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REVIEW

Investigation of Genetic Polymorphism in Autism Spectrum Disorder: a Pathogenesis of the Neurodevelopmental Disorder

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Abstract

Objectives Autism spectrum disorder (ASD) is a neurodevelopmental condition marked by stereotyped behavior and poor social interaction. Although the etiology of this illness is unknown, research clearly shows that it has a genetic foundation due to complicated inheritance. It affects about 52 million individuals worldwide. Several risk factors for autism converge into possible pathways for other neurodevelopmental diseases, with onsets occurring at various stages of development.

Methods In the study's literature review, the genes included were identified in articles published over the previous 30 years in databases such as the web of sciences, PubMed, Google Scholar, Embase, and other databases. Candidate genes associated with ASD are *CHD8*, *SHANK3*, *SLC6A4*, *RELN*, *DISC1*, and *ITGB3*.

Results Several prenatal risk factors cause neurological vulnerability, which increases the probability of autism and other neurodevelopmental problems. Genomic research has allowed tremendous progress in discovering ASD risk genes during the last decade. Recent technological advancements have demonstrated that certain genetic mutations and modifications may serve as useful biological markers, risk indicators, and therapeutic targets for illnesses.

Conclusions In large cohorts, high-throughput next-generation sequencing uncovers a varied and complicated genetic landscape of new risk genes. More studies are needed to understand better the environmental variables that play a crucial role in disease development. Currently, there is less clinical data to support the function of ASD. However, the prevailing research facts for many researched ASD new candidate genes support their links and identify ASD etiologic processes for establishing an early diagnostic marker.

Keywords Autism · Neurodevelopmental disease · Genetic polymorphism · Behavioral disorder · Neuronal injury

Autism spectrum disorders (ASDs) are a set of neurodevelopmental illnesses characterized by three primary behavioral impairments. Limited interests, repetitive activity, inability to participate in reciprocal social relationships, and language and communication difficulties are characteristics of behavioral disorders (Peça et al., 2011; Zoghbi and Bear, 2012). Individuals with ASD also show limited behavior patterns or interests, such as motor stereotypies, emphasis on sameness and routine inflexibility, and focused interests. In addition, it is common to have hypo- or hypersensitivity to sensory stimulation. ASD is frequently associated with neurological diseases such as epilepsy, schizophrenia, intellectual impairment, and clinical symptoms such as dysmorphic features, gastrointestinal issues, and sleep difficulties. Autistic behaviors can also be a symptom of genetic syndromes, such as monogenic diseases (e.g., Fragile X syndrome, Rett syndrome) or chromosomal abnormality-related syndromes (Betancur, 2011; Kohane et al., 2012). The Diagnostic and Statistical Manual of Mental Disorders (DSM) classifies diseases such as pervasive developmental disorder (PDD) as a category of its own. Using the DSM-Third Edition as a guideline, psychologists could now identify a more extensive range of social communication problems. Currently used diagnostic systems, such as the International Classification of Diseases 11th Revision (ICD-11) and the DSM of Mental disorders, utilize the term "ASD" and apply clinical modifiers to identify individuals (Lord et al., 2006; Risi et al., 2006). The diagnosis of autism spectrum disorder (ASD) typically

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involves conducting clinical assessments to identify the presence of core symptoms such as difficulties interacting with others, communication problems, and restricted interests and behaviors (Oh et al., 2021). Many children with ASDs have cognitive symptoms that range from severe intellectual disability and self-injury to excellent functioning, despite poor language use and social abilities, and above-average intelligence (IQ) (Baron-Cohen et al., 2001; Gillberg and Coleman, 2000). Despite the average IQ distribution being lower than usual because of autism, the likelihood of intellectual disbility increases as brain dysfunction becomes more widespread. It impairs a wide range of complex human skills and can be caused by several inherited and nongenetic factors (Rasmussen et al., 2001; Yeargin-Allsopp et al., 2003). ASD affects around one in every 68 persons, with a male to female ratio of three to four times higher than the general population (Brugha et al., 2018). There are less apparent correlations and hence falsely inflated prevalence estimates in population-level tests than in more general passive screening studies that look at administrative data (e.g., medical records) due to lower sex ratios (Brugha et al., 2018). Depending on the assessment methodologies employed and the definition, sample, and amount of impartial population case assessments in a complete study administration-based source assessment, estimates of autism superiority differ between communities and situations. According to the Global Burden of Disease research from 2010, there are 52 million autistic persons globally, or one in every 132 people (Baxter et al., 2015). However, given the available data sets, statistical power to identify any impacts was limited, particularly in low-income nations. According to some research, migrant populations have a higher incidence of autism; however, several apparent variables could lead to a higher prevalence of autism in the Afro-Caribbean community in countries with higher incomes without any indication of geographic variation in incidence (Elsabbagh et al., 2012; Magnusson et al., 2012).

While the cause of ASD is unknown, genetics has long been recognized as a risk factor (Sandin et al., 2017). Attention deficit hyperactivity disorder (ADHD), anxiety, depression, gastrointestinal issues, and sleep difficulties are common in children with ASD (Jokiranta-Olkoniemi et al., 2016). Many risk factors for autism have been found; they converge into causative pathways for other neurodevelopmental disorders, with onsets happening at various stages of development. Each factor is linked to autism in different studies, with varying degrees of consistency (Modabbernia et al., 2017). Each set of variables converges on a plausible causal mechanism shared with other developmental circumstances or strongly supported by animal models. Because of the temporal gap between their impact on prenatal development and a verified diagnosis starting at age 3, such processes are challenging to examine directly in autism (Emberti Gialloreti et al., 2019; Mandy and Lai, 2016).

Several perinatal risk factors increase the likelihood of autism and other neurodevelopmental disorders by causing neurological susceptibility. Hypoxic-ischemic damage, which causes inflammation, signaling pathway dysregulation, and neuronal damage and death, is one of the causative mechanisms arising from this collection of risk factors. In addition, some cases of autism have monogenetic origins, whereas others have disorders that influence prenatal or perinatal conditions, resulting in neurological susceptibility. Thus, autism can occur due to mutational or epigenetic changes interfering with brain development and functioning; autoimmune activation altering prenatal brain growth, neuronal death, or injury around the time of birth. Future studies may aid in identifying biological subtypes arising from diverse causal pathways, for which targeted treatments may be beneficial at different stages of development (Pellerin et al., 2018).

Autism is caused by genetic risk factors that alter early brain development and function, including synaptic transmission. Advanced paternal age is considered to raise the risk of autism by raising the rate of de novo mutations and epigenetic changes (Solek et al., 2018). It is also linked to immune system sensitivity in pregnant women, hypothesized to combine with genetic factors to enhance susceptibility. A family history of autoimmune illness, maternal infection during pregnancy, and maternal autoimmune disease is all known risk factors for autism (De Cossío et al., 2017).

Pathophysiology

Although the particular pathomechanism of ASD is unknown, several factors have been identified in the etiology of autistic diseases. In many cases, genetic factors are responsible for co-occurring and related diseases, including fragile X syndrome, Rett syndrome, and tuberous sclerosis (Shen et al., 2010; Silver and Rapin, 2012). Rare variant mutations and de novo copy number mutations influencing neuroanatomical and behavioral characteristics were identified in the individual or their related ancestors in animal models and human genetic research of ASD. In addition, researchers have detected dysregulation in synapse-related genes in these studies (Malhotra and Sebat, 2012; Zoghbi and Bear, 2012).

Structural abnormalities can cause ASD in several scaffolding proteins, synaptogenesis-related transmembrane, and dysregulation of genes involved in signal transduction and synaptogenesis. Because multiple genes have been discovered and their interactions have been discovered, epigenetic factors and environmental modifiers in ASD account for 25%

of patients with ASD despite genetic causes such as single gene defects, diagnosable medical conditions, and cytogenetic problems (Miles, 2011; Muhle et al., 2004).

According to Casanova et al. (2013; Casanova, 2014), the aberrant migration of daughter cells to their target areas is caused by the heterochronic division of germinal cells. There are smaller pyramidal neurons and interneurons in ASD patients' frontal lobes, which can be found in small clusters throughout their brains. Pathological anomalies have been associated with sensory and motor deficits, epileptic convulsions, and other symptoms of illness and disease. A recent link has also been made between the autism-epilepsy phenotype and the pathological condition known as rapid brain development in early childhood, which results in ASD (Casanova et al., 2013; Casanova, 2014).

Numerous studies have found that autistic people are more likely to suffer from gastrointestinal issues such as heartburn, nausea, vomiting, and gastroesophageal reflux disease. In a recent study, gastrointestinal (GI) issues were found to play a role in the etiology of this disease (Hsiao, 2014). Inflammation, inflammatory response, and immunological activation have all been linked to ASD's etiology (Singh, 2009). The blood–brain barrier (BBB) is essential for the proper functioning of the brain and for preventing disease. Evidence suggests that children with ASD may have impaired BBB function due to elevated inflammatory cytokines in the brain. Autistic people have aberrant immune responses in the gastrointestinal tract and other organs, peripheral circulation, and the brain (CNS) (Bjørklund et al., 2016). On the other hand, immunological abnormalities in children have been linked to infection or inflammation in the mother and autoimmune illnesses in families with ASD children (Bjørklund et al., 2016).

Genome-Wide Association Study (GWAS)

The Psychiatric Genomic Consortium's (PGC) current ASD GWAS meta-analysis shows how the genetic landscape of ASD has altered over the previous 10 years. PGC has put in much effort to increase the sample size to 10,000 cases and controls and develop well-defined quality control and imputation methods. Only 53 of the 93 genome-wide significant markers found in the most recent ASD GWAS meta-analysis were replicated in separate cohorts. rs910805 (chromosome 20) and rs10099100 (chromosome 8) were the most often related SNPs. On the other hand, GWAS data may be analyzed using a gene-based analysis (GBA) approach. Over the past decade, a growing number of single nucleotide polymorphisms (SNPs) and other forms of variation (e.g., copy number variations, rare structural variants) have been related to ASD in genome-wide association studies (GWAS) and genetic research (Grove et al., 2019).

Genetics of ASD

The genetics involved in autism is essential as they help us identify various genes, proteins, and signaling pathways found in ASD. The study of genes and genetic changes found in patients with ASD can help unravel the genetic architecture underlying ASD and aid in early diagnosis and clinical treatment. Many genes associated with ASD are found in circadian entrainment, which indicates a heterogeneous genetic etiology for ASD (Nisar et al., 2019). CNVs are found to be a source of autism risk. A study conducted on autism-affected families reported excess gene duplications and deletions in affected autistic individuals compared to the normal controls. Rare de novo and inherited events found in pathogenic CNVs involved genes associated with autism, such as CHD2, HDAC4, GDI1, SETD5, HDAC9, and MIR137. CNVs were highly penetrant in females with autism and individuals with X syndrome protein targets. It was also found that de novo CNV–affected genes converge on neuronal signaling and networks associated with synapses' functioning and chromatin regulation (Pinto et al., 2014). Many genes associated with ASD are found in circadian entrainment, which indicates a heterogeneous genetic etiology for ASD (Oron and Elliott, 2017). In large-scale genomic studies, hundreds of genes have been associated with autism. In epidemiological research, environmental variables have begun to be identified as potential risk factors, but much remains unclear about how they interact with a genetic predisposition to contribute to ASD etiology (Rylaarsdam and Guemez-Gamboa, 2019).

Genes Involved in ASD

A genetic predisposition to ASD may include one or more interrelated genetic networks, including neurogenesis, neuronal migration, synaptogenesis, axon pathfinding, and regionalization of neuronal or glial structure. Association studies that focus on the candidate genes are known as function-targeted studies (Gilbert and Man, 2017). Researchers have identified that the candidate genes that have been strongly associated with the ASD are *CHD8*, *SHANK3*, *SLC6A4*, *RELN*, *DISC1*, and *ITGB3* which are listed out in Table 1 (Cardoso and Almeida, 2019).

Chromodomain Helicase DNA–Binding Protein 8 (*CHD8*) Gene

The *CHD8* gene, found on chromosome 14 (14q11.2), encodes the *CHD8* protein, which has been related to autism. This protein regulates the Wnt signaling pathway by

Table 1 Genes associated with autism spectrum disorder

Gene symbol	Gene name	Location	Exon	Amino acid	Function	SNP	References
CHD-8	Chromodomain helicase DNA–binding protein-8	14q11.2	39	2581	By regulating beta-catenin activity, it acts as a negative regulator of the Wnt signaling pathway	c.4984C > T, p. Arg1662Ter	(Katayama et al., 2016; Alotaibi and Ramzan, 2020)
SHANK-3	SH3 and multiple ankyrin repeat domains 3	22q13.33	23	1731	Plays a role in the functioning of synapses, which are the connections between nerve cells where cell-to-cell communication occurs	rs9616915	(Mashayekhi et al., 2016)
SLC6A4	Human serotonin transporter	17q11.2	15	630	Plays an important function in regulating the availability of serotonin to other serotonergic receptors	c.86A > G(p. Asp29Gly), c.978 T > G (p.Asp326Glu), c.412G > A (p.Ala138Thr)	(Adamsen et al., 2014
RELN	Reelin	7q22.1	65	3460	Microtubule function in neurons and neuronal migration are regulated by this protein	g.504742G > A	(Tian, 2012)
DISC-1	DISC-1 scaffold protein	1q42.2	19	854	Neuronal proliferation, differentiation, migration, cAMP signaling, cytoskeletal modulation, and translational control are all mechanisms that regulate neural development and brain maturation via diverse signaling pathways	rs1322784	(Kilpinen et al., 2008)
GB-3	Integrin subunit beta 3	17q21.32	15	788	Provides instructions for making the beta3 subunit of a receptor protein called integrin alphaIIb/beta3	rs15908 rs12603582	(Schuch et al., 2014)

binding directly to β-catenin and inhibiting its transactivation activity. Thus, it is a potential regulator of WNT signaling, which is essential in development and morphogenesis (Thompson et al., 2008; Nishiyama et al., 2012). This gene is also required for transcription factor activation, regulating cell cycle progression and maturation. Abnormalities in the *CHD8* gene thus provide a distinct pathway in the formation of ASD, resulting in a distinct pathological state for ASD (Subtil-Rodríguez et al., 2014) (Fig. 1). During human brain development, *CHD8* interacts and controls the co-expression of other ASD–risk genes (Cotney et al., 2015). The RE-1 silencing transcription factor (REST), which suppresses the transcription of several neuro genes, is activated abnormally in *CHD8* haploinsufficiency. During whole-exome sequencing of a patient with ASD, a de novo heterozygous loss-of-function mutation in the *CHD8* gene (c.4984C > T, p. Arg1662Ter) was found (Katayama et al., 2016; Alotaibi and Ramzan, 2020).

SH3 and Multiple Ankyrin Repeat Domains 3 (*SHANK3*) Genes

SHANK3 is found on chromosome 22 (22q13.33) regions, essential for 22q13 deletion syndrome, including autistic behavior. *SHANK3* haploinsufficiency is thought to have a role in the 22q13 deletion syndrome (Wilson et al., 2003). It is mainly located in the cerebellum and cerebral cortex as a synaptic scaffolding protein. Thanks to its many protein interaction domains, this molecule interacts directly

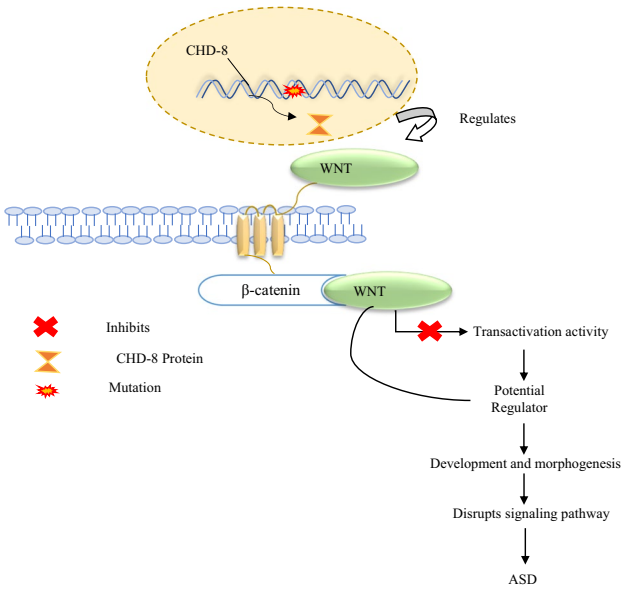

Fig. 1 Role of CHD-8 gene in ASD

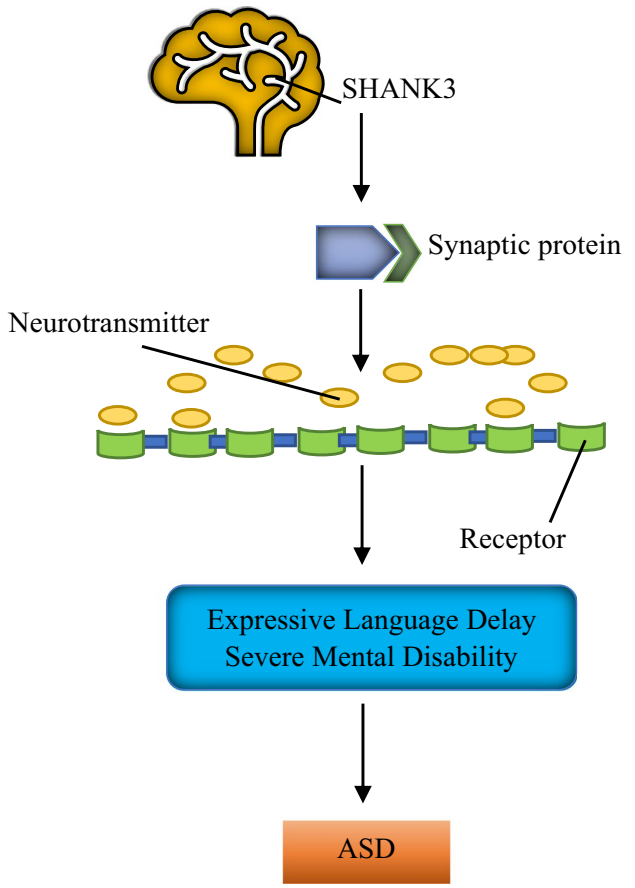

Fig. 2 *SHANK3* mechanism in ASD

with neurotransmitter receptors and cytoskeleton proteins. It also assists in forming functional synapses and the growth, maturation, and expansion of dendritic spines. As a result, the phenotype comprises expressive language delay, severe mental disability, and an autistic spectrum disorder, as illustrated in Fig. 2 (Proepper et al., 2007). This gene is very likely to be involved in the genesis of various ASD and 22q13 deletion syndrome symptoms, including delayed expressive speech. Furthermore, the clinical phenomenology of this syndrome is comparable to that of ASD (Wilson et al., 2008). A single nucleotide polymorphism (rs9616915) causes isoleucine to threonine substitution in exon 6, directly affecting *SHANK3* gene activity (Mashayekhi et al., 2016). Some investigations have revealed de novo changes in this gene and their implications in the etiology of autism Boeckers et al. (2005).

Human Serotonin Transporter (*SLC6A4*) Gene

This gene is located on chromosome 17 (17q11.2), which contains 14 exons of 35 kb each, with the first two exons transcribed alternately. The selective serotonin reuptake inhibitors (SSRIs) target the serotonin transporter gene, one of the critical modulators of serotonergic neurotransmission (Kim et al., 2002). Because of the effectiveness of serotonin transporter inhibitors and increased blood serotonin levels in some autistic patients, this gene was identified as a potential autism gene (Kim et al., 2002). In addition, the 5-HTTLPR (serotonin transporter-like promoter region) promoter insertion-deletion polymorphism, an intron two-variable nucleotide tandem repeat, and SNPs have all been linked to autism in several studies (Cantor et al., 2005; Sutcliffe et al., 2005). There were three heterozygous variants found in the *SLC29A4* gene by Adamsen and his colleagues: two patients had a c.86A > G mutation, five had a c.412G > A mutation, and one had a c.978 T > G mutation (p. Asp326Glu). Even though brain serotonin levels were low, the expression in cells of the mutations p. Ala138Thr and p. Asp326Glu significantly reduced serotonin and dopamine transport, associating these mutations to ASD. Furthermore, as a result of this protein defect, serotonin levels rise in the womb, inhibiting the growth of serotonin networks and the production of local serotonin (Adamsen et al., 2014)

Reelin (*RELN*) Gene

The human *RELN* gene, located on chromosome 7(7q22.1), codes for a protein that aids in cell migration and the formation of neural connections, which has been studied as a potential candidate gene for autism (Bartlett et al., 2005).

To control neuron migration, lamination, and connection throughout embryonic brain development, it encodes a serine protease-active extracellular matrix glycoprotein that acts as a signaling protein. It is most abundant in the brain, but it may also be found in the blood, spinal cord, and other organs and tissues throughout the body (He et al., 2011). According to previous research, frequent mutations in the *RELN* gene might be utilized to predict autism risk, as shown in Fig. 3. Many *RELN* gene SNPs have been linked to autism (Rice and Curran, 2001). Low levels of *RELN* protein and mRNA in various parts of the brain are linked to various neurogenetic illnesses, including schizophrenia and bipolar disorder. The following genetic alterations are noteworthy: To increase the number of GGC haplotypes, two nucleotides in one exon must be replaced (Skaar et al., 2005). According to Tian (2012), the g.504742G > A polymorphism in exon60 of the *RELN* gene has been linked to autism (Tian, 2012).

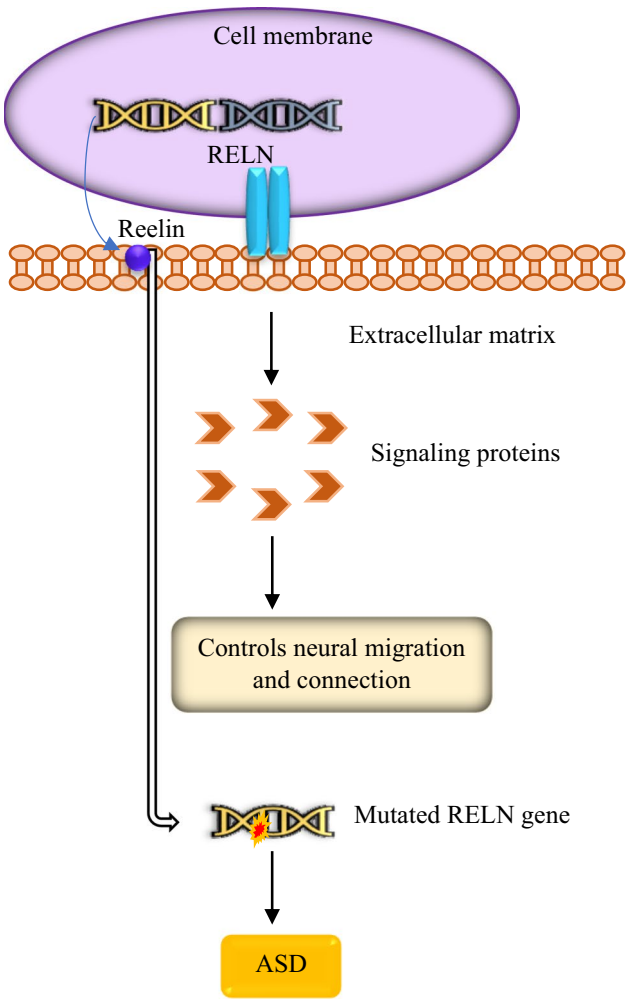

Fig. 3 Role of RELN gene in ASD

DISC1 Scaffold Protein (*DISC1*) Gene

DISC1 gene is located in chromosome 1 (1q42.2) region, which also contains the TRAX (Translin-associated factor X) and *DISC2* genes, which control the expression of the *DISC1* gene (Millar et al., 2001). This gene encodes a *DISC1* protein involved in neuronal migration and development; synaptogenesis; glutamatergic neurotransmission, one of the most common synaptic modifying molecular processes in the CNS; and cAMP signal transduction (Austin et al., 2003). Millar et al. (2005) proposed that *DISC1* abnormal expression regulation was directly related to the mental disorders reported in translocation carriers. These SNPs have been related to schizophrenia, bipolar illness, major depression, autism, and Asperger syndrome (Millar et al., 2005). Research suggests that there is a link between autism and a variant of the *DISC1* intragenic microsatellite (D1S2709). Rs1322784, a single nucleotide change in the *DISC1* gene, has also been linked to ASD in males (Kilpinen et al., 2008).

Integrin Subunit Beta 3 (*ITGB3*) Gene

This gene codes for β-integrin 3 and is found on chromosome 17 (17q21.32). This protein is found on the surface of cells, particularly platelets. Integrins have a role in cell adhesion, metabolism, and serotonin neurotransmission (5-HT). Integrin receptors have demonstrated that they play a crucial function in signaling by influencing transcription and translation (Napolioni et al., 2011). The presence of an SNP in the *ITGB3* gene's 5' terminal is strongly associated with increased plasma levels of 5-HT, a frequent autistic characteristic (Weiss et al., 2006). Cross et al. (2008) has found interactions between allelic variants of the *ITGB3* gene and the 5-HT transporter gene (Cross et al., 2008). According to the findings, the rs15908 and rs12603582 polymorphisms are associated with several ASD symptoms, including echolalia, seizures, and aggressivity (Schuch et al., 2014).

Contactin-Associated Protein 2 (*CNTNAP2*) Gene

The *CNTNAP2* gene, which is 2.4 megabytes in size and includes 24 exons, is found on chromosome 7q35-q36.1; encodes CASPR2, a transmembrane scaffolding protein that clusters voltage-gated potassium channels at the Nodes of Ranvier; and is only expressed in neurons. It is present in myelinated axons near potassium channels and vital in synaptic plasticity. It generates the CAM protein, which regulates neuronal signaling and large neurons that impact language and development. It significantly impacts

how persons with autism develop their "linguistic skills." It is a component of a cortical–striatal–thalamic circuit that is engaged in a variety of higher-order cognitive functions (Agarwala and Ramachandra, 2021). In the past, SNP clusters in intronic regions have been linked to communicative behavioral problems in healthy adults. The presence of genetic variation at this locus suggests that it may be involved in linguistic endophenotypes (Rodenas-Cuadrado et al., 2014). *CNTNAP2* has been linked to significant autistic symptoms and speech and language difficulties (Peñagarikano and Geschwind, 2012). ASD and related features have been linked to *CNTNAP2* SNPs rs7794745, rs2710102. *CNTNAP2* rs7794745 has been linked to ASD in several studies, including people of various ethnic backgrounds. Rs7794745 has been related to ASD (Khalid et al., 2020), according to recent studies in the Pakistani population.

Neurexin (*NRXN1*) Gene

NRXN1, which has 22 exons, 1477 amino acids, and 7505 base pairs and is situated on chromosome 2p16.3, is a well-known risk gene for neurodevelopmental illnesses (Bourgeron, 2015). Rare exonic deletions overlapping *NRXN1* have initially been discovered in people with ASD (Szatmari et al., 2007) and intellectual disability (ID) Zahir et al. (2008). Biallelic mutations in *NRXN1* produce Pitt-Hopkins–like syndrome-2, a rare autosomal recessive ID syndrome (Harrison et al., 2011). Rare exonic *NRXN1* deletions are responsible for around 0.2% of ID, ASD, and SCZ cases (Lowther et al., 2017). Small and substantial deletions in the *NRXN1* gene may have a role in the development of ASD. Furthermore, missense and nonsense mutations in the *NRXN1* gene might have a role in the disease's pathogenesis (Feng et al., 2006). The NRXN2 rs12273892 polymorphism's T allele and AT genotype have been linked to an increased risk of ASD (Wang, 2018).

Homeobox A 1 (*HOXA1*) Gene

HOXA1 is a paralogous gene in the *HOX* gene family of homeobox transcription factors involved in developing the hindbrain during neural tube formation; it is found on chromosome 7p (Song et al., 2011). The homeobox gene *HOXA1* (homeobox A1) comprises the development of structures in the hindbrain. Several lines of indirect evidence point to *HOXA1* malfunction as a probable factor in autism (Collins et al., 2003). A218G is a *HOXA1* gene variation that replaces one histidine in a sequence of histidine repeats with an arginine codon (H73R). According to Ingram et al., several *HOX* genes, particularly *HOXA1*, may have a role in autism susceptibility (Ingram et al., 2000). *HOXA1* polymorphism has been found to increase the head growth rate in autistic children (Hashem et al., 2020).

MET Proto-Oncogene, Receptor Tyrosine Kinase (*MET*) Gene

The human gene *MET* proto-oncogene hepatocyte growth factor receptor is situated on chromosome 7q21.3-7q34. It is a 126-kb gene that encodes a high-affinity transmembrane receptor tyrosine kinase for hepatocyte growth factor/scatter factor (HGF/SF). It stimulates epithelial cell mitogenesis, morphogenesis, invasion, and motility. It is generated by mesenchymal cells. *MET* and its ligand are present in many organs; however, they are predominantly expressed in mesenchymal and epithelial cells. The *MET* promoter polymorphism rs1858830 C allele has been related to the ASD–associated maternal antibodies to embryonic brain proteins (Sousa et al., 2009). It is a well-known risk factor for ASD, a highly heritable mental condition marked by abnormal brain connectivity ontogeny (Geschwind and Levitt, 2007). The human *MET* gene's rs1858830 'C' allele, which inhibits *MET* transcription and translation, has been related to an increased risk of ASD (Campbell et al., 2007). Furthermore, FOXP2 and MeCP2, both connected to the establishment of ASD–related circuits in humans (Konopka et al., 2009), may modulate human *MET* gene transcription.

Biological Pathways

A study incorporating the identification of novel candidate genes in ASD–associated pathways identified many deletions and gene disruptions in a substantial proportion of ASD patients. Many ASD genes are related by a mechanism that governs neuronal and synaptic homeostasis. A single copy mutation, for example, causes social impairment and communication problems in ASD patients. Many mutations have been discovered in CHD8, an ATP–dependent chromodomain helicase that regulates the CTNNB1 and p53 pathways (Nishiyama et al., 2012). Using whole-genome analysis of mRNA levels and CNVs to detect aberrant brain gene expression patterns in autistic brains, researchers discovered that the adenosine A2A receptor-signaling pathway was substantially dysregulated in young autistic people (Chow et al., 2012). In addition, researchers discovered unusual and harmful variations in the SHANK3, TSC1, and TSC2 genes in non-syndromic autistic people during an ASD inquiry that revealed distinct changes in the mGLUR signaling pathway (Kelleher et al., 2012). Differences in fMRI activation and

deactivation patterns in response to social stimuli and structural and functional connectivity in the temporal-parietal region of the brain in ASD patients indicated abnormalities in the gene-brain pathway depending on the rs1858830 MET risk allele (Rudie et al., 2012). The protein–protein interaction (PPIs) network is the foundation for cellular signaling circuitry, which directs cellular responses to environmental and genetic inputs. Understanding how ASD–related quantitative aspects affect fetal and adult cortex PPIs could lead to identifying pathways that regulate cortical development and ASD risk (Golovina et al., 2021).

Future Prospective

Autism is a disorder caused by the environment when it was first identified. It has been revealed to be a highly complex and complicated genetic disorder due to decades of study. Epigenetics, sex-linked modifiers, CNVs, double-hit mutations, and environmental influences are examples of such modifiers. Many decades of study may be required before the scientific community has a solid understanding of how these modulators contribute to the development of ASD. A simplified genetic testing methodology, such as a microarray with known risk loci, might be a quick and low-cost way to determine what is causing the problem. More research is needed, but it will ultimately lead to a better understanding of how causal genetic components and disease modifiers interact to create ASD (Rylaarsdam and Guemez-Gamboa, 2019). Neuroimaging markers that may predict the diagnosis of ASD in the early presymptomatic stage have been established in both functional and anatomic neuroimaging investigations (Emerson et al., 2017). Young children with ASD do not respond to socially significant point-light displays of biological motion or other socially meaningful stimuli like normal children do. A proposed early behavioral biomarker of ASD is aberrant early visual attention to socially essential items (Klin et al., 2015). Biomarkers have the potential to help identify people who are at risk of developing ASD before diagnostic behaviors emerge. Maternal–fetal brain autoantibodies seem to be the most promising prenatal biomarker, with high specificity for offspring developing ASD. Although postnatal pre-symptomatic neuroimaging indications are promising, further research is required to confirm their usefulness. Individuals' responses to ASD therapy vary greatly; therefore, biomarkers that predict treatment response might help improve personalized treatment regimens and end in a specialized precision medicine approach (Frye et al., 2019).

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RV designed the study, corrected, and approved the manuscript for submission (rkgenes@gmail.com).

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