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Clinical and Genetic Heterogeneity of Autism

Yu Wang and Nanbert Zhong

1. Introduction

Autism (MIM 209850) comprises a heterogeneous group of disorders with a complex genetic etiology, characterized by impairments in reciprocal social communication and presence of restricted, repetitive and stereotyped patterns of behavior [1]. With an early onset prior to age 3 and prevalence as high as 0.9–2.6% [2,3], autism occurs predominantly in males, with a ratio of male: female of 4 to 1. It is one of the leading causes of childhood disability and inflicts serious suffering and burden for the family and society [4].

Diagnosis of autism is based on expert observation and assessment of behavior and cognition, not etiology or pathogenic mechanism. This is further emphasized by the current trend in the DSM-V, in which the category of Asperger syndrome is removed and the diagnostic criteria for autism are modified under the new heading of autism spectrum disorder (ASD). The change in diagnostic criteria is not based on known similarities or differences in causation between these clinically defined categories, but rather on the consensus of opinions of expert clinicians. For autism, several diagnostic instruments are available. Two are commonly used in autism research: the Autism Diagnostic Interview-Revised (ADI-R) that is a semi-structured parent interview [5], and the Autism Diagnostic Observation Schedule (ADOS) uses observation and interaction with the child(ren) [6]. The Childhood Autism Rating Scale (CARS) is used widely in clinical environments to assess severity of autism based on observation of children [7]. The M-CHAT was developed in the late 1990s as a first-stage screening tool for ASD in toddlers' age 18 to 24 months, with a sensitivity of 0.87 and a specificity of 0.99 in American children [8, 9].

2. Clinical heterogeneity of ASD

Autistic conditions are a spectrum of disorders, rather than a distinct clinical disorder, which means that the symptoms can be present in a variety of combinations with a range of severity. The disease has variable cognitive manifestations, ranging from a non-verbal child with mental retardation to a high-functioning college student with above average IQ with

inadequate social skills [10]. Clinical heterogeneity of autism showed three major categories: idiopathic autism, autistic spectrum disorder (ASD), and syndromatic autistics that usually resulted from an identified syndrome with known genetic etiology. Traditionally, ASD includes autism, Asperger syndrome, where language appears normal, Rett syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS), in which children meet some but not all criteria for autism. Rett syndrome (RTT), occurring almost exclusively in females, is characterized by developmental arrest between 5 and 18 months of age, followed by regression of acquired skills, loss of speech, stereotypic movements (classically of the hands), microcephaly, seizures, and intellectual difficulties. These disorders share deficits in social communication and show variability in language and repetitive behavior domains [1]. Autistic individuals may have symptoms that are independent of the diagnosis. Mental retardation is present in approximately 75% of cases of autism, seizures in 15 to 30% of cases, attention deficit hyperactivity disorder (ADHD) in 59-75% of cases, schizophrenia (SZ) in 5% of cases, obsessive-compulsive disorder (OCD) in about 60% of cases and electroencephalographic abnormalities in 20 to 50% of cases [11]. In addition, approximately 15 to 37% of cases of autism have a comorbid medical condition such as epilepsy, sensory abnormalities, motor abnormalities, sleep disturbances, and gastrointestinal symptoms. Five to 14% of cases had a known genetic disorder or chromosomal anomaly. The 4 most common conditions associated with autistic phenotypes are fragile X syndrome, tuberous sclerosis, 15q duplications, and untreated phenylketonuria. Other conditions associated with autistic phenotypes include Angelman syndrome, Cowden disease, Smith-Lemli-Opitz syndrome, cortical dysplasia-focal epilepsy (CDFE) syndrome, Neurofibromatosis, and X-linked mental retardation.

3. Autism is a complex genetic disorder

It is widely held that autism is largely genetic in origin; several dozen autism susceptibility genes have been identified in the past decade, collectively accounting for about 20% of autistic cases. There is strong evidence from twin and family studies for the importance of complex genetic factors in the development of autism [12, 13]. Family studies have shown that a recurrence rate of autism in siblings of affected proband is as high as 8–10% [12, 14]. Thus, the recurrence risk in siblings is roughly 100 times higher than that found in the general population. The substantial degree of familial clustering in ASD could reflect shared environmental factors, but twin studies strongly point to genetics. Several epidemiological studies among sex-matched twins have clearly demonstrated significant differences of concordance rates in the monozygotic (MZ) and dizygotic (DZ) twins. The largest of these studies [15] found that 60% of the MZ pairs were concordant for autism compared with none of the DZ pairs, suggesting a heritability estimate of >90% assuming a multifactorial threshold model. This is what is observed in every twin study in autism, and is overall consistent with heritability estimates of about 70–80% [15, 16]. One exception is a very recent study with a large sample of twins, which, despite showing a concordance of about 0.6 for MZ twins and 0.25 for DZ twins, comes to the conclusion that shared environment plays a larger role than genetic factors [17]. However, the question of how a shared environment

would have a more major role than genetics is not clear. Moreover, studies in families show that first-degree relatives of an autistic proband have a markedly increased risk for autism relative to the population, consistent with a strong familial or genetic effect observed in twins [18]. This is not to dispute the role of the environment but to emphasize that genes play an important role. Similar to other common diseases with genetic contributions, autism was thought to fit a model in which multiple variants, each with small to moderate effect sizes, interact with each other and perhaps in some cases, environmental factors, to lead to autism; a situation referred to as complex genetics [13].

4. Genetic heterogeneity of autism

Although autism is highly heritable, the identification of candidate genes has been hindered by the heterogeneity of the disease. Autism genetics is highly complex, involving many genes/loci and different genetic variations, including translocation, deletion, single nucleotide polymorphism (SNP) and copy number variation (CNV) [13, 19, 20]. The most obvious general conclusion from all of the published genetic studies is the extraordinary etiological heterogeneity of autism. No specific gene accounts for the majority of autism; rather, even the most common genetic forms account for not more than 1–2% of cases [21]. Further, these genes, including those mentioned earlier, represent a diversity of molecular mechanisms that include cell adhesion, neurotransmission, synaptic structure, RNA processing/splicing, and activity-dependent protein translation. Genetic heterogeneity of autistic cases has been documented by identification of single gene mutations and genomic variations including CNV. The mutant genes identified from autistic patients are: *FMR1, MECP2, CNTNAP2, PTEN, DHCR7, CACNA1C, UBE3A, TSC2, NF1, ARX, NLGN3, NLGN4, NRXN1, FOXP1, FOXP2, GRIK2,* and *SHANK3* (Table 1). Genomic variation including copy number deletion or duplication at loci of 1q21.2, 1q42.2, 2q31.1, 3p25.3, 7q11.23, 7q22.1, 7q36.3, 11q13.3, 12q14.2, 15q11-13, 16p11.2, 16q13.3, 17q11.2, 17q12, 17q21.32, 22q13.33, or Xp22.11 may also associate with autism.

5. Genotype/phenotype correlation in ASD

The presence of genetic and phenotypic heterogeneity in autism with a number of underlying pathogenic mechanisms is highlighted in this current review. There are at least three phenotypic presentations with distinct genetic underpinnings: (1) autism with syndromic phenotype characterized by rare, single-gene defects (Table 2); (2) broad autistic phenotypes caused by genetic variations in single or multiple genes, each of these variations being common and distributed continually in the general population but resulting in variant clinical phenotypes when it reaches a certain threshold through complex gene-gene and gene-environment interactions; and (3) severe and specific phenotype caused by 'de-novo' mutations in the patient or transmitted through asymptomatic carriers of such mutations (Table 3) [48, 49]. Understanding the neurobiological processes by which genotypes lead to phenotypes, along with the advances in developmental neuroscience and neuronal networks at the cellular and molecular level, are paving the way for translational research

involving targeted interventions of affected molecular pathways and early intervention programs that promote normal brain responses to stimuli and alter the developmental trajectory [50]. Recent genetic results have improved our knowledge of the genetic basis of autism. Nevertheless, identification of phenotypic markers remains challenging due to phenotypic and genotypic heterogeneity.

Gene	Genetic alteration	Location	Reference
FMR1	The number of CGG in *FMR1* alleles is classified as intermediate mutation (45 to 55), premutation (55 to 200), or full mutation ($>$200)	5'untranslated region	22-24
MECP2	T158M, T158A	Missense mutation	25
CNTNAP2	3709delG	Exon 22	26
	G731S, I869T R1119H, D1129H, I1253T, T1278I	Exon 14, 17 Exon 20, 21, 23, 24	27
	H275A	Exon 6	28
	CNV (microdeletion)	Promoter	29
PTEN	Deletion	Exon 2	30
CACNA1C	G406R	Missense mutation	31
UBE3A	D15S122	5' end of *UBE3A*	32, 33
TSC2	SNP	Intron 4, 9; exon 40	34
NF1	SNP	Intron 27	35
NLGN3	R451C	Missense mutation	36, 37
NLGN4	1186insT	Frameshift mutation	37
NRXN1	*De novo* 320-kb deletion	Promoter and initial coding exons	38, 39
	Missense structural variant	Neurexin1ß signal peptide region	40
FOXP1	*De novo* intragenic deletion	Exons 4-14	41
FOXP2	Del CAA;	Exon 5	42, 43
	Frequency of the TT allele	Intron 15	
GRIK2	SNP	M867I	44
SHANK3	*De novo* Q321R	Stop codon	45
	1-bp insertion	Exon 11	46
	De novo 7.9-Mb deletion	22q13.2-qter	47

Table 1. Genetic alteration identified from autism

Gene/loci	Chromosome	Phenotype (human/mouse)	Mechanism involved	Risk of autism	Reference
CNTNAP2	7q35-q36.1	Recessive EPI syndrome, ASD, ADHD, TS, OCD	Chromosomal rearrangements and large deletions, disruption of the transcription factor *FOXP2*, SNP	Not conclusive	51-54
CHD7	8q12.1	CHARGE	Mutations/deletions of gene *CHD7*, Chromatin remodeling; disruption of the transcription factor *FOXP2*; SNP;	15–50%	55, 56
TSC1	9q34.13	Tuberous Sclerosis type I.	Mutation in gene *TSC1* and subsequent hyperactivation of the downstream mTOR pathway, resulting in increased cell growth and proliferation.	Not conclusive	57
PTEN	10q23.31	Cowden disease.	Mutation of gene *PTEN*	Not conclusive	30
DHCR7	11q13.4	Smith-Lemli-Opitz syndrome	Mutations of gene *DHCR*, leading to a deficiency of cholesterol synthesis and an accumulation of 7-dehydrocholesterol	15–50% 3%	58-60 61, 62
CACNA1C	12p13.33	Timothy syndrome.	Missense mutations in the calcium channel gene *CACNA1H*	Not conclusive	63
UBE3A	15q11.2	Angelman syndrome	Maternal deletion, paternal UPD, deletions and epimutations at IC, mutations of *UBE3A*, Lack of expression of maternally expressed gene *UBE3A*	Not conclusive	32, 33
TSC2	16p13.3	Tuberous Sclerosis type II	Mutation in gene *TSC2* and subsequent hyperactivation of the downstream mTOR pathway, resulting in increased cell growth and proliferation.	Not conclusive	57
NF1	17q11.2	Neurofibromatosis	Polymorphisms within the intron-27, including the (AAAT)(n) and two (CA)n	Not conclusive	35
DMD	Xp21.2	Duchenne muscular dystrophy	Mutations of *DMD* gene resulting in absence of dystrophin protein	Not conclusive	64
ARX	Xp21.3	LIS, XLID, EPI, ASD	Naturally occurring mutations. Nonsense mutations, polyalanine tract expansions and missense mutations	Not conclusive	65
FMR1	Xq27.3	Fragile X syndrome	CGG repeat expansion and DNA methylation of FMR1 gene, reduced FMR1 expression	60–67% in males, 23% in female	66
MECP2	Xq28	Rett syndrome	Mutations in *MECP2* and *CDKL5*	Overlap in symptoms Infancy	67, 68

Abbreviations: LIS, lissencephaly; XLID, X-linked intellectual disability; EPI, epilepsy; OCD, obsessive compulsive disorder; TS, Tourette syndrome; ADHD, attention deficit hyperactivity disorder.

Table 2. Autism plus syndromic ASD caused by rare, single-gene disorders

| Gene	Chromosome	Phenotype (human/mouse)	Mechanism involved in ASD	Reference
NRXN1	2p16.3	ASD, ID, SCZ, Language delay	De novo 320-kb deletion that removes the promoter and initial coding exons of the *NRXN1* gene, resulting in deletion of neurexin 1a	39
			Missense structural variants in the neurexin 1b signal peptide region	40
			CNV	69, 70
			Translocations and intragenic rearrangements in or near *NRXN1*gene	71, 72
FOXP1	3p13	ID, ASD, SLI	*De novo* intragenic deletion encompassing exons 4-14 of *FOXP1*, *de novo* nonsense mutation (c.1573C>T) in the conserved fork head DNA-binding domain	73
GRIK2	6q16.3	ASD, Recessive ID	SNP1 and SNP2 of gene *GRIK2* were associated with autism	74
FOXP2	7q31.1	ASD, SLI	Directly bind intron 1 of the *CNTNAP2* gene and regulate its expression	74
	11p15.5	Beckwith-Wiedemann syndrome	Overexpression of paternally expressed *IGF2*, due to a gain of DNA methylation at paternal allele of *IC1* and suppression of maternally expressed suppressing factor *CDKN1C*	75
	15q11-q13	Prader-Willi syndrome	Paternal deletions, maternal UPD at15q11–13, deletions and epimutations of *IC*, translocations disrupting *SNRPN*	76, 77
		Maternal duplication of 15q11-13 region	Maternal duplications of 15q11-13 region	78
SHANK3	22q13.33	ASD	Mutation at an intronic donor splice site, one missense mutation in the coding region	79
NLGN4X	Xp22.32-p22.31	ASD, ID, TS, ADHD	Frameshift mutation (1186insT)	37
NLGN3	Xq13.1	ASD	R451C mutation within the esterase domain of neuroligin 3	36, 37

Abbreviations: ID, intellectual disability; SCZ, schizophrenia; TS, Tourette syndrome; SLI, speech and language impairment; ADHD, attention deficit hyperactivity disorder

Table 3. Severe and specific phenotype with rare variants of genes

6. Copy number variation (CNV): A paradigm shift in autism

The strong genetic contribution shown in family studies and the association of cytogenetic changes, but apparent lack of common risk factors in autism, led to a hypothesis that rare sub-microscopic unbalanced changes in the form of CNVs likely contribute to the autism

phenotype. With the development of microarrays capable of scanning the genome at sub-microscopic resolution, there is accumulating evidence that multiple CNVs contribute to the genetic vulnerability to autism [80]. *de novo* CNV has been identified in up to 7–10% of sporadic autism [81, 82], but are less frequent in multiplex families, in which CNV accounts only for about 2% of families screened [80, 83]. This could possibly suggest different genetic liabilities in simplex and multiplex autism. Recurrent CNVs at 15q11-13 (1-3% of autism patients), 16p11 (1% of autism patients), and 22q11-13 have been confirmed in multiple studies [80, 83-86]. This hypothesis also has been proven largely successful in identifying autism-susceptibility candidate genes, including gains and losses at *SHANK2* [87], *SHANK3* [88], *NRXN1* [13], *NLGN3* and *NLGN4* [37], and *PTCHD1* [89, 90]. Neurexins and neuroligins are synaptic cell-adhesion molecules (CAMs) that connect pre- and postsynaptic neurons at synapses, mediate trans-synaptic signaling, and shape neural network properties by specifying synaptic functions. The Shank family of proteins provides scaffolding for signaling molecules in the postsynaptic density of glutamatergic synapses. Genes encoding CAMs play crucial roles in modulating or fine-tuning synaptic formation and synaptic specification. Localization and interacting proteins at the synapse is shown in Figure 1.
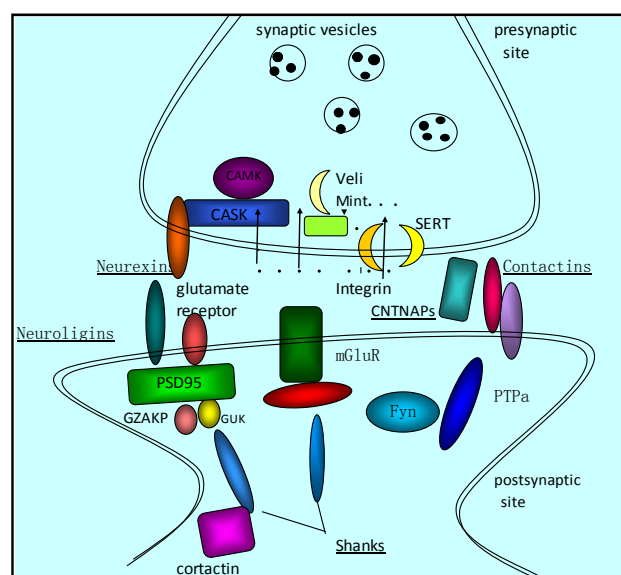
Figure 1. Localization of cell-adhesion molecules and their interacting proteins at the synapse. Proteins associated with ASD are underlined.

It is apparent that many different loci, each with a presumably unique yet subtle contribution to neurodevelopment, underlie the phenotype of autism. These observations have resulted in a paradigm shift away from the previously held "common disease-common variant" hypothesis to a "common disease-rare variant" model for the genetic architecture of autism. The central tenet of this model suggests a role for multiple, rare, highly penetrant, genetic risk factors for ASD, many of which are in the form of CNV. To make sense of the contribution of CNVs to autism, a "threshold" model has been proposed [80]. The model posits that different CNVs exhibit different penetrance depending on the dosage sensitivity and function (relative to autism) of the gene(s) they affect. Some CNVs have a large impact

on autism susceptibility and these are typically *de novo* in origin, cause more severe autistic symptoms, are more prevalent among sporadic forms of autism, and are less influenced by other factors like gender and parent of origin. Other CNVs have moderate or mild effects that probably require other genetic (or non-genetic) factors to take the phenotype across the autistic threshold.

7. Epigenetics plays an important role in autism

In addition to structural genetic factors that play causative roles for autism, environmental factors also play an important role in autism by influencing fetal or early postnatal brain development, directly or *via* epigenetic modifications. Epigenetic modifications include cytosine methylation, post-translational modification of histones, small interfering RNA and genomic imprinting. Involvement of epigenetic factors in autism is demonstrated by the central role of epigenetic regulatory mechanisms in the pathogenesis of Rett syndrome and fragile X syndrome (FXS), both are the monogenic disorders resulted from single gene defects and commonly associated with autism [38-40]. FXS is a result of a triplet expansion of CGG repeats at the 5′ untranslated region of *FMR1* gene, which encodes the FMRP (fragile X mental retardation protein). FMRP is proposed to act as a translation regulator of specific mRNAs in the brain and involved in synaptic development and maturation, through its nucleo-cytoplasmic shuttle activity as an RNA-binding protein. It has been shown that FMRP uses its arginine-glycine-glycine (RGG) box domain to bind a subset of mRNA targets that form a G-quadruplex structure. FMRP has also been shown to undergo the post-translational modifications of arginine methylation and phosphorylation [91, 92]. Our recent study demonstrated that alteration of methylation patterns at loci of *Neurex1* and *ENO2* are associated with autism [Wang and Zhong, manuscript in preparation].

Genomic imprinting is the classic example of regulation of gene expression *via* epigenetic modifications, such as hypemethylation, that leads to parent of origin-specific gene expression. In addition, a growing number of genes that are not imprinted are regulated by DNA methylation, including Reelin (*RELN*) [41, 93-96], which has been considered as a candidate for autism. Several of the linkage peaks overlap or are in close proximity to regions that are subject to genomic imprinting on chromosomes 15q11-13, 7q21-31.31, 7q32.3-36.3 and possibly 4q21-31, 11p11.2-13 and 13q12.3, with the loci on chromosomes15q and 7q demonstrating the most compelling evidence for a combination of genetic and epigenetic factors that confer risks for autism [97-101]. Genes in the imprinted cluster on chromosome 15q11–13 include *MKRN3, ZNF127AS, MAGE12, NDN, ATP10A, GABRA5, GABRB3*, and *GABRG3* [102, 103]. Genes in the imprinted cluster on chromosome 7q21.3 include *SGCE, PEG10, PPP1R9A, DLX5, CALCR, ASB4, PON1, PON2*, and *PON3* [104, 105].

Research has recently focused on the connections between the immune system and the early development of brain, including its possible role in the development of autism [106]. Immune aberrations consistent with a deregulated immune response may target neuronal

development and differentiation [107, 108]. Our study has suggested that a close contact with natural rubber latex (NRL) could trigger an immunoreaction to Hevea brasiliensis (Hev-b) proteins in NRL and resulted in autism [109]. This led us to a hypothesis that immune reactions triggered by environmental factors could damage synapse formation and neuronal connections, which would result in missing normal structure or function of synaptic proteins that are encoded by genes *NLGNs, NRXN1, CNTNAPs, SHANKs, or in deregulation of gene expression of FMR1, PTEN, FOXPs,* and *GRIK2.*

8. Converging molecular pathways of autism

Autism is a heterogeneous disorder with a fundamental question of whether autism represents an etiologically heterogeneous disorder in which a myriad of genetic or environmental risk factors perturb common underlying molecular pathways in the brain [110]. Two recent studies have suggested there could be convergence at the level of molecular mechanisms in autism. The first study on molecular convergence in autism identified protein interactors of known autism or autism-associated genes [111]. This interactome revealed several novel interactions, including between two autism candidate genes, *SHANK3* and *TSC1*. The biological pathways identified in this study include synapse, cytoskeleton and GTPase signaling, demonstrating a remarkable overlap with those identified by the gene expression. The second, an analysis of gene expression in postmortem autism brain, provides strong evidence for a shared set of molecular alterations in a majority of cases of autism. This included disruption of the normal gene expression pattern that differentiates frontal and temporal lobes and two groups of genes deregulated in autistic brains: one related to neuronal function, and the other related to immune/inflammatory responses [111]. Genes associated with neuronal function were enriched in metabolic signal pathways, providing evidence that these changes were causal, rather than the consequence of the disease [112]. In contrast, the immune/inflammatory changes did not show a strong genetic signal, indicating a non-genetic etiology for this process and implicating environmental or epigenetic factors instead. These results provide strong evidence for converging molecular abnormalities in autism, and implicating transcriptional and splicing deregulation as underlying mechanisms of neuronal dysfunction in this disorder.

9. In summary

Autism is a heterogeneous set of brain developmental disorders with complex genetics, involving interactions between genetic, epigenetic and environmental factors. The heterogenerous genetics involves many genes/loci and different genetic variations in autism, such as deletion, translocation, SNP and CNV. Recent studies have also suggested there could be convergence at the level of molecular mechanisms in autism. Although the genetic basis is well documented, considering phenotypic and genotypic heterogeneity, correspondences between genotype and phenotype have yet to be well established.

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