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Review Article: Autism Spectrum Disorders

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Genetics of Autism Spectrum Disorder: Current Status and Possible Clinical Applications

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Autism spectrum disorder (ASD) is one of the most complex behavioral disorders with a strong genetic influence. The objectives of this article are to review the current status of genetic research in ASD, and to provide information regarding the potential candidate genes, mutations, and genetic loci possibly related to pathogenesis in ASD. Investigations on monogenic causes of ASD, candidate genes among common variants, rare *de novo* mutations, and copy number variations are reviewed. The current possible clinical applications of the genetic knowledge and their future possibilities are highlighted.

Key words: Autism spectrum disorder, Syndromic autism, *de novo* mutations, Genetic diagnosis

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by very early onset of dysfunction in social communication and interaction, repetitive behavior, and limited interest. It is now believed that ASD is a result of complex gene–environment interactions, with strong and clear genetic influences. Studies of twin pairs, high-risk infant siblings, families, and populations have estimated concordance rates and segregation of the disorder within families. The concordance rate was reported as 60–70% in monozygous twins and as 5–30% in siblings; this is in agreement with a recent large prospective study revealing a recurrence rate of 18% in infant siblings and of 33% in multiplex families [1, 2]. However, it is currently believed that over 50% of the risk of developing ASD is attributed to genetic variation [3, 4].

Advances in genetic technologies, large cohort studies, and widespread database sharing have contributed to the discovery and validation of causative genes in ASD [5]. Knowledge from genetic studies of ASD also provides insight into other neurodevelopmental disorders, as ASD shares both behavioral characteristics and endophenotypes. However, ASD is one of the most heterogeneous neurodevelopmental disorders, with great variation observed in behavioral manifestations and cognitive profiles, which makes determination of the single most important genetic risk factor extremely difficult.

Identifying biomarkers has been one of the primary goals of biological research of ASD, and current research efforts are directed predominantly toward the identification of markers for risk and early diagnosis [6]. There have been intense research efforts to identify the genetic basis of ASD, with an assumption that the genetic markers can be utilized as essential biomarkers in the diagnosis of, and the development of pharmacological treatments for, ASD. The objective of this paper is to review the current knowledge of genetic variations in ASD, and its role in the identification of genetic biomarkers of ASD for diagnostic and therapeutic purposes.

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GENETIC VARIANTS

Common variants

The genetic architecture of ASD is diverse in frequency (common vs. rare variation), mode of inheritance (inherited vs. *de novo* variation), type of variation (single nucleotide, indel, or copy number variation [CNV]) and mode of action (dominant, recessive, or additive) [3, 7]. Common variation refers to genetic variation from the reference genome, which is present in >1% of the population. Common variants with small effects are thought to act additively in the development of complex traits in ASD [8]. One recent investigation reported that the liability of ASD is mostly attributed to common variation in the genetic architecture, and that rare *de novo* mutations contribute to individual liability (49% of common inherited variants, 3% of *de novo*, 3% of rare inherited variants, and 41% of unaccounted) [7].

Confirmation of the most specific, consistently replicated, and highly effective common variants involved in the pathogenesis of ASD is another issue. The first molecular genetic studies of autism were candidate gene association studies that aimed to discover common genetic variants in the form of single-nucleotide polymorphisms (SNPs). However, a large disadvantage of this is that it requires existing physiological, biochemical, or functional knowledge, which is either finite or unavailable [9]. These investigations have been hindered by inadequate sample sizes and sparse genotyping, resulting in a lack of reproducible markers except for a few plausible genes [9, 10].

The most consistently reported genes among the common variants include the gamma-aminobutyric acid (GABA) A receptor, beta 3 (*GABRB3*); oxytocin receptor (*OXTR*); reelin (*RELN*); serotonin transporter (*SLC6A4*); N-methyl-D-aspartate receptor (*NMDA*; *GRIN2B*); arginine vasopressin receptor 1A (*AVPR1A*); engrailed homeobox 2 (*EN2*); integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61; *ITGB3*); met proto-oncogene (hepatocyte growth factor receptor; *MET*); and contactin-associated protein-like 2 (*CNTCAP2*) genes [11-22]. *GABRB3*, which is localized to chromosome 15q11–q13 and is involved in genome instability, gene expression, imprinting, and recombination, was investigated in the first era of ASD genetic research [13, 23]. This region became a major subject of attention because deletion of this locus is related to monogenic causes of ASD, Prader–Willi syndrome, and Algelman's syndrome, and because GABA may be a pharmacological therapeutic target [13, 24, 25]. Oxytocin acts as a neuromodulator in the central nervous system, and induces social/affective bonding in animal models. The *OXTR* is a promising biomarker candidate, due to its genetic variants, functions on behavior, and positive results in human clinical trials [17, 26, 27].

However, these candidate gene studies also revealed that common variation has a weak effect when individual SNPs are investigated. A genome-wide association study (GWAS) avoids the need for *a priori* hypotheses for the primary cause of illness, and is a more appropriate approach for genetic studies of complex disorders such as autism [10]. GWASs have been applied to psychiatric disorders with complex phenotypes, and several variants have been reported [28]. Several GWASs have been conducted for ASD, and a few well-designed studies reported that common genetic variants on 5p14.1 and 5p15 were highlighted and replicated in two independent samples, each carrying a small increased risk (OR 1.2) or protective effect (OR 0.6) [29-31]. A significant association was observed with the *CDH9* and *CDH10* genes, but replications of this association was inconsistent [29-33]. Several studies identified significant SNP markers that were replicated in two or more independent samples and were associated with specific phenotypes of ASD, but the effect sizes were relatively small [29-35]. However, significant genome-wide results were not consistently reproduced across studies and ethnicities [33, 35].

Those inconsistencies can be attributed to the phenotypic heterogeneity of ASD and to relatively small sample sizes. Researchers attempted to decrease phenotypic heterogeneity by subphenotyping or using quantitative phenotypes, but this was unsuccessful in enhancing the substantial power of GWAS, resulting in the necessity of very large sample sizes, such as 50,000 individuals [5, 33, 34].

Rare variants and monogenic autism

Rare variation is genetic variation that is present in the population at a frequency of ≤1%. ASD can be expressed as the behavioral manifestation of known genetic syndromes, called syndromic autism, as opposed to idiopathic autism, which does not have known genetic causes. Syndromic autism often has dysmorphic features characterized by the genetic syndrome it belongs to and equal male:female ratios, unlike idiopathic autism, which occurs 4–5 times more frequently in males than in females [36]. Single-gene disorders, including fragile X (mutations in *FMR1*), tuberous sclerosis complex (mutations in *TSC1* and *TSC2*), Dup15q syndrome, deletions in the 16p11.2 region, Rett syndrome (mutation in *MeCP2*), and neurofibromatosis (mutations in *NF1*), are detected in 3–5% of subjects with ASD, and are well-known as having an ASD phenotype as well as comorbid intellectual disabilities and epilepsy [37].

Recent development of whole-exome sequencing (WES) techniques has revealed that more than 25% of individuals with

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ASD have identifiable, causative, and protein-disrupting rare genetic mutations [5]. However, single mutations account for no more than 1% of cases, mainly due to phenotypic heterogeneity and variable penetrance. Though the prevalence is not strikingly high, syndromic autism helps to understand core deficits of ASD as one of the phenotypes that specific genetic mutations carry, and acts as a gateway to explore the genetic etiology of ASD. The representative examples of monogenic autism and their clinical implications are summarized in Table 1.

Table 1. Examples of monogenic "syndromic" autism and related phenotypes

	Mutations	Phenotypes
Fragile X syndrome	*FMR1*	Large, protruding ears, long face, hyperextensible joint, macroorchidism, *hypotonia*, *learning problem*, *intellectual disability*, *language impairment*, *developmental delay*, *attention problem*, *ASD* [120]
Rett's syndrome	*MECP2*	*Developmental regression, microcephaly, cognitive and motor impairment, epilepsy, stereotyped hand movement, severe repetitive behavior, severe ASD* [36]
Tuberous sclerosis	*TSC1, TSC2*	Brain tumors, multi-organ involvement (kidneys, lungs, heart, eyes and skin), *learning difficulties, intellectual disability, self-injurious behavior, obsessive compulsive disorder, attention deficit hyperactivity disorder, aggression, epilepsy, ASD* [121]
Neurofibromatosis 1	*NF1*	Café au lait spots, neurofibromas, scoliosis, iris tumor, *cognitive dysfunction, epilepsy, autism* [122]
Cornelia de Lange syndrome	*SMC1A/SMC3*	Low birth weight, facial abnormalities, hearing and vision abnormalities, limb differences, heart defect, cleft palate, *self-stimulation, self-injurious behavior, aggression, ASD* [123]
Cohen syndrome	*COH1*	Ocular abnormalities, obesity, thin arms and legs, micrognathia, deafness, *intellectual disability, epilepsy, ASD* [124]
Timothy syndrome	*CACNA1C*	Congenital heart disease, cardiac arrhythmias (long QT syndrome), webbing of fingers and toes (or syndactly), immune deficiency, *cognitive abnormalities, ASD* [125]
Smith-Lemli-Opitz syndrome	*DHCR7*	Facial abnormalities (bitemporal narrowing, ptosis, short and upturned nose), micrognathia, finger and feet abnormalities, *microcephaly, developmental delay, learning disability, behavioral abnormalities, hand mannerism, ASD* [126]
Williams-Beuren syndrome	7q11.23 del	Cardiac and gastrointestinal problems, hyperacusia, phonophobia, strabismus, esotropia, problems with visual processing, *cerebellar signs, hypertonia, motor delay, intellectual disability, strong interest in people, lack of social inhibition, ASD* [127]
Dup15q syndromes	Dup 15q11–q13, *GABRB3*	Hypotonia, facial dysmorphism (flat nasal bridge, epicanthal folds, deep set ear, high arched palate), small stature, *gross and fine motor delays, cognitive delays, speech/language delays, behavior problems, sensory processing problem, epilepsy, ASD* [128]
Prader-Willi syndrome	Del 15q11–q13 (paternal allele)	Specific face, hypogonadism, small hands and feet, hypopigmentation, hyperphagia, severe obesity, *obsessive compulsive disorder, mood and behavior problem, ASD* [37]
Angelman syndrome	Del 15q11–q13 (maternal allele, *UBE3A*)	Strabismus, unique facial dysmorphism, prominent mandible, wide mouth, *sleep disturbance, severe developmental delay, speech impairment, ataxia, attention problem, frequent laughter, easily excitable personality, epilepsy, ASD* [37]
16p11.2 deletion syndrome	16p11 del	Minor unusual facial and physical features, hypotonia, overweight, *language delay, learning difficulty, epilepsy, ASD* [49]
Smith-Magenis syndrome	17p11.2 del	Facial dysmorphism (broad, square shaped face, deep set eyes, prominent lower jaw), short stature, scoliosis, eye abnormalities, *reduced sensitivity to pain and temperature, sleep disturbances, behavioral problem, self-injurious behavior, stereotyped behavior (finger licking, flipping books), ASD* [129]
22q11 duplication syndrome	22q11.2 dup	Growth retardation, hypotonia, *delayed psychomotor development, learning difficulty, intellectual disability, ASD* [130]
DeGeorge syndrome (velocardiofacial syndrome)	22q11.2 del	Multi-organ involvement (heart, kidney, gastrointestinal system, skeletal abnormality), cleft palate, facial dysmorphism, immune system abnormality, low calcium level, hearing loss, *developmental delay, learning difficulty, mental illnesses (schizophrenia, anxiety, mood disorders), attention deficit hyperactivity disorder, ASD* [131]
Phelan-McDermid syndrome	23q13.3 del	Dolichocephaly, hand and facial dysmorphism, ptosis, kidney problems, neonatal hypotonia, *global developmental delay, intellectual disability, reduced sensitivity to pain, absent or severely delayed speech, ASD* [59]

ASD, autism spectrum disorder.

Copy number variation

Copy number variants (CNVs) are variations (duplication or deletion) in chromosomal structure of greater than 1,000 nucleotides, usually a section of DNA with a length from 1 kb to several Mb. CNVs can be either common or rare, transmitted or *de novo*, and are widely distributed in human genome, accounting for a substantial proportion of genetic variation [5, 38]. Studies have revealed an increased frequency of CNVs in individuals with ASD compared to normal controls and several *de novo* CNVs in children with autism, suggesting excessive genomic instability. The frequency of *de novo* CNVs in ASD has been reported as 3–19% in ASD from simplex and multiplex families, compared to approximately 1% in healthy controls [39-41].

Genomic imbalances associated with ASD are classified as recurrent and nonrecurrent events. Recurrent events are non-allelic homologous recombination, with reciprocal dosage imbalances (deletion and duplication) in different individuals [42]. Notable examples of recurrent CNVs are microdeletions and duplications in chromosome 1q21, 15q13, and 16p11.2, and microdeletion syndrome in chromosomes 2p15-2p16.1, 17p11.2, and 17q12 [43-49]. CNVs are associated with a wide range of phenotypic heterogeneity, including dysmorphic features, intellectual disabilities, language impairments, attention problems, hyperactivity, aggression and other behavioral problems, mood disorders, and schizophrenia, which implicates those variants might not be a specific cause of social disability in ASD [18].

Synaptic genes

Of the genetic variations studied regarding ASD, the most consistently reported genetic abnormalities are mutations in synaptic genes, including neuroligins (*NLGN*), SH3 and multiple ankyrin repeat domains (*SHANK*), neurexin (*NRXN*) families, and contactin associated protein-like 2 (*CNTNAP2*) [50-62]. Mutations in synaptic genes are not specific to ASD, and are also found in other neuropsychiatric disorders, such as schizophrenia and Alzheimer's disease [63, 64]. However, as these neuropsychiatric conditions share common features with ASD, such as cognitive dysfunction, limited emotional expression, and lack of social reciprocity, synaptic dysfunction is still considered a common pathway of these major, chronic neuropsychiatric illnesses [5, 18].

NLGNs are known to act as splice site-specific ligands for beta-neurexins and be involved in the formation and remodeling of central nervous system synapses (http://www.ncbi.nlm.nih.gov/gene/54413). The identification of a *de novo*, loss of function mutation in neuroligin 4, X-linked (*NLGN4X*) in an affected mother that was transmitted to two affected boys first suggested the possibility of synaptic dysfunction involvement in ASD [65]. This was followed by the identification of a single-base missense mutation of *NLGN3* in another family [53]. These findings have been replicated in other studies, and *NLGN3*, *NLGN4*, and *NLGN4Y* were found to be possibly associated with ASD. However, mutation of those genes in ASD is relatively low (0.6–3.3%), and the clinical phenotypes and neurobiological characteristics of these mutations are also quite diverse, including ASD, intellectual disabilities, and Tourette syndrome, and inconsistent across ethnicities [51, 54, 55, 61, 62].

A second family of genes possibly associated with ASD is the SHANK genes (*SHANK1*, *SHANK2*, and *SHANK3*), encoding synaptic proteins that may function as molecular scaffolds in the postsynaptic density of excitatory synapses (http://www.ncbi.nlm.nih.gov/gene/22941). *SHANK3* is the most widely studied, but *SHANK1* and *SHANK2* are also implicated by *de novo* deletions observed in subjects with ASD [50, 57-59]. Durant et al. (2007) reported eight non-synonymous mutations in ASD patients that were not present in healthy controls; rare *de novo* mutations in *SHANK3* located in chromosome 22q13.3 were identified in probands and families with ASD in many studies [50]. Rare mutations and genomic deletions have been reported in different *SHANK3* loci, with a frequency of 0.2–0.8% of probands in ASD [50, 57, 66-69]. Mutations in *SHANK3* are gaining attention, as they are related to Phelan-McDermid syndrome (PMS) and 22q13 deletion syndrome, and are one of the known genetic causes of ASD. PMS is characterized by autism or autistic-like behavior in more than 50% of subjects, and is accompanied by neurological deficits, including global developmental delay, moderate to severe intellectual impairment, absent or severely delayed speech, and neonatal hypotonia [59].

The transmission pattern of *SHANK3* mutations is variable; inheritance from healthy parents and existence in unaffected siblings were reported [50, 57, 67]. Recently, Nemirovsky et al. (2015) reported germline mosaicism for a heterozygous cytosine deletion in exon 21 of *SHANK3* by whole-genome sequencing in three male siblings from a segregated family exhibiting phenotypes of severe intellectual disability, absence of language, autism spectrum symptoms, and epilepsy [58]. As with other potential candidates, the associated phenotypes of *SHANK3* mutations are not specific for ASD, but *SHANK3* is regarded as one of the potential causative genes and therapeutic targets of ASD, based on animal and cellular model studies.

Other important synaptic genes are *NRXN1*, *NRXN2* and *NRXN3*, encoding neuroligins. This trans-synaptic complex is required for efficient neurotransmission, and they are involved in the formation of synaptic contacts by interaction with

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neurexins [60]. Neuroligin aggregation is synaptogenic, but exhibits specificity: *NLGN1*, *NLGN3* and *NLGN4* link only to glutamatergic postsynaptic proteins, but *NLGN2* links to both glutamatergic and GABAergic postsynaptic proteins [52]. In the earlier era of ASD genetic studies, CNVs were found to disrupt the locus containing *NRXN1*, but this was inconsistent, with a high unaffected carrier frequency of deletions [70-73]. More recently, there have been relatively large cohort studies that describe a higher rate of deletions in the *NRXN1* region located in the probands of chromosome 2p16.3 associated with ASD, compared to healthy controls, with an overrepresentation of small-sized inverted repeats [72, 74]. Shared psychopathologies related to the deletions were developmental delays, speech delays, abnormal behaviors, including ASD, and some degree of dysmorphism [72].

CNTNAP2 is another candidate gene suggested to be associated with ASD by human and animal model studies. Family-based association studies identified a common variant (rs7794745) that was associated with increased risk of autism, and another study revealed an amino acid substitution in the CNTNAP2 protein in children with autism [75-77]. Variation of the *CNTNAP2* gene and age at first word, a language development phenotype, are both related to autism rather than to the diagnosis itself, and raises the implication that genetic variants of a quantitative phenotype of ASD interact with *FOXP2* [75]. The functional relevance of *CNTNAP2* genetic variants has been validated in animal models; CNTNAP2 (-/-) mice exhibited deficits in all three core behavioral deficits of ASD, as well as hyperactivity and epileptic seizures, and improved repetitive behavior of mutant mice [78]. A large-sized GWAS study failed to demonstrate a significant association of the marker noted in the previous studies, and no associations between rare heterogeneous mutations of *CNTNAP2* and ASD were observed [29, 79]. However, a recent investigation revealed the possible involvement of novel functional variants of the 5'-promotor region, mediated by alterations in transcription-binding sites in subjects with ASD. *CNTNAP2* is still regarded as one of the potential causative genes of ASD that warrants further research [80].

These findings indicate the possibility that ASD might be caused by abnormalities in *synaptic plasticity*, as indicated by proteins that play essential roles in synaptic development and modification. There is evidence that NRXN (presynaptic) and NLGN (postsynaptic) interact as synaptic adhesion molecules, providing mechanistic support in synaptic formation and maintenance [81]. Alternate splicing of NLGN controls selective binding with α- and β-NRXN, provides synaptic diversity, and regulates function. Alternate splicing also controls the variable interaction of NRXN with other postsynaptic ligands, such as in glutamatergic, GABA-ergic, and cholinergic synapses [81, 82]. The SHANK family includes postsynaptic scaffolding proteins, which link multiple receptor signaling complexes and the actin cytoskeleton that are essential for maintaining synaptic function [83]. SHANK3 directly and indirectly binds to CNTN and NLGNs and interacts with presynaptic glutamatergic receptors [83, 84]. The molecular function of CNTNAP2 is relatively unclear, but it is known to encode a neuronal transmembrane protein member of the NRXN superfamily that is involved in neural–glia interactions and clustering of potassium channels in myelinated axons (http://www.omim.org/entry/604569).

Overall, despite of low frequency of *de novo* mutations in affected individuals, inconsistencies in genetic analysis results, and phenotypic heterogeneity, synapse-related genes are crucial candidates of ASD, and provide baseline evidence for testing compounds that can enhance synaptogenesis for the treatment of the core symptoms of ASD [25].

Genetic networks

For some of the identified genes, genetic pathways were identified at the cellular and molecular level based on genetic network analyses and genetic functional studies. Besides synaptic development and function mentioned in the previous section, protein synthesis and metabolism, modulation of transcription process, chromatin remodeling, calcium signaling, and mTOR and oxytocin pathways have also been implicated [85-87]. This suggests that genes involved in ASD might be related each other in several convergent functional units, especially in neuronal development, modulation, and intracellular transcriptional mechanisms. As more and more causative genes of ASD are identified, their interaction within the context of functional significance would be clarified. Molecular pathways possibly involved in pathogenesis of ASD are summarized in Fig. 1 [86].

Genes and brain circuits

Theoretically, ASD is an end-product of gene-environment interaction, mediated by changes in brain physiology, function, and morphology causing cognitive and behavioral dysfunction. Multiple brain areas involving facial recognition, emotion evaluation, empathy, mentalization, social cognition and behavior are known to be associated with ASD as part of the "social brain network" [88]. Alterations in brain connectivity and morphology might be a potential endophenotypes of ASD. However, not many human studies have explored associations between specific genetic variants and brain circuits or morphological phenotypes. One recent study examined phenotypic characteristics of subjects with ASD carrying germline heterogeneous PTEN mutations

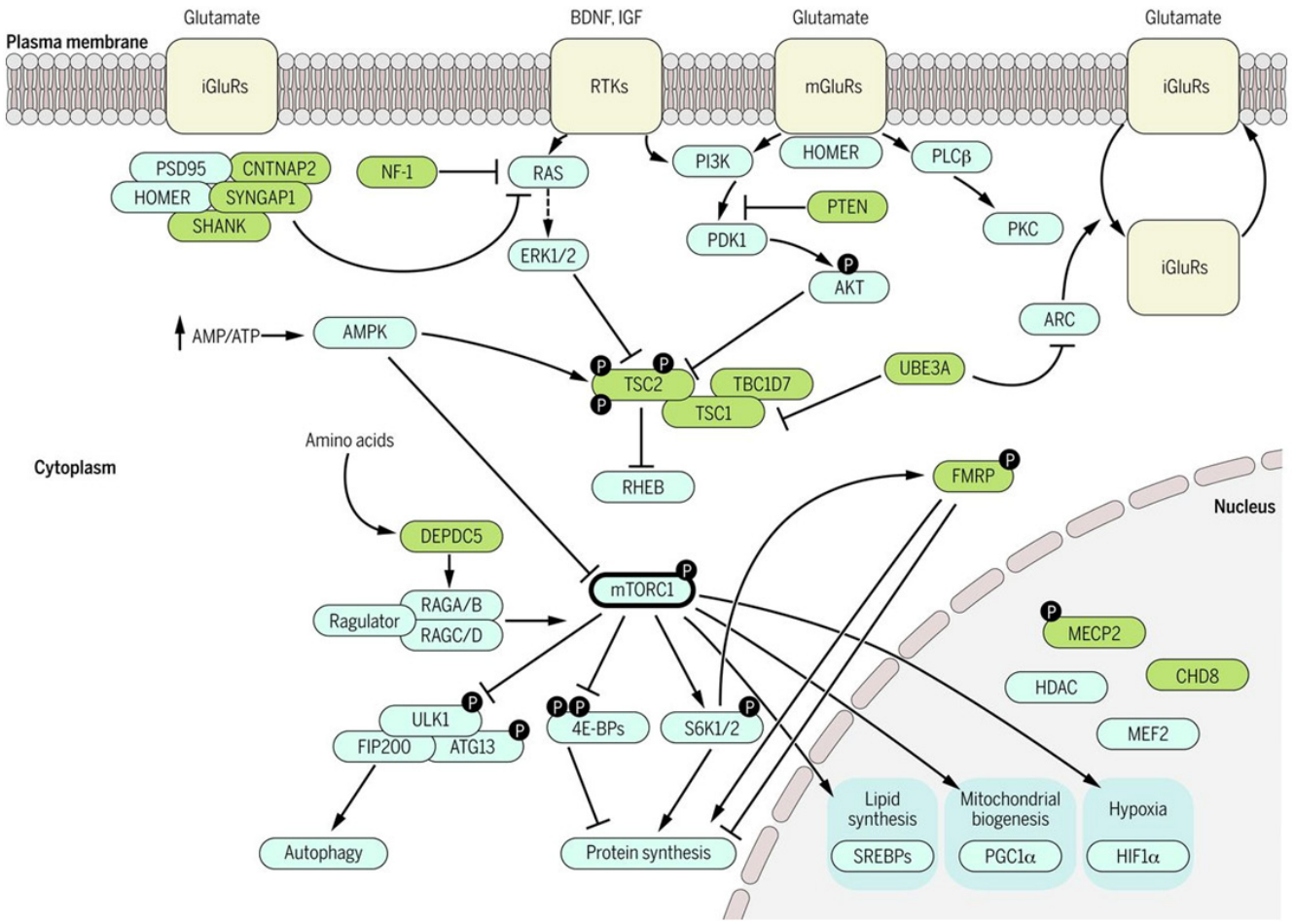

Fig. 1. Molecular pathways implicated in neurodevelopmental disorders. RTKs, receptor tyrosine kinases; iGluRs, metabotropic glutamate receptors; PGC-1α, peroxisome proliferator–activated receptor gamma coactivator 1-alpha; SREBP, sterol regulatory element–binding proteins; HIF1α, hypoxia–inducible factor 1 alpha; ULK1, unc-51–like kinase 1; ARC, activity-regulated cytoskeleton-associated protein; UBE3A, ubiquitin protein ligase E3A; MeCP2, methyl CpG binding protein 2; FMRP, fragile X mental retardation protein; PI3K/mTOR , phosphatidylinositol 3-kinase/mammalian target of rapamycin; PSD-95, postsynaptic density protein 95; CNTNAP2, Contactin-associated protein-like 2; NF1, neurofibromin 1; PLCβ, Abstract Phospholipase C β; SYNGAP1, Synaptic Ras GTPase-activating protein 1; ERK1/2, extracellular signal-regulated kinase; PTEN, Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; PDK1, Pyruvate dehydrogenase lipoamide kinase isozyme 1; PKC, Paroxysmal kinesogenic choreoathetosis, neurological disorder Protein kinase C; AKT, Protein kinase B; AMPK, AMP-activated protein kinase; TSC2, Tuberous Sclerosis Complex 2; TSC1, tuberous sclerosis 1; RHEB, GTP-binding protein Rheb; DEPDC5, DEP domain-containing 5; mTORC1, mammalian target of rapamycin complex 1; mGluR, metabotropic glutamate receptor; SHANK, Shank protein; ATG13, Autophagy-related protein 13; HDAC, Histone deacetylases; CHD8, Chromodomain-helicase-DNA-binding protein 8; MEF2, myocyte enhancer factor-2; RAS, Ras protein; TBC1D7, TBC1 domain family, Member 7; 4E-BPs, eIF4E-binding proteins; FIP200, a ULK-interacting protein; S6K1/2, Anti-RIBOSOMAL S6 KINASE 1/2; HOMER, homer scaffolding protein; RAGA/B, Ras-related GTP binding A/B ortholog; RAGC/D, Ras-related GTP binding C/D ortholog. From M. Sahin and M. Sur, Genes, circuits, and precision therapies for autism and related neurodevelopmental disorders, Science 350, aab3897 (2015). DOI: 10.1126/science.aab3897. Reprinted with permission from The American Association for the Advancement of Science (AAAS).

(PTEN-ASD); compared to subjects with idiopathic (non-PTEN) ASD and healthy controls, subjects with PTEN-ASD showed prominent cognitive dysfunction and white-matter abnormalities, mediated by reductions in the PTEN protein [89]. Moreover, significant differences in fMRI activation and deactivation patterns to social stimuli as well as functional and structural connectivity in the temporo-parietal region based on the existence of the rs1858830 MET risk allele (C/C) highlighted alterations in gene-brain pathway in ASD [14]. More data are necessary to understand the complex pathways connecting specific genetic mutation/genotype and brain changes, which have a direct impact on specific behavioral phenotypes of ASD.

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GENETICS USED FOR DIAGNOSIS AND THERAPEUTIC TARGETS: CLINICAL REALM

The ultimate goal of the evaluation of genetic etiology in complex disorders is the discovery of biomarkers for risk assessment, diagnosis, and prediction of therapeutic responses and prognoses, and the development of therapeutic components. The current best estimate diagnosis of ASD is based on behavioral observation and developmental history, assisted by standardized diagnostic instruments. While it is strongly suggested that early intervention in ASD can promote better prognoses, reduce secondary behavioral complications, and even induce normalization of brain activity [90], diagnostic confirmation before 2 years of age based only on the behavioral observations has limitations. Thus, the identification of genetic markers will provide useful information to aid in the early diagnosis of ASD in infants and begin early intervention.

However, the current status of genetic diagnoses of ASD is insufficient in clinical utility and precision for general applications. While known genetic causes are identified in 20–25% of ASD, each of those mutations/variants are rare and account for only 1–2% of the probands [6, 91, 92], which means there are no single predictable genetic markers for the development of ASD. As described previously, scientists believe that ASD is the product of the interplay between multiple common and rare genetic variants, and that genetic diagnosis should involve a combination of multiple genetic markers as a form of targeted gene panels. There have been attempts to make a gene set to diagnose ASD: for example, Skafidas et al. (2012) identified a group of SNPs selected by pathway analysis, and applied machine learning to the identified SNPs to generate a predictive classifier for ASD diagnosis. By applying 237 highly significant SNPs to three independent cohorts, there was a high level of diagnostic accuracy observed in genetically homogenous populations (84.3–85.6%), but not in an ethnically distinct cohort of Han Chinese (56%) [93]. Despite small sample sizes and the preliminary nature of the methodology, other researchers applied gene panels on subgroups of ASD and observed 75–90% accuracy in classification [94]. These studies may imply that development of a diagnosis based on genetic markers needs consider ethnic diversity and phenotypic heterogeneity. There are several gene panels offered by clinical molecular laboratories, but their clinical validity has not yet been fully evaluated [95]. In the future, next generation sequencing (NGS) is expected to produce a level of resolution down to the single base pair level and to enhance the assay precision level, but diagnostic validity should proceed so that the technology works in a clinically valid way [96].

In its current status, clinical value is primarily focused on the identification of known genetic causes of ASD. It is recommended that once a clinical diagnosis of ASD is made, genetic testing should be initiated [96]. This includes single-gene tests for monogenic causes of ASD, including fragile X syndrome, tuberous sclerosis complex, Rett syndrome, Angelman syndrome, Prader-Willi syndrome, phosphatase and tensin homolog (PTEN)-associated disorders, Noonan syndrome, cortical dysplasia-focal epilepsy syndrome (associated with *CNTNAP2*), and Phelan-McDermid syndrome, by detecting point mutations, microdeletions, duplications, and large repeat expansions using sequencing, fluorescence in situ hybridization (FISH), and Southern blotting technologies [95]. An assay for CNVs with array comparative genomic hybridization (aCGH) is also available for known variations of ASD [96]. At the clinical level, practice guidelines of the American College of Medical Genetics (ACMG) recommends a three generation family history with pedigree analyses; an initial evaluation for known syndromes associated with ASD, especially if the subject has dysmorphic features or specific clinical indicators; a chromosomal microarray; and DNA testing for fragile X for all male children suspected of an ASD as the first tier genetic evaluation. ACMG recommends sequencing and duplication testing for the *MECP2* gene in female patients, and *PTEN* testing for those with macrocephaly as second tier genetic testing [97, 98].

There are ethical considerations of the clinical use of genetic testing and counseling for ASD. First, it is important that biomarker discovery, especially commercialization of biomarker data in autism, does not result in children being given a biological label that fixes and defines their potential and treatment [99, 100]. Second, genetic biomarker results have a huge impact on parental decision-making toward reproduction; therefore, more research and communication is needed for a better understanding of parental needs and attitudes [100].

Pharmacological treatment of ASD is primarily focused on improving comorbid behavioral emotional symptoms, such as irritability, aggression, anxiety, tics, self-injurious behaviors, and epilepsy [101]. One of the ultimate goals of the discovery and validation of biomarkers is developing molecular therapeutics to treat the core symptoms of ASD, based on knowledge about disease modifying mechanisms. Identification of causative genes, especially from high-throughput methods such as NGS, is paving the way for developing pharmacological agents to treat the core symptoms of ASD, including abnormal reciprocal social interaction and communication. Several recent well-designed studies have modeled human genetic variants associated with ASD in mice, using *SHANK3*, *CNTNAP2*, *MECP2*, *UBE3A*, and

FMR1 genes, and are refining potential therapeutic mechanisms [78, 102-106]. These studies refine the function of genetic biomarkers of autism and relate them to behavioral phenotypes, and suggest potential target compounds for recovery of function. However, it is only the beginning of the discovery of therapeutic molecules for human subjects, covering the heterogeneity and complexity of the molecular pathways of autism.

A few empirical trials have begun for syndromic autism with well-known monogenic etiology, with hopes to expand the trial for idiopathic ASD. Tuberous sclerosis is one of the examples; the *TSC1* and *TSC2* genes encode proteins regulating the mTORC1 protein complex. mTOR plays an important role in protein synthesis, cell growth, and axon formation. mTOR inhibitors (including rapamycin and everolimus) are currently being tested for their effect on neurocognitive outcomes in children with tuberous sclerosis complex, with outcome measurements that include autism symptoms, cognition, language skills, and behavior [79, 107]. Also clinical trials using mechanism-based targeted treatment for Dup15q syndrome (duplication of 15q11.2-q13) and fragile X syndrome are also under way [37, 98, 107].

Oxytocin is neuromodulatory hormone involved in various social behaviors in humans and animals, including parents–offspring bonding, affection, social recognition, and social antagonism [17]. Although inconsistencies in genetic studies of *OXTR* in ASD, positive associations have been reported in multiple studies and across multiple ethnicities. Significant hypermethylation of critical sites of *OXTR* was observed in subjects with ASD and in the brother of a proband with *OXTR* deletion implicated epigenetic modification of the OXTR gene in ASD [26, 108, 109]. *OXTR* knock-out animal models show various characteristics of social behavior including parental nurturing, pair bonding, and social memory as well as brain changes in the limbic and paralimbic regions [110, 111]. Based on strong coherent evidence from human and animal studies across genetic, neural, and behavioral levels, oxytocin has been chosen as a pharmacological agent targeting core symptoms of ASD. A few randomized controlled trials have showed the efficacy of intravenous or nasal administration of oxytocin in core domains of ASD, such as social cognition and behavior. A few well-designed studies have reported enhanced performance in empathy tasks accompanied by increased anterior insula activity and coordination in the medical prefrontal cortex [112-114]. Although there are unmet limitations in the generalizability of subjects, establishment of dosage and route of administration, and maintenance of effect and safety in children, oxytocin might be a potential therapeutic agent for core symptoms of ASD with the most achievable clinical utility.

NGS IN ASD GENETICS

High-throughput technologies have facilitated gene discovery in ASD. The most recent development, NGS, which include whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted sequencing, promotes the precise identification of genetic variants at base-by-base levels. NGS promotes the identification of rare alleles to a degree not possible using genotyping platforms, and allows identification of single gene defects and partial variations of gene function [37, 115]. NGS in ASD is still emerging; it is useful to identify novel *de novo* variants not observed by conventional methods. Recent studies have confirmed *de novo* CNV loci in large-sized cohorts of idiopathic ASD families, observed new candidate loci, and confirmed *de novo* mutations in subjects with ASD and other neuropsychological abnormalities [58, 116-118]. Regarding diagnostic utility, one recent study reported complicated results that the diagnostic yield of WES is comparable to chromosomal microarray, while combined diagnostic yield is higher among children with more complex morphological phenotypes, emphasizing the importance of phenotypic classification [119].

Although NGS is not yet widespread due to its relatively high cost and the demand for techniques involving large-scale data and bioinformatics, it is predicted that large-scale investigations combining NGS technology and accumulated clinical data will facilitate the genetic study of ASD from diagnoses to targeted treatments in the future [5].

CONCLUSION

A wide range of genetic variation is involved in ASD, with interplays of gene–gene and gene–environment interactions. Both genotypic and phenotypic heterogeneity contribute to the difficulty in the thorough exploration and confirmation of causative genetic factors. However, recent technological developments, including NGS, and the accumulation of clinical information are bridging the gap in the application of genetic knowledge towards clinical practice.

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