CNV number and size. Indeed, two large datasets have lately uncovered highly heterogeneous *de novo* copy-number variants collectively affecting several loci and presumably accounting for 5–8% of cases of simplex forms of ASD [51,52]. Network-based functional analysis of these rare CNVs confirms the involvement of these loci in synapse development, axon targeting, and neuron motility [53].

Although most of CNVs are private, recurrent microdeletion syndromes have also been identified (Table 2) [54–58]. Overall, CNVs are linked to a broad variety of clinical features, including major or minor malformations, facial dysmorphisms, severe neurological symptoms, full-blown autism, milder autism-spectrum traits, or even behavioral disorders outside of the autism spectrum. Thus, the variable penetrance and great phenotypic heterogeneity characterizing CNV expressivity make it often difficult to determine whether in a given patient a CNV is the sole cause of autism, confers vulnerability to the disease, or represents a chance finding. Indeed, the majority of CNVs are inherited from either one of the parents, who may display some autistic traits, but clearly without satisfying criteria for autistic disorder. Notably, many CNVs found in ASD patients have been found also in patients with other psychopathologies, especially intellectual disability and schizophrenia.

2.3. "Synaptic" genes: neuroligins, SHANK and neurexins

Several neuroligins, SHANK and neurexin genes, encoding proteins crucial to synapse formation, maturation and stabilization, have been found to host mutations responsible for behavioural phenotypes, including autism [59–61]. At the extracellular level, postsynaptic neuroligins interact with presynaptic α- or β-neurexins stimulating the formation of the presynaptic bouton [62,63]; at the intracellular level, neuroligins associate with postsynaptic scaffolding proteins, such as SHANK3 [64].

Neuroligins are encoded by the *NLGN1*, *NLGN2*, *NLGN3*, *NLGN4X*, and *NLGN5* genes. Among them, only *NLGN3*, *NLGN4*, and *NLGN4Y* genes have been found to harbour mutations possibly causative of autism. However, the frequency of *NLGN* gene mutations among idiopathic ASD patients is low, as collectively confirmed by multiple studies (Table 3) [12]. Mouse mutants carrying the human *NLGN3* R451C mutation, initially reported by Jamain et al. [65], display a mild behavioral phenotype [66,67], characterized by reduced ultrasonic vocalizations in males and impaired social novelty preference. Surprisingly enhanced spatial learning abilities and increased inhibitory synaptic transmission were also reported [66]. In fact, at the neuronal level, the R451C mutation causes on one hand defective vesicle trafficking with partial retention of *NLGN3* in the endoplasmic reticulum, blunted *NLGN3* delivery to the cell membrane, and reduced synapse induction [68–70]; on the other hand, contrary to the neocortex, where glutamate-driven excitation is reduced, in the hippocampus AMPA-driven excitation, NR2B subunit delivery and long-term potentiation are all upregulated by approximately twofold [71]. A different *NLGN3* mutation, R704C, initially reported by Yan et al. [72], causes a major and selective decrease in AMPA receptor-mediated synaptic transmission, leaving the number of synapses unchanged [73]. Also for *NLGN* mutation carriers, the clinical phenotype is highly heterogeneous, ranging from severe autism to Tourette's Syndrome (Table 3).

The SHANK gene family consists of three members (*SHANK1*, *SHANK2*, and *SHANK3*), which encode scaffolding proteins required

Table 3
Mutations and cytogenetic abnormalities, either *de novo* or segregating, affecting "synaptic" genes (neuroligins, SHANK and neurexins).

Gene	Reference	Mutations/del	Incidence
NLGN3	[65]	R451C	1/158 (0.6%)
NLGN4	[65]	D396X	1/158 (0.6%)
	[226]	D429X	1 family with 13 affected males
	[72]	G99S	1/148 (0.7%)
		K378R	1/148 (0.7%)
		V403M	1/148 (0.7%)
		R704C	1/148 (0.7%)
	[227]	Exons 4, 5, 6 del	1 family with one affected male
	[228]	−355G>A	1/96 (1.0%)
	[229]	K378R	1/169 (0.6%)
	[230]	T787M	1/20 (5.0%)
	[231]	R87W	1 family with 2 affected males
	[232]	Exon 4 del	1/30 (3.3%)
NLGN4Y	[233]	I679V	1/290 (0.3%)
SHANK1	[84]	63.8 kb del	1 family with 3 affected males
		63.4 kb del	1 family with 1 affected male
SHANK2	[82]	69 kb del exon 6, 7	1/396 (0.2%)
		R26W	1/396 (0.2%)
		P208S	2/396 (0.5%)
		S231Y	1/396 (0.2%)
		R462X	1/396 (0.2%)
		L1008_P1009dup	1/396 (0.2%)
		T1127M	1/396 (0.2%)
		A1350T	2/396 (0.5%)
	[83]	421.2 kb del	1/260 (0.4%)
		R174C	2/455 (0.4%)
		R185Q	1/455 (0.2%)
		R443C	1/455 (0.2%)
		R598L	1/455 (0.2%)
		V717F	1/455 (0.2%)
		A729T	1/455 (0.2%)
		E1162K	1/455 (0.2%)
		G1170R	1/455 (0.2%)
		V1376I	1/455 (0.2%)
		D1535N	1/455 (0.2%)
		L1722P	1/455 (0.2%)
	[50]	66 kb del	1/996 (0.1%)
		68 kb del	1/996 (0.1%)
SHANK3	[79]	142 kb del	1/227 (0.4%)
		E409X	1/227 (0.4%)
		800 kb del	1/227 (0.4%)
		R12C	1/227 (0.4%)
		A198G	1/227 (0.4%)
		R300C	1/227 (0.4%)
		G1011V	2/227 (0.8%)
		R1066L	1/227 (0.4%)
		R1231H	1/227 (0.4%)
		S1566G	1/227 (0.4%)
	[80]	277 kb del	1/400 (0.25%)
		3.2 Mb del	1/400 (0.25%)
		4.36 Mb del	1/400 (0.25%)
		Q321R	1/400 (0.25%)
	[78]	L68P	1/427 (0.23%)
		c. 2265C + 1delG	1/427 (0.23%)
	[81]	106 kb del	1/221 (0.4%)
		c.1339_1340insG	1/221 (0.4%)
		c.3931delG	1/221 (0.4%)
		P141A	1/221 (0.4%)
		1820-4 G4A	1/221 (0.4%)
	[234]	D204E	1/290 (0.3%)
		H255Y	1/290 (0.3%)
		R300C	1/290 (0.3%)
		A307G	1/290 (0.3%)
		P439S	1/290 (0.3%)
		G446V	1/290 (0.3%)
		A1254V	1/290 (0.3%)
		P1255L	1/290 (0.3%)
		P1279L	1/290 (0.3%)
		P1342L	1/290 (0.3%)
		G1469R	1/290 (0.3%)
		G1469V	1/290 (0.3%)
		R1497Q	1/290 (0.3%)
		G1574R	1/290 (0.3%)

Table 3 (*Continued*)

Gene	Reference	Mutations/del	Incidence
	[235]	440–446 del. GPGPAP	1/128 (0.8%)
		R656H	1/123 (0.8%)
		c.1497 + 9 10bp/ins	3/128 (2.3%)
		c.1497 + 9 10bp/del	1/128 (0.8%)
	[236]	L68P	1/427 (0.2%)
		A224T	1/427 (0.2%)
		S755Sfs×1	1/427 (0.2%)
NRXN1	[237]	S14L	3/264 (1.1%)
		T40S	1/264 (0.4%)
	[50]	300 kb del at 2p16	2/196 (0.5%)
	[238]	ins(16;2)(q22.1;p16.1p16.3)	Case report
		t(1;2)(q31.3;p16.3)	Case report
		L18Q	1/57 + 0/53 (0.9%)
		L748I	1/57 + 2/53 (2.7%)
	[239]	R8P, L13F, c1024 + 1 G>A, T665I, E715K	1/116 (0.9%) each 5/116 (4.3%) total
	[240]	180 kb del + p.S979X	1/179 (0.6%)
	[241]	451 kb del	1 family with 1 affected male
	[242]	Y282H	1/313 (0.3%)
		L893V	1/313 (0.3%)
		I1135V	1/313 (0.3%)
	[243]	−3G>T	1/86 (1.1%)
		3G>T	1/86 (1.1%)
		R375Q	1/86 (1.1%)
		G378S	1/86 (1.1%)
	[244]	Exons 1–19 del (1.15 Mb) del	All case reports
		Exons 1–5 (0.61 Mb) del	
		Exons 1–4 (0.61 Mb) del	
		Exons 1–5 (0.40 Mb) del	
		Exons 2–9 (0.40 Mb) del	
		Exons 1–5 (0.33 Mb) del	
		Exons 1–5 (0.32 Mb) del	
		Exons 1–5 (0.27 Mb) del	
		Exons 1–3 (0.18 Mb) del	
		Exons 1–5 (0.18 Mb) del	
		Exons 4–5 (0.11 Mb) del	
		Exons 17–18 (0.093 Mb) del	
		Exons 1–5 (0.48 Mb) del	
	[245]	Exons 1–5 (0.69 Mb) del	All case reports
		Exons 3–5 (0.12 Mb) del	
		Exons 3–5 (0.09 Mb) del	
		Exons 6–17 (0.36 Mb) del	
		Exons 13–17 (0.12 Mb) del	
		Exons 19–20 (0.06 Mb) del	
	[246]	Exons 1–2 (0.32 Mb) del	All case reports
		Exons 1–3 (0.11 Mb) del	
		Exons 1–4 (0.09 Mb) del	
		Exons 1–5 (0.16 Mb) del	
		Exons 1–5 (0.23 Mb) del	
		Exons 1–5 (0.29 Mb) del	
		Exons 4–5 (0.13 Mb) del	
		Exons 6–18 (0.38 Mb) del	
		Exons 6–18 (0.38 Mb) del	
		Exons 19–20 (0.32 Mb) del	
		Exons 20–24 (0.27 Mb) del	
		Exons 23–24 (0.16 Mb) del	
		Exons 23–24 (0.16 Mb) del	
	[94]	S14L	Case report
		P911fs	Case report
NRXN2	[94]	c2733delT	Case report
NRXN3	[98]	63 kb del	1 family with 1 affected male
		292 kb del	1 family with 1 affected male and 1 affected female
			1 family with 1 affected male
		336 kb del	1 family with 1 affected male
		247 kb del	

for the proper formation and function of neuronal synapses. *SHANK3*, located on chromosome 22q13.3, is predominantly expressed in the cerebral cortex and cerebellum, and it is localized at excitatory synapses where it binds to neuroligins in post-synaptic boutons [74]. It contains multiple protein–protein interaction domains and functions as a master organizer of the postsynaptic density (PSD). As for neuroligins, several studies reported rare mutations or genomic deletion encompassing the *SHANK3* locus in as many as 0.85% all ASD individuals (Table 3). These ASD subjects are characterized by severe language impairment, often accompanied by ID and neurodevelopmental delay [12]. Notably, *SHANK3* is located in the minimal critical region of the 22q13 deletion syndrome, also known as Phelan–McDermid Syndrome, which is also characterized by severe ID, absence of

speech or a severely expressive speech delay, hypotonia, normal to accelerated growth, and mild dysmorphic features [75]. No evidence of association was found in large samples, demonstrating that the *SHANK3* gene hosts rare, but not common variants [76,77]. Beside the common feature of language impairment, *SHANK3* mutations/deletions display highly variable phenotypic expression. They are frequently inherited from an apparently healthy parent and can also be found in unaffected siblings of probands with autism. Two *de novo* mutations, R536W and R1117X, never reported in ASD patients, were detected in individuals with schizophrenia [78]. Notably, autistic carriers of inherited 22q13 deletions involving *SHANK3* due to a paternal balanced translocation, have siblings with partial 22q13 trisomy diagnosed with Asperger's syndrome, showing early language development and ADHD [79,80]. These results demonstrate a physiological window of expression, whereby both excessive or deficient expression lead to opposite linguistic phenotypes and different behavioural disorders. A recent report also showed a significant association of SNP rs76224556 with PDD-NOS, highlighting an interesting genotype/phenotype correlation within the autism spectrum [81]. Mutations of *SHANK2* have also recently been reported both in ASD and in ID (Table 3) [50,82]. Using a combination of genetic and functional approaches, Leblond et al. [83] identified a *de novo* loss of one *SHANK2* allele and several mutations observed in autistic patients, shown to reduce neuronal cell contacts *in vitro*. Interestingly, three patients with *de novo SHANK2* deletions also carried inherited 15q11–q13 CNVs previously associated with neuropsychiatric disorders. In two cases, the nicotinic receptor *CHRNA7* was duplicated and in one case the synaptic translation repressor *CYFIP1* was deleted [83]. These results strongly support an oligogenic, "multiple hit" model for the genetic underpinnings of most cases. A hemizygous *SHANK1* deletion was found to segregate with high-functioning ASD in male carriers belonging to a four-generation family [84]. A *de novo SHANK1* deletion was also detected in an unrelated male with "high-functioning" ASD, and no equivalent *SHANK1* mutations were found in over 15,000 controls [84].

The third crucial player in the autism-related synaptic network is represented by neurexins, encoded by the three highly conserved genes, *NRXN1*, *NRXN2* and *NRXN3*. Each gene has two independent promoters: α-neurexins are transcribed from a promoter upstream of exon 1, whereas β-neurexins are transcribed from a downstream, intragenic promoter, resulting in a shorter form of neurexins [85]. As described above, the interaction between neuroligins and neurexins triggers the formation of functional pre-synaptic boutons both in neuronal [59–61] and even in non-neuronal cells [62,63]. Moreover, neurexins are important mediators for neurotransmitter release by linking calcium (Ca^{2+}) channels to synaptic vesicle exocytosis [86,87]. Several studies have reported rare sequence variants or CNVs affecting the *NRXN1* locus, as summarized in Table 3. As for neuroligins, also *NRXN1* mutation/deletion carries display striking clinical heterogeneity. Indeed, disruptive *NRXN1* variants have been linked to ID [88,89] and schizophrenia [90–94], while a large retrospective study involving 3540 individuals, identified 12 carriers of exonic *NRXN1* microdeletions causing vastly different clinical phenotypes, ranging from ASD, to ID, specific language disorder, and muscle hypotonia [95]. Surprisingly, *Nrxn1α* deficiency is not always detrimental in rodents: mice with a homozygous (−/−) deletion of *Nrxn1α* spend more time grooming, but also show improved motor learning [96]. *Nrxn1α* heterozygous knock-out (+/−) mice display increased responsiveness to novelty and accelerated habituation to novel environments compared to wild type (+/+) litter-mates [97]. Moreover, this effect is mainly observed in male mice, strongly suggesting that gender-specific mechanisms play an important role in Nrxn1α-induced phenotypes [97]. Recently, rare deletions at *NRXN3* locus have been also found in four ASD patients; three of these deletions were inherited from either subclinical or apparently healthy parents, underscoring issues of penetrance and expressivity at this locus [98].

2.4. Chromatin architecture genes (*MECP2*)

DNA methylation is the major modification of eukaryotic genomes and plays an essential role in mammalian development. MeCP2, a member of the methyl-CpG-binding domain family of proteins, binds to methylated CpG dinucleotides, recruiting histone deacetylase 1 (HDAC1) and other proteins involved in chromatin repression at specific gene promoters. The *MECP2* gene is thus required for correct brain function and development: loss of MeCP2 has been shown to delay neuronal maturation and synaptogenesis, and *MECP2 de novo* loss-of-function mutations cause Rett syndrome in approximately 70% of affected females, while they are generally lethal in males [99,100]. However, *de novo MECP2* mutations can occasionally result in relatively asymptomatic phenotypes, mild mental retardation and verbal Rett variants, depending upon the specific mutation [101], the genetic background of the patient, and most importantly on X-inactivation pattern, which tends to be highly skewed in the presence of mutations affecting X-linked genes, such as *NLGN3* and *MECP2*, albeit not being skewed in ASD families altogether [102]. In addition, *MECP2* mutations have also been found in non-syndromic autistic girls (Table 4). Most variants are *de novo*, but some are inherited from mothers usually with borderline cognitive functioning (Table 4). Importantly, at the time of

Table 4
Mutations and cytogenetic abnormalities, either *de novo* or segregating, affecting the *MECP2* gene.

MECP2	[101]	IVS2 + 2delTAAG	1/21F (4.8%)
	[247]	–	0/59 (42M, 17F)
	[248]	–	0/202 (154M, 48F)
	[249]	1157del41, R294X	2/69F (2.9%)
	[250]	R133C, R453X	2/19F (4.7%)
	[251]	c.1638 G>C, c.6809 T>C, P376R	1/24 (4.1%) each 3/24 (12.5%) total
	[252]	–	0/99 (58M, 41F)
	[253]	–	0/65 (49M, 16F)
	[254]	c.1461 G>A	1/31M (3.2%)
	[255]	–	0/401 (266M, 135F)
	[256]	G206A	1/172 (0.6%) (141M, 31F)
		Twelve 3′UTR variants, c.27-55G>A, c.377 + 18C>G	1/172 (0.6%) each
	[257]	T240S	1/287 (0.3%)
	[258]	22 Mb dup	1 family with two affected males
	[259]	T160S	1/60 (1.7%)
	[260]	R309W	1/285 (0.4%)
	[261]	R106W	Case report

their first diagnosis young girls with autism carrying *MECP2* mutations typically display none of the clinical features characteristic of Rett syndrome (epilepsy, microcephaly, wringing hand stereotypies, and breathing problems). These signs and symptoms will develop when they grow older, usually at age 6–9 [103].

2.5. Morphogenetic and growth-regulating genes (HOXA1, PTEN, EIF4E)

Many syndromic patients display facial dysmorphisms, minor or major malformations, microcephaly or macrocephaly either isolated or as part of a broader microsomia or macrosomia, respectively. Also children with idiopathic autism often display minor facial dysmorphisms [104] and abnormal head/body growth rates [105,106]. Macrocephaly is recorded in approximately 20% of autistic children [105], with head overgrowth seemingly occurring during the first few years of life [107]. In the majority of the patients, macrocephaly is part of a broader macrosomia [105,106]. In contrast, a small subset of patients with idiopathic autism is instead microcephalic and usually also microsomic [105].

Hox genes play a crucial role during embryonic patterning and organogenesis. Of the 39 Hox genes, *HOXA1* (located on chromosome 7p15.3) is the first to be expressed during embryogenesis and it is necessary for the proper development of the brainstem, cerebellum, several cranial nerves, middle and internal ear, occipital and hyoid bones [108,109]. Ingram et al. [110] first identified a common *HOXA1* polymorphism, an A-to-G substitution at codon 218, changing the codon for one histidine in a series of histidine repeats to an arginine at position 73. This polymorphism exerts an equally sizable effect on head growth rates both in autistic and in typically developing children, with the G allele yielding faster head growth and smaller cerebellar volumes [111–115]. A recent meta-analysis shows a lack of association of the A218G polymorphism with autism risk [116], in line with this polymorphism exerting head growth-modulating effects in all children, regardless of autism. Instead, two rare pathogenic *HOXA1* gene variants have been found: a c.84 C>G mutation resulting in the introduction of a stop codon (Y28X) was detected in a Turkish patient with autism, while a 175-176insG causing a reading frame shift with premature protein truncation was found in nine Saudi Arabian patients belonging to five consaguineous families [117,118]. Although these patients display significant interindividual variability, they share some common phenotypic features, including horizontal gaze abnormalities, deafness, focal weakness, hypoventilation, vascular malformations of the internal carotid arteries and cardiac outflow tract, mental retardation and autism. This array of clinical traits defines the Bosley–Salih–Alorainy syndrome (BSAS) [118], and the partially overlapping the Athabascan brainstem dysgenesis syndrome [119].

The phosphatase and tensin homolog (*PTEN*) gene, located on chromosome 10q23, harbours mutations associated with a broad spectrum of disorders, including Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome, Proteus syndrome, and Lhermitte–Duclos disease [120]. *PTEN* is a tumor suppressor gene which favours cell-cycle arrest in G1 and apoptosis, while balancing the stimulation physiologically exerted on cell proliferation and body growth by nutrient availability, insulin release, and pro-inflammatory cytokines through the ERK/PI3K/mTOR pathway [121]. Genetic syndromes linked to *PTEN* germline haploinsufficiency are often associated with autism or mental retardation [122]. Indeed, several studies reported missense mutations affecting evolutionarily conserved aminoacid residues in macrocephalic individuals affected by idiopathic autism (Table 5). Interestingly, *PTEN* knockout mice display macrosomy, macrocephaly, CNS overgrowth with thickening of the neocortex and cytoarchitectonic abnormalities in the hippocampus, excessive dendritic and axonal growth, and increased numbers of synapses [123]. Subjects with autism carrying *PTEN* mutations are characterized by severe to extreme macrocephaly; in some cases the overgrowth starts prenatally, whereas for other *PTEN* mutation carriers macrocephaly occurs only postnatally, as generally reported for macrocephalic ASD children [107]. Behavioral traits in *PTEN* mutation carriers are heterogeneous and some mutations can be inherited from apparently healthy parents [124]. The incidence of *PTEN de novo* mutations in macrocephalic ASD patients has been estimated at 4.7% (6/126) [12]. Importantly, these patients are at increased risk of developing a variety of *PTEN*-related cancers during adulthood.

Table 5
Mutations and cytogenetic abnormalities, either *de novo* or segregating, affecting morphogenetic and growth-regulating genes (*HOXA1*, *PTEN*, *EIF4E*). For PTEN, percentages refer to the entire sample or to "macrocephalic cases" only.

HOXA1	[117]	c84 C>G (Y28X)	1 patient from a Turkish consanguineous family
	[118]	175–176insG	9 patients from 5 Saudi Arabian consanguineous family
PTEN	[122]	Y178X	Case report
	[262]	H93R, D252G, F241S	3/18 (16.6%) macrocephalic cases
	[263]	I135R	Case report
	[264]	D326N	1/88 (1.1%)
	[265]	Y176C, N276S	1/40 (2.5%) each
		H118P	1/40 (2.5%)
	[124,266]	520insT, R130X, E157G, L139X, IVS6-3C>G	Collectively 5/60 (8.3%) total, 5/27 (18.5%) among macrocephalic cases
	[267]	H141TFS*39	1/69 (1.4%)
		L70V	1/69 (1.4%)
		M1I	2/69 (2.9%)
		Splice-site mutation, intron 3	1/69 (1.4%)
	[268]	P38H	1/33 (3.0%)
		R130X	1/33 (3.0%)
		Y68N	1/33 (3.0%)
		R130L	1/33 (3.0%)
		V255A	1/33 (3.0%)
	[269]	Exon 2 del	Case report
	[270]	R355X	Case report
	[271]	R173H	1/39 (2.6%)
		H123Q	1/39 (2.6%)
EIF4E	[125]	46,XY,t(4,5)(q23;q31.3)	Case report
		C8-4EBE	2/120 (1.6%) multiplex families ($N = 4$ subjects)

Table 6
Mutations and cytogenetic abnormalities, either *de novo* or segregating, affecting calcium-related genes (*CACNA1C*, *CACNA1F*, *KCNMA1* and *SCN2A*).

CACNA1C	[128]	G406R	13 patients with Timothy syndrome
CACNA1F	[129,130]	I745T	1 pedigree with 3 ASD males out of 10 mutation carriers
CACNA1H	[272]	R212C, R902W, W962C	1/491 (0.2%) each, 3/491 (0.6%) total
		R1871Q + A1874V	3/491 (0.6%)
KCNMA1	[131]	46,XY, t(9,10)(q23,q22)	Case report
		A138V	1/116 (0.9%)
SCN2A	[132]	R1902C	1/229 (0.4%) families

Finally, the eukaryotic translation initiation factor 4E gene (*EIF4E*, located on chr. 4q21–q25) plays a pivotal role in protein translation downstream of mTOR. Recently, a balanced translocation disrupting the *EIF4E* locus was found in a boy with ASD displaying regression of language and social interactions at 2 years of age [125] (Table 5). In the same study, both affected children of 2/120 multiplex families were found to inherit from an apparently unaffected father a C insertion, extending to eight a stretch of seven cytosines located in the basal promoter element of the *EIF4E* gene (4-EBE), resulting in a twofold increase in gene expression [125]. Interestingly, eIF4E overexpressing mice display enhanced neuronal excitation/inhibition ratio, increased translation of neuroligins, and autistic-like behaviours, which normalize following pharmacological inhibition of eIF4E activity or down-regulation of neuroligin 1 [18,126].

2.6. Calcium-related genes (CACNA1C, CACNA1F, KCNMA1 and SCN2A)

A body of recent genetic evidence suggests that at least some ASD cases may result from abnormal Ca^{2+} homeostasis during neurodevelopment [127]. Moreover, several genetic studies have identified autism-related genes encoding proteins either directly or indirectly controlling intracellular Ca^{2+} levels or regulated by cytosolic Ca^{2+} transients (Table 6). These molecules include ion channels, receptors, and Ca^{2+}-regulated signaling proteins, often times crucial to CNS development. Gain-of-function mutations in the L-type voltage-gated Ca^{2+} channel Cav1.2 (*CACNA1C*) cause Timothy syndrome, a multisystem disorder including mental retardation and autism [128]. Similarly, mutations in the L-type voltage-gated Ca^{2+} channel Cav1.4 (*CACNA1F*) cause the incomplete form of X-linked congenital stationary night blindness (CSNB2): gain-of-function mutations cause CSNB2 frequently accompanied by cognitive impairment and either autism or epilepsy, whereas CSNB2 inactivation due to loss of-function mutations is not accompanied by neurological symptoms [129,130]. All of these gain-of-function mutations prevent voltage-dependent channel inactivation, leading to excessive Ca^{2+} influx. Also, mutations and chromosomal abnormalities indirectly yielding increased cytosolic Ca^{2+} levels or amplifying intracellular Ca^{2+} signaling by hampering Ca^{2+}-activated negative feedback mechanisms have been found associated with autism [131]. A balanced translocation disrupting one copy of the *KCNMA1* gene, resulting in a more depolarized resting membrane potential and in a relatively less efficient control of neuronal excitability has been found in a boy with autism [131]. The R1902C mutation in the *SCN2A* gene, found in one ASD patient, decreases its binding affinity for calmodulin, thus destabilizing the inactivation gate and promoting sustained channel activity during depolarization [132].

2.7. Mitochondrial forms

Biochemical parameters linked to mitochondrial function are frequently abnormal in autism [133,134]. However, mitochondrial dysfunction appears secondary to the pathophysiology underlying ASD in the vast majority of cases [135]. Only in rare instances do mutations in mitochondrial DNA (mtDNA) or in nuclear DNA (nDNA) heavily involved in mitochondrial function explain the disease. In fact, a recent comprehensive investigation including 1298 autistic patients failed to provide any evidence of common contributions by mtDNA variation or heteroplasmy to ASD [136]. Children with mitochondrial disease thus represent a small percentage (<1%) of all autistic patients. These children are characterized by several atypical clinical features, including oculomotor abnormalities, dysarthria, ptosis, hearing deficits, hypertonia and movement disorders [134,135]. A peculiar characteristic of this ASD subgroup is behavioral regression, especially in association with fever [137,138]. From a phenotypic point-of-view, microcephaly and microsomy, as well as neuroanatomical abnormalities, are relatively frequent [137–139]. Ragged Red Fibers, clumps of diseased mitochondria accumulating in the subsarcolemmal region of the muscle fiber, a typical feature of MERRF syndrome (OMIM*545000), are usually visible in muscle biopsies of adults, but in most affected children muscle tissue histology is negative.

Genetic and genomic defects affecting mtDNA or nuclear DNA (nDNA) are detected in approximately 20% of autistic children with biochemical and clinical signs of mitochondrial disease; each mtDNA mutation or chromosomal rearrangement is reported in $\leq$0.1% of all cases (Table 7). Chromosomal rearrangements in nDNA possibly affecting mitochondrial function, include deletions in 15q11–q13 (cytochrome *C* oxidase subunit 5A, *COX5A*), 13q13–q14.1 (mitochondrial ribosomal protein 31, *MRPS31*), 4q32–q34.68 (electron-transferring-flavoprotein dehydrogenase, *ETFDH*), 2q37.3 (NADH dehydrogenase ubiquinone 1 alpha subcomplex 10, *NDUFA10*) [140]. Except for cases of mitochondrial depletion, family history is positive for mitochondrial diseases along the maternal lineage. In summary, truly mitochondrial ASD forms are indeed rare, as mitochondrial dysfunction appears to be secondary in most patients, *i.e.*, downstream of other pathophysiological abnormalities such as excessive oxidative stress [135].

3. Non-syndromic autism: the role of common variants

In a complex disease like autism, it is conceivable that functional common polymorphisms can confer vulnerability or protection. Thus, according to Falconer's threshold model [141], a host of unfavourable common variants could even cause a disease phenotype, either directly, or by lowering the sensitivity threshold to the point of conferring pathogenicity to widespread environmental agents. This scenario is supported by several recent studies, demonstrating, for example, a moderate to high heritability for autistic traits in the general population, which does not differ between extreme scoring groups or between the extreme scoring groups and the general population [142]. Indeed, this evidence clearly supports the idea for conceptualizing ASD as the quantitative extreme of a neurodevelopmental continuum [142]. Analyzing common variation throughout the genome, Klei et al. [143] demonstrated that common genetic variants, acting additively, are a major source of risk for autism, estimating the fraction of total variation in liability conferred by common variants at 40% and 60% or above for ASD individuals from simplex and multiplex families, respectively.

Table 7
Mutations and rearrangements affecting mitochondrial DNA and related to autism.

Ref.	Mutation	mtDNA gene	N. of patients
[273]	8363G>A	*tRNA^{Lys}*	2 siblings
[274]	Large mtDNA deletions		5 ASD patients
[275]	3243A>G	*tRNA$^{Leu(UUR)}$*	2 ASD and their 2 mothers
	?	mtDNA? genomic DNA?	1 ASD with mitochondrial DNA depletion
[137]	3397A>G	*MT-ND1*	25 ASD patients with primary mit. disorder (3/25 mtDNA mutation carriers)
	4295A>G	*tRNA^{Ileu}*	
	11984T>C	*MT-ND4*	
[276]	8251G>A	*MT-CO2*	2/24 (8.3%)
	8269G>A	*MT-CO2*	1/24 (4.2%)
	8271A>G	*MT-NC7*	1/24 (4.2%)
	8472C>T	*MT-ATP8*	3/24 (12.5%)
	8684C>T	*MT-ATP6*	1/24 (4.2%)
	8697G>A	*MT-ATP6*	5/24 (20.8%)
	8701A>G	*MT-ATP6*	1/24 (4.2%)
	8836A>G	*MT-ATP6*	3/24 (12.5%)
	8865G>A	*MT-ATP6*	1/24 (4.2%)

Notably, data for simplex ASD families closely follow the expectation for additive models, while data from multiplex families display some deviation, possibly due to parental assortative mating [143]. Hence common variants collectively confer a sizable amount of vulnerability to autism [143], with each variant exerting a weak effect [144]. Although a detailed review of candidate gene studies in autism is beyond the scope of this article, a list of the most consistently replicated genes is reported in Table 8. Several common variants have been found associated with autism, as reviewed in detail elsewhere [145–147], but evidence from independent replications and from functional studies is not equally strong for all of them [147]. Importantly, within the framework of a polygenic disease, by definition no single gene variant should be expected to be associated with the disease in each and every sample, as the host of common variants conferring autism vulnerability is predicted to vary widely from patient to patient. However, gene variants providing the most consistent contributions should be expected to be replicated in over half of independent samples of sufficient size. The vast array of functional effects exerted by each single gene further highlights the complexity of the physiopathological underpinnings of ASD.

3.1. Genome-wide association studies in ASD

Genome-wide association studies (GWAS) have emerged as the method of choice for the unbiased search of common variants most consistently contributing to a complex disease, like autism, in genetically homogeneous populations [148]. While several studies have shown that rare structural variants (deletions/duplications or point mutations) can have substantial effects on disease risk [149,150], GWAS have generally not identified any common variant strongly and consistently associated with autism in multiple studies. Associations that reach (fully or nearly) stringent genome-wide significance levels in one study typically do not replicate in other GWAS, although patients are apparently recruited according to superimposable selection criteria.

The first GWAS carried out by Weiss and colleagues [151] reported no statistically significant SNP association in over 1000 families. However, when the top results ($P < 10^{-4}$) were followed-up in independent replication samples, one locus at 5p15 replicated, and the meta-data reached genome-wide significance for association. This association fell between genes encoding *SEMA5A*, a member of the semaphorin family of proteins involved in axon guidance, and *TAS2R1*, a bitter-taste receptor. Independent evidence was presented of reduced expression of *SEMA5A* in lymphoblastoid cell lines, whole-blood and brain samples of autistic individuals compared to controls [151].

Another GWAS by Wang et al. [152] utilized two populations, one largely overlapping with the sample used by Weiss et al. [151] and the other including over 1200 cases and nearly 6500 controls. Combining these samples, one region of genome-wide significance was identified at chr. 5p14. This locus was replicated

Table 8
The most consistently replicated genes hosting common variants associated with autism, listed in alphabetical order.

Gene	Chr. position	Protein	Cellular function
CNTNAP2	7q35	Contactin associated protein-like 2	A member of the neurexin family, functioning in the vertebrate nervous system as cell adhesion molecule and receptor
EN2	7q36	Engrailed homeobox 2	Homeodomain-containing protein implicated in pattern formation during development of the central nervous system
GABRB3	15q12	Gamma-aminobutyric acid (GABA) A receptor, beta 3	The encoded protein is one of at least 13 distinct subunits of a multisubunit ligand-gated chloride channel that serves as the receptor for gamma-aminobutyric acid, the major inhibitory transmitter present in the brain
ITGB3	17q21.32	Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	Integrin participates in cell adhesion- as well as cell surface-mediated signaling
MET	7q31	Met proto-oncogene (hepatocyte growth factor receptor)	Pleiotropic receptor with tyrosine kinase activity, it mediates HGF signaling and is essential for brain development and wound healing
OXTR	3p25	Oxytocin receptor	G-protein coupled receptor which binds oxytocin and activates the phosphatidylinositol-calcium pathway as second messenger system
RELN	7q22	Reelin	Large secreted extracellular matrix protein critical for neuronal migration in many brain regions during development
SLC6A4	17q11.2	Serotonin transporter	Integral membrane protein that transports the neurotransmitter serotonin from the extracellular space into the presynaptic bouton

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in an independent cohort of nearly 450 families, and the combined evidence exceeded criteria for genome-wide significance [152]. The association signal came from a region between *CDH10* and *CDH9*, two genes encoding neuronal cell-adhesion molecules [152]. This association was also replicated by Ma et al. [153], who performed an unbiased GWAS using as a discovery dataset 487 Caucasian families from the Collaborative Autism Project and for validation an independent publicly available family-based GWAS dataset from the Autism Genome Research Exchange (AGRE) including 680 multiplex families. This interesting association with 5p14.1 markers may be driven not by *CDH10* and *CDH9*, but rather by a 3.9 kb noncoding RNA encoded by the antisense strand of moesin pseudogene 1 (*MSNP1*), and thus designated *MSNP1AS* (moesin pseudogene 1, antisense) [154].

Ronald et al. [155] undertook the first GWAS of social and non-social autistic-like traits in the general population using dimensional measures (*i.e.*, DSM-IV-based social and non-social autistic behavior scales). In their male-only sample, a nominal association was found between social autistic traits and rs11894053, a SNP mapping to a hypothetical protein located in an intergenic region at chr. 2p21. When using the whole sample, two additional SNPs reached nominal significance, namely rs17622673, located in an intergenic region on chr. 6q16.3 downstream from *GRIK2* and associated with social autistic-like traits, and rs12578517, associated with nonsocial autistic-like traits and located on chr. 12p12.3, upstream from *PTPRO*. None of these three SNPs were associated with diagnosed ASD in the AGRE sample.

The Autism Genome Project (AGP) Consortium in 2010 genotyped at 1 million SNPs and analyzed 1558 rigorously defined ASD families [156], identifying genome-wide association with rs4141463, located in the *MACROD2* gene, as crossing a preset significance threshold of $P < 5 \times 10^{-8}$. They also found strong signals coming from several genes possibly involved in autism physiopathology, namely *KIAA0564*, *PLD5*, *POU6F2*, *ST8SIA2*, and *TAF1C* [156].

Another GWAS of 990 nuclear families ascertained for two or more children with ASD from the AGRE repository, revealed two SNPs exceeding genome-wide significance by using genome-wide joint tests allowing for sex differences [157]. Indeed, the SNPs found to be associated with ASD are located in two autism candidate genes, namely the Ryanodine Receptor 2 (*RYR2*), involved in intracellular Ca^{2+} homeostasis relevant to autism (see Section 2.6), and uridine phosphorylase 2 (*UPP2*), previously linked and associated with autism in independent samples [158].

Inconsistencies among independent GWAS reports, despite the great wealth of data gained from each single study, have been interpreted as stemming from the large phenotypic and genetic heterogeneity of the disease [148–150]. Thus, current efforts are aimed at finding autism subtype-related genetic variants, also by searching for quantitative trait loci (QTL). Using genome-wide association data from the study by Wang et al. [152] and categorizing ASD patients according to symptomatology based on scores obtained administering the Autism Diagnostic Interview-Revised (ADI-R) [159], novel highly significant associations with 18 SNPs were reported [160]. Symptom categories include deficits in language usage, non-verbal communication, social development, and play skills, as well as insistence on sameness or ritualistic behaviors [160]. It is noteworthy that in this study no association survived a Bonferroni correction when all 1867 ASD cases were combined into a single sample and compared against 2438 controls [160]. If these associations will be at least partly replicated, they will demonstrate that despite a smaller sample size, clinically homogeneous subgroups of individuals with ASD may enjoy greater statistical power in GWAS than large but clinically admixed samples [160]. A similar strategy was applied more recently on 2165 participants, by examining the association between genomic loci and individual items from the ADI-R, the Autism Diagnostic Observation Schedule, and the Social Responsiveness Scale [161]. Significant associations were found between several phenotypes and a number of loci, including *KCND2* (overly serious facial expressions), *NOS2A* (loss of motor skills), and *NELL1* (faints, fits, or blackouts).

Homozygous haplotype (HH) mapping represents another strategy to reduce heterogeneity by detecting homozygous segments of identical haplotype structure shared at higher-than-random frequency amongst ASD patients compared to parental controls. Applying HH to 1402 trios from the AGP, Casey et al. [162] identified 25 known and 1218 putative ASD candidate genes in the discovery analysis including *CADM2*, *ABHD14A*, *CHRFAM7A*, *GRIK2*, *GRM3*, *EPHA3*, *FGF10*, *KCND2*, *PDZK1*, *IMMP2L* and *FOXP2*. Importantly, regions of HH are significantly enriched in previously reported ASD candidate genes and the observed associations are independent of gene size [162]. One methodological issue that continues being generally overlooked in the GWAS literature and instead likely plays a major role in the inconsistencies among different GWAS studies, is that association is based on linkage disequilibrium (LD) patterns which differ significantly depending on race and ethnicity *regardless* of health and disease. Hence, in addition to clinical heterogeneity, also population genetic heterogeneity is bound to diminish statistical power in GWAS analyses unless these are performed contrasting ethnically and genetically homogeneous cases and controls. To our knowledge, no GWAS reports preliminary "population control" analyses to verify for the absence of significant genetic dyshomogeneity within and between case and control samples. Even recruiting from a single racial group, ethnically heterogeneous populations such as Caucasian-Americans differ significantly in LD patterns and larger samples may actually suffer from lower than higher statistical power, as suggested by Hu et al. [160]. "Genetic isolates", such as Iceland, Finland, and Sardinia, represent the ideal setting for GWAS of autism. These populations have historically undergone less population admixture, and are more genetically homogeneous and thus better fit to highlight differences truly associated with disease mechanisms.

4. Recent advances in the genetics of autism spectrum disorder: the impact of whole-exome sequencing

Traditional approaches for gene mapping from candidate gene studies to positional cloning strategies have been applied for Mendelian disorders. Since 2005, next-generation sequencing (NGS) technologies are improving as rapid, high-throughput and cost-effective approaches to fulfil medical sciences and research demands [163]. Whole-exome sequencing (WES) has recently been introduced to identify rare or novel genetic defects from genetic disorders. Particularly, ASD is a model disease to apply WES, because multiple loci are involved in its development with relatively weak genotype–phenotype correlation.

Four initial WES studies [164–167] have demonstrated the importance of *de novo* mutations in the etiology of ASD, while also showing that (a) the vast majority may increase risk but does not "cause" the disease, further supporting an oligogenic/polygenic model, and that (b) there may be several hundred genes in which high risk-conferring *de novo* mutations can occur. In particular, these four studies [164–167], collectively screening 965 patients, identified many *de novo* mutations predicted to disrupt gene function in the affected child. However, only a fraction of these mutations are expected to be causative, and those that do confer risk are distributed in many autism-related genes, collectively increasing disease risk by 5- to 20-fold but nonetheless incompletely penetrant, meaning they are not sufficient to cause the disease [164–167]. Secondly, these results further highlight the extreme genetic heterogeneity of ASD, while pointing towards a

relatively small number of implicated biological pathways. Many of the disrupted genes were found to impact important gene networks (synaptic plasticity, β-catenin/chromatin remodelling), and several *de novo* mutations were found in genes previously implicated in other neurodevelopmental disorders and in intellectual disability (*e.g.*, *SCN1A*, *SCN2A*, *GRIN2B*) [164–167]. Two of these studies also found *de novo* mutations come mostly from the paternal line in an age-dependent manner [166,167], a finding consistent with the modest, yet detectable increase in autism risk for children of older fathers [168]. From a pathophysiological standpoint, the results of these four initial WES studies have been interpreted as confirming the hypothesis that the origin of ASD is at the synapse [164–167]. However, their meta-analysis and integration with gene expression data from the developing human brain highlights that many of the recently identified mutations affect genes encoding chromatin-related proteins involved in transcriptional regulation, especially during prenatal brain development [169].

Other investigators used WES to find candidate recessive mutations in autistic probands with known shared parental ancestry [170–173]. Applying this strategy, Chahrour and colleagues [170] identified four novel candidate genes, namely *UBE3B*, *CLTCL1*, *NCKAP5L* and *ZNF18*, which encode proteins involved in proteolysis, GTPase-mediated signaling, cytoskeletal organization. Notably, the expression of these genes is dependent upon neuronal activity. Bi et al. [171] screened a cohort of 20 ASD patients by WES and identified a *de novo* missense mutation, S1569A, in the Ankyrin 3 (*ANK3*) gene. Given the known association of *ANK3* with other neuropsychiatric disorders (bipolar disorder and schizophrenia) [172], they sequenced the *ANK3* gene in an additional 47 ASD subjects, identifying the S1569A mutation in another unrelated patient, and two other novel heterozygous missense variants, T3720M and T4255P, located near the C-terminal death domain of *ANK3*, both inherited from apparently unaffected parents [171]. Screening consanguineous families with autism, epilepsy, and intellectual disability, Novarino and co-workers [173] identified homozygous inactivating mutations in the *BCKDK* gene (Branched Chain Ketoacid Dehydrogenase Kinase), resulting in blunted mRNA and protein expression, E1a phosphorylation and plasma levels of branched-chain aminoacids. Interestingly, *Bckdk* knockout mice show abnormal brain aminoacid profiles and neurobehavioral deficits that respond to dietary supplementation, thus representing a potentially treatable syndrome [173]. Finally, screening three Old Order Amish and Mennonite sibships encompassing seven affected individuals, Puffenberger et al. [174] found a homozygous missense mutation in *HERC2* (c.1781C>T, p.Pro594Leu) associated with global developmental delay and ASD. The phenotypic overlap with *Herc1* and *Herc2* mouse mutants, as well as with Angelman syndrome, support the pathogenic role of *HERC2* in nonsyndromic intellectual disability, autism, and gait disturbance [174].

Mutations in X-linked genes associated with ASD have been sought by sequencing the entire chromosome X exome in 12 unrelated families with two affected males [175]. Thirty-six possibly deleterious variants were found in 33 genes, including *PHF8* and *HUWE1*, previously implicated in intellectual disability [175]. A nonsense mutation in *TMLHE*, which encodes ε-N-trimethyllysine hydroxylase catalyzing the first step of carnitine biosynthesis, was identified in two brothers with autism and intellectual disability. Screening 501 male patients with ASD, two additional missense substitutions were identified in the *TMLHE* coding sequence [175]. Functional analyses demonstrated that these *TMLHE* mutations lead to loss-of-function, resulting in elevated plasma levels of trimethyllysine, the biosynthetic precursor of carnitine [175].

WES studies have identified many *de novo* mutations in ASD, but few recurrently disrupted genes. Therefore O'Roak et al. [176] developed a modified molecular inversion probe method enabling ultra-low-cost candidate gene resequencing in very large cohorts. By capturing and sequencing 44 candidate genes in 2446 ASD probands, 27 *de novo* events in 16 genes were found, 59% predicted to truncate proteins or disrupt splicing. Recurrent disruptive mutations in six genes, namely *CHD8*, *DYRK1A*, *GRIN2B*, *TBR1*, *PTEN*, and *TBL1XR1*, were thus estimated to contribute to approximately 1% of sporadic ASD cases. Moreover, these data support associations between specific genes and reciprocal subphenotypes, such as macrocephaly and microcephaly in *CHD8* and *DYRK1A* mutation carriers, respectively [176]. Another study investigated by whole-genome sequencing global patterns of germline mutations in monozygotic twins concordant for ASD and their parents [177]. *De novo* mutations detected in twin samples impacted a total of 34 genes, including 29 protein-coding genes and 5 noncoding RNAs. The frequency of *de novo* mutations in these 29 protein-coding genes was then investigated in larger exome data sets including a total of 962 cases and 590 controls from recent studies of ASD [164–167]. While no exonic hit was reported in controls, seven *de novo* coding mutations were detected among cases in five genes, with two genes (*KIRREL3* and *GPR98*) hit twice [177]. The genetic overlap between genes mutated in concordant monozygotic twins and sporadic ASD cases is thus significant for total number of hits ($P = 0.006$), number of double hits ($P = 0.005$), and number of genes ($P = 0.04$) [177].

Although rare causal inherited variants have been identified in some families, no population-based WES study has demonstrated a significant role for deleterious inherited variants in ASD risk, leaving the contribution of this class of genetic variation unknown [178]. ASD risk has been found increased when two rare variants deleteriously affect both copies of a protein-coding gene, consistent with a role for pseudo-recessive inheritance of nonsynonymous mutations in autism. Screening for homozygous or compound heterozygous loss-of-function variants in 933 cases and 869 controls, Lim et al. [179] reported the doubling of rare, putative recessively acting autosomal mutations in ASD patients compared with controls (6% *vs* 3.3%, respectively), confirming this observation in an independent set of 563 probands and 4605 controls. This class of genetic variants was estimated to confer an overall 3% contribution to ASD risk [178,179]. In addition, rare hemizygous mutations on the X chromosome, also yielding protein depletion in males, were enriched in male ASD cases compared to controls (4.8% *vs* 3.1%), with an estimated involvement in 1.7% of male patients [178,179]. These studies fill an important gap in our knowledge of the genetic architecture of ASD, by estimating that about 5% of ASD cases may be affected by rare inherited loss-of-function homozygous, compound heterozygous, or X chromosome mutations in males [178]. This mechanism was confirmed performing WES in ASD consanguineous and nonconsanguineous families [180]. Biallelic mutations underlying familial ASD were identified in six disease genes (*AMT*, *PEX7*, *SYNE1*, *VPS13B*, *PAH*, and *POMGNT1*), with at least some of these genes showing biallelic mutations in nonconsanguineous families as well [180]. Often these mutations are only partially disabling, demonstrating that partial loss of gene function can indeed play a major pathogenic role in some cases of autism. As occurs in many other monogenic autisms, frequently these mutations do not produce clinical phenotypes consistent with Mendelian disorders due to more deleterious mutations affecting the same genes.

5. Conclusions

The latest advances in the field of autism genetics highlight the striking complexity of its underlying pathophysiology. It is expected that high-throughput molecular screenings, such as high resolution array-CGH, whole-exome and whole-genome

sequencing, as well as transcriptomic analysis, will further increase our understanding of the genetic underpinnings of ASD. Specific rare genetic variants have been convincingly shown to cause autism, at least in some cases. However, genotype–phenotype correlations are extremely labile. The same mutation can cause behavioural and morphological phenotypes displaying a surprising degree of variability in different patients, even in affected members of the same extended family. These phenotypic differences further underscore the importance of common genetic variants, parental age-related epigenetics, and gene–environment interactions in determining the penetrance and expression of rare variants, especially when inherited from apparently healthy parents. The genomic location of CNVs and *de novo* mutations is fundamental to attribute a pathogenic or causal potential to a given variation [164–167,181]. More effort in addressing the functional relevance of each genetic variation found in ASD patients is clearly warranted. A promising approach is the application of bioinformatic tools and databases to link apparently discrete ASD genes into common functional pathways or convergent networks [13]. Such heuristic genetic patterns may correlate with ASD endophenotypes and/or overlap with other brain and developmental disorders [13].

From a translational perspective, the decreasing costs and progressive transfer of NGS from the laboratory into clinical practice, paired with already wide-spread array-CGH technologies, will indeed enhance the ability of clinicians to detect an increasing number of genomic/genetic abnormalities in their autistic patients. The bottleneck will then become the estimation of the functional consequences of CNVs and mutations, and the translation of this knowledge into personalized molecular pharmacology [182]. These tasks will require the integration of functional and pharmacological data from cellular, animal, and human studies into large, gene-network based bioinformatic tools, paired with sensitive and specific panels of biomarkers drawn from multiple levels of analysis (genomic, epigenomic, transcriptomic, proteomic and metabolomics) [183] to reliably support clinical decisions towards personalized molecular pharmacological interventions. To this aim, a very initial example of a genetic test providing combinatorial autism risk estimates has recently been published [184]. However, multi-level biomarker panels, including but not limited to genetic markers, may provide significantly greater predictive power. In general, this diagnostic approach will be most useful in estimating autism risk in (a) newborn siblings of children already diagnosed with autism, and (b) sporadic cases displaying initial behavioural abnormalities at 1–2 years of age and potentially evolving by age 3 toward normal behaviour, or into full-blown autism, softer ASD traits, specific language impairment, ADHD, or other behavioural syndromes. Diagnostic testing of this sort will also be increasingly sought, as early behavioral intervention programs, targeted to address ASD signs and symptoms much earlier than age 3, have begun showing significant efficacy in controlled trials [185]. Autism genetics had an earlier start compared to methylomics, transcriptomics, proteomics and metabolomics: the much greater wealth of available data concerning CNVs, rare variants, common variants, and gene pathways involved in autism is indeed spearheading this translational effort, currently exemplified in Europe by the EU-AIMS consortium with joint academia-pharmaceutical industry participation [186], ultimately aimed at significantly improving the life of autistic individuals and their families within the next four years.

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