Clinical Neurology and Neuroscience
2024, Vol. 8, No. 4, pp. 47-53
https://doi.org/10.11648/j.cnn.20240804.11

Research Article

Effect of Genetics on Autism Spectrum Disorders: A Review Study

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Abstract

Autism Spectrum Disorders (ASD) are intricate neurodevelopmental conditions marked by challenges in social interaction, communication, and repetitive behaviors. The etiology of ASD is multifaceted, involving genetic mutations, perinatal, nutritional and environmental factors. This review explores the various genetic mutations implicated in the development of ASD for the purpose of examining the diverse genetic factors contributing to the pathogenesis of ASD such as SHANK3, SCGN, ADNP, ARID1B, CHD8, DYRK1A, KMT2C, OT, AVP and zinc transporter genes. A comprehensive review of literature was conducted to gather information on genetic influences related to ASD. Studies investigating the complex interplay of those factors were analyzed to elucidate how they contribute to the development of ASD. Results found that genetic mutations in genes like Shank3 and SCGN have been identified as playing a role in the pathogenesis of ASD through their impact on glutamic excitatory pathways and oxytocin signaling. ADNP, ARID1B, CHD8, DYRK1A, KMT2C, OT, AVP and zinc transporter genes have also been linked to an increased risk of ASD and associated cognitive and neurological impairments. In conclusion, research on different genetic mutations and deletions affecting autism spectrum disorder (ASD) highlights the complexity of the disease. Key genes such as SHANK3, SCGN, ADNP, ARID1B, CHD8, DYRK1A, and KMT2C are implicated, each contributing uniquely to ASD. Genetic variations, mutations, and heritability play significant roles, with factors like zinc deficiency and advanced paternal age also linked to increased ASD risk. While genomic technology has identified specific markers and pathways, the effect of multiple genetic mutations on symptom severity remains unclear. Understanding these genetic factors is crucial for improving diagnostic precision and developing targeted therapies, necessitating continued interdisciplinary research.

Keywords

ASD, SHANK3, SGGN, ADNP, ARID1B, CHD8, DYRK1A, KMT2C

1. Introduction

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental conditions defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as challenges in social communication and interaction, restricted interests and repetitive behaviors. ASD can be diagnosed at any age, but symptoms usually start manifesting during early childhood. Therefore, early diagnosis of ASD might be associated with better prognosis for an individual. While no cure for ASD is found to date, family education is important for a better quality of life and adaptation with the

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Received: 18 October 2024; **Accepted:** 4 November 2024; **Published:** 26 November 2024

disease. Treatment modalities for the child such as behavioral therapies, speech and language therapy and occupational therapies are also important. [1] The purpose of this paper is to review and synthesize current knowledge regarding the genetic factors associated with ASD. By exploring these genetic underpinnings, this research aims to enhance our understanding of the biological mechanisms driving ASD and to identify potential avenues for targeted interventions. The significance of this research lies in its potential to bridge gaps in our understanding of ASD's complex genetic landscape. Insights gained from this study could pave the way for more accurate diagnostic tools and personalized therapeutic approaches, ultimately improving outcomes for individuals with ASD. As the field continues to evolve, interdisciplinary research efforts will be crucial in unraveling the intricate relationship between genetic predisposition and neurodevelopment, fostering better support for individuals on the autism spectrum.

2. Genetic Factors

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition influenced by a myriad of genetic factors. Research has identified numerous genes implicated in ASD, contributing to its heterogeneous nature. From synaptic communication regulators to genes involved in neuronal development, these genetic variations offer crucial insights into the underlying mechanisms of ASD. [2]

2.1. SHANK3 Gene Deletion/Mutation

SHANK3 is a scaffolding protein that helps bind glutamate excitatory neurotransmittor to postsynaptic terminal in the brain. Therefore, deletion of the protein will lead to the loss of excitatory synapse and the underactivation of those receptors. This deletion is thought to contribute to some of the characteristics of ASD patients. [3]

Peça et al. studied Shank3 homozygous mutant mice which displayed autistic like behavior. SHANK3 deletion demonstrated social interaction deficits which is the main recognizable symptom in people with ASD. [4]

Guo et al. also found evidence that SHANK3 gene mutation in the anterior cingulate cortex (ACC) lead to the loss of dendritic spines and impairment of the synaptic excitatory pathway in the ACC region of the brain resulting in the underactivity of the area which results in the social interaction deficits seen in patients with ASD. [5]

Zhou et al. studied the relation of SHANK3 genes to ASD symptoms in monkeys. They used the CRISPR-Cas9 technology to produce mutations in SHANK3 genes in macaques monkeys and their first generation offspring. Their results showed that mutations in the genes altered brain circuit connectivity exhibiting sleeping disturbances, motor deficits, social and learning impairments as well as repetitive behaviors all typical symptoms of ASD. In addition, Zhou et al. also demonstrated that SHANK3 mutant macaques demonstrated reduced overall activity on actigraphy compared to controls. They also demonstrate longer sleep latency and increased awakening both indicating reduced efficiency of sleep a symptom in ASD patients. [6]

Malara et al. found that mutations in the SHANK3 gene leads to myelination in the central and peripheral nervous system contributing to Phelan-McDermid Syndrome (PMDS), a subset of ASD. Patients with PMDS have mutations in chromosome 22 and exhibits autistic like behavior in addition to chewing of non-food items, decreased perception of pain and regression of skills. They found SHANK3 gene expression in oligodendrocytes and schwann cells responsible for myelination in the nervous system. Magnetic resonance imaging revealed that SHANK3 mutant mice showed reduced volume in the corpus callosum as seen in PMDS patients. They also observed alteration in the number and maturation of myelin related cells in the nervous system in SHANK3 mutant mice. All these changes contributed to the symptoms found in PMDS patients. [7]

Vyas et al. found an interesting relationship between the SHANK3 mutation and zinc. They found that SHANK3 mutations caused a decrease in synaptic density and excitatory neurotransmission as mentioned earlier. However, the interesting part of the research is the prevention of structural and functional deficits in SHANK3 deleted genes with in vitro zinc supplementation. Thus, zinc supplementation has been indicated as a potential therapy in those patients. This in turn also explains why mutation in some zinc transporter genes mentioned below have been implicated in ASD. [8]

2.2. Secretagogin Gene (SCGN) Deletion

Liu and colleagues conduced a cohort study using whole exome sequencing of ASD bands on 168 children and their parents. Individuals were recruited based on diagnosis of ASD by Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC). Among 168 participants two male patients were identified to carry heterozygous mutation in the SCGN gene both inherited from their mothers. This mutation altered the 5' intron splicing at the site following exon 10 resulting in protein degradation and loss of function. These participants presented with autistic like behavior such as defects in communication, social interaction, and developmental delay. [9] They also examined oxytocin levels in brains of children with ASD and healthy volunteers and found that in healthy control oxytocin levels ranged from 24-47 pg/ml compared to ASD diagnosed patients with levels approximating 13-19 pg/ml. [10]

Another article by Liu et al. found that Secretagogin gene (SCGN) deficiency is another risk factor for ASD. SCGN is a gene that regulates synaptic transmission of oxytocin. Deletion of SCGN in zebrafish and mice models showed disruption of oxytocin signaling at the synaptic cleft causing inflammation. The consequence of this is the development of

autistic like behavior and an impairment of brain development. [11]

Liu et al. then used the CRISPR/Cas9 editing tool to generate animal models with SCGN deletion to study the effect on Zebrafish behavior. In a swimming test, homozygous SCGN rich zebrafish (SCGN+/+) were found to prefer swimming shorter distances compared to both homozygous and heterozygous SCGN deficient zebrafish (SCGN -/- and SCGN +/-). In another test, two Zebrafish were placed on one side of a plastic board and a single animal of SCGN+/+, SCGN -/- and SCGN +/- was placed on the other side of the board. SCGN+/+ exhibited higher tendency to move towards the group of two zebrafish than either SCGN -/- and SCGN +/- thus establishing the effect of gene deletion on social interaction and grouping preference seen in ASD patients. The amount of time interacting with others spent by each zebrafish in a visually mediated social preference test conducted by the researchers was found at 63.1%, 8.2% and 6.1% of the time for each of SCGN+/+, SCGN +/- and SCGN -/- respectively. [12]

Finally, researchers continued their study to see the effect on brain development of those knockout animals. Their results showed that 25% of the SCGN +/- and 37% of SCGN -/- were microcephalic compared to 2% of SCGN +/+ zebrafish. They also used cell proliferation marker pHH3 and found that homozygous SCGN depleted Zebrafish displayed a one-third reduction of pHH3 levels and hence reduced cell proliferation compared to SCGN +/+ models. PCR technique was also conducted on the hypothalamus of SCGN +/+ and SCGN -/- zebrafish animals. This test established that SCGN deficiency results in up-regulation of pro-inflammatory cytokines IL-6 and TNF as well as a disruption in oxytocin pathway related genes such as Oxt, Ppp3cb and Plcb3 produced by the hypothalamus. Oxytocin related genes were found decreased by 31% in SCGN deficient zebrafish. [11]

2.3. ADNP Gene Mutation

The activity dependent neuroprotector homeobox (ADNP) gene, essential for brain formation, has been associated with increased risk of ASD. Within 116 participants, Arnett et al. found that mutations in the ADNP gene led to disruptions in intellectual disability compared to controls. In addition, mutations in the gene has been associated with social impairment as well as restricted and repetitive behaviors seen in ASD patients. [13]

More specifically, the ADNP gene mutation has been shown to particularly mimic the autism-like ADNP syndrome. This syndrome is characterized by developmental delay, intellectual disability, speech impairments, motor dysfunction and autism. It is caused by mutations in ADNP gene which is involved in chromatin regulation and DNA methylation. [14] Sragovich et al. developed ADNP mutant mice which exhibited the same symptoms as autism-like ADNP syndrome in humans. Their mice displayed the same defect in synaptic density and gene expression patterns as well as characteristics of ADNP syndrome such as developmental, motor and cognitive delays. [15]

2.4. ARID1B Gene Mutation

AT-Rich Interaction Domain 1B (ARID1B) gene has been shown to modulate bone growth via the regulation of Wnt/B-catenin pathway leading to growth and development. Mutations in such gene has been associated with intellectual disability and ASD. [16] Moffat et al. used ARID1B gene knockout mice to determine its association with ASD. Their results showed that mutation in the gene resulted in decreased cell proliferation in the cortical and ventral neural cells as well as alteration in cell cycle regulation and increased cell death. Therefore, gene mutation has been shown to affect neurogenesis and the inhibitory progenitor cells with effects leading to typical manifestations of ASD. Therefore, Understanding the role of ARID1B in neural function and growth regulation sheds light on the pathogenesis of ASD and provides insights for potential therapeutic interventions. [17]

Smith et al. produced mutations were one allele of the ARID1B gene was deleted either in the parvalbumin or somatostatin interneurons to examine symptoms of ASD and intellectual disability. ARID1B deletion in the parvalbumin interneuron (PV) resulted in ASD symptoms of social and emotional impairments, while deletion in the somatostatin interneurons (SST) caused stereotypical behaviors, learning and memory deficits. These findings indicate importance of the ARID1B gene in the PV and SST interneurons and its relation to phenotypic characteristics of ASD patients. [18]

2.5. CHD8 Gene Mutation

Chromodomain helicase DNA-binding 8 (CHD8) gene has been associated with risk of ASD. The gene mutation has been found to disrupt inhibitory and excitatory neurons leading to developmental alterations which mimic ASD symptoms. [19] Shi et al. generated two embryonic stem cells with CHD8 loss of function mutation and examined the effect. Electrophysiological studies revealed a 3-fold decrease in neuronal firing and synaptic activity because of this mutation. There was also a large effect on chromatin structure especially near a transcription regulator implicated in ASD known as autism susceptibility candidate 2 (AUTS2). These mutations resulted in intellectual disability and symptoms of ASD compared to healthy control. [20]

Kerschbamer et al. results showed that suppression of CHD8 gene altered histone maintenance and RNA processing, important regulatory processes in ASD. They studied the effect of CHD8 suppression on histone modification by analyzing pluripotent neural progenitor stem cells. CHD8 suppression led to 47.82% reduction in histone expression impacting transcription factors and alteration in splicing

mechanism of genes involved in RNA processing. This alteration in transcription mechanisms and histone expression are factors that contribute to increased risk of ASD. [21]

While another study by Li et al. used the CRISPR-Cas9 technology to show how CHD8 gene mutations cause an enlargement in brain size also known as macrocephaly in non-human primates. Mutations in CHD8 gene in monkeys led to increased number of glial cells and gliogenesis resulting in macrocephaly, a phenotypic feature of some ASD patients and contributed to other symptoms of the disease. [22]

Ellingford et al. studied the effect of CHD8 gene on ASD-associated cortical circuits by studying synaptic transmission in prefrontal cortex in CHD8 mutated mouse model. They report alteration in excitatory and inhibitory synaptic transmission associated with disruption of homeostatic plasticity mechanisms and ASD-relevant circuits in the cortex. [23]

2.6. DYRK1A Gene Mutation

Dual-specificity tyrosine phosphorylation-regulated kinase 1 (DYRK1) is a gene that was found to be disrupted in ASD patients which exhibits phenotypic features of the disease. Mutations in one allele of the DYRK1A gene resulted in intellectual disabilities and speech difficulties. Earl et al. found that 89% of patients with DYRK1A mutations presented with at least five autistic like symptoms. [24]

Raveau et al. developed frameshift mutations in the gene in mouse models resulting in elimination of its kinase activity. Those mice models demonstrated impairments in cognition, communication and social interaction like in ASD patients. [25]

2.7. KMT2C Gene Mutation

Lysine N-methyltransferase 2C (KMT2C) is an enzyme involved in histone modification. Brauer et al. used CRISPR/Cas9 gene editing tool to study the effect of KMT2C gene knockout in mouse model. Those knockout animals exhibited ASD related symptoms such as repititive behavior, social deficits and intellectual disability. [26]

2.8. Oxytocin and Vasopressin Receptors

Studies have found an association between oxytocin (OT) and vasopressin (AVP) receptors genes and ASD phenotype. Single nucleotide polymorphisms in AVPR1 and OXTR receptors were genotyped in families with ASD. Mutations in those receptors was associated with social withdrawal and repititive behaviors related to ASD. [27]

In addition, genetic polymorphism in the AVPR1A promotor region has been identified to be associated with social deficits in autistic children. [28]

2.9. Zinc Transporter Genes Mutation/Deletion

In another study a group of 0-3 years old male and female patients with autism there was a total zinc reduction of 43.5% and 52.5%, respectively. This deficiency contributes to neuropsychological symptoms of autism and learning impairment by affecting glutamate excitatory effect on the synapse. Toxic levels of glutamate are also associated with seizures, thus why some patients with Autism suffer from epilepsy. [29]

Yoo et al. suggested that zinc transporter 3 (ZnT3) deletion during early brain development may contribute to ASD. Their results found that at 4-5 weeks of age, male mice with ZnT3 deletion demonstrated autistic like behavior as well as increased cortical volume and neuronal density. [30]

2.10. Neuroglinin-3 (NLGN3) Gene

An interesting journal published by Camasio et al. linked neuroanatomical abnormalities with genes associated with autism. Researchers found that decreased grey matter volume was associated with autistic related genes in areas responsible for dorsal attention and cerebellar network. In addition, increased grey matter volume was associated with genes located in the somatomotor, limbic and thalamic systems. The most significantly correlated gene found was Neuroligin-3 (NLGN3), associated with both decrease and increase in grey matter volume. The NLGN3 is a cell adhesion protein important in neuronal synaptic signalling pathway. This gene has been previously found to be associated with autism. [31] A study by Gutierrez et al. found that ASD caused mutations in the Neuroligin-3 (NLGN3) gene which causes decreased synchronicity and signalling between different brain regions which in turn causes decreased neuronal connectivity. [32] Other genes associated include the SHANK3 gene involved in neural signalling spoken of earlier. [31]

3. Genetic Imprinting and Hypomethylation

Advanced paternal age

Reichenberg et al. found an association between advanced paternal age and risk of Autism in offspring. Their results suggest that men over the age of 40 are 5.75 times more likely to have children born with ASD than men under the age of 30 years. The cause of this finding is likely due to de novo mutations and genetic imprinting that occur with advanced paternal age. Genetic imprinting is the expression of either maternal or paternal allele. When the imprinted gene expressed is of paternal origin, the maternal gene is silenced, i.e. not expressed and vice versa. [33]

Atsem et al. studied the role of demethylation in certain genes found in Autism. In their study methylation process of two alleles FOXK1 and KCNA7 in sperm samples of 25-35 years old and 40-55 years old. FOXK1 is a transcription reg-

ulator and KCNA7 is a gene that codes for potassium channel. Their results showed that sperm of older men displayed reduced methylation and a tendency towards hypomethylation compared to younger sperm. [34]

The journal of neuroscience published a paper by Foldi et al. that also studied the effect of advanced paternal age on Autism. They compared mice of 12-18 month old with 4 month old controls through behavioral testing and neuroanatomy. Overall, their older mice showed a phenotype characteristic of Autism such as increased anxiety and exploration tendency and decreased learning compared to controls. Their older mice also showed a thinner cortex at birth and increased cortical volume as adults, both characteristics of autistic brain. [35]

4. Conclusion

In conclusion, the study of genetic factors associated with autism spectrum disorder (ASD) underscores the complexity and diversity of its etiology. While significant progress has been made in understanding various aspects of ASD, much remains to be elucidated. Research has highlighted the significant role of genetic variations, mutations, and heritability in predisposing individuals to ASD. The studies reviewed highlight various genes such as SHANK3, SCGN, ADNP, ARID1B, CHD8, DYRK1A, KMT2C, and others, each contributing uniquely to the complex genetic landscape of ASD. Furthermore, studies on zinc transporter genes underscore the importance of micronutrient regulation in neuronal function, implicating zinc deficiency in ASD-related cognitive impairments and epilepsy. Additionally, genetic imprinting and hypomethylation processes have been linked to increased ASD risk, particularly with advanced paternal age. Overall, these findings underscore the intricate interplay between genetic predisposition and neurological development in ASD. While advances in genomic technology have facilitated the identification of specific genetic markers and pathways linked to ASD, the role of acquiring multiple genetic mutations in one individual and its effect on symptom severity remains unclear. Understanding these genetic factors not only enhances diagnostic precision but also holds promise for the development of targeted therapies and interventions aimed at improving the lives of individuals affected by ASD. Continued interdisciplinary research efforts are essential to unravel the intricate genetic architecture of ASD and translate findings into meaningful clinical applications. Ultimately, a comprehensive understanding of ASD will empower healthcare professionals, educators, and caregivers to provide optimal support and improve outcomes for individuals across the autism spectrum.

Abbreviations

ASD	Autism Spectrum Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
SHANK3	SH3 and Multiple ankyrin repeat domains 3
ACC	Anterior Cingulate Cortex
PMDS	Phelan-McDermid Syndrome
CARS	Childhood Autism Rating Scale
ABC	Autism Behavior Checklist
SCGN	Secretagogin Gene
ADNP	Activity Dependent Neuroprotector Homeobox
ARID1B	AT-Rich Interaction Domain 1B
PV	Parvalbumin Interneuron
SST	Somatostatin Interneurons
CHD8	Chromodomain Helicase DNA-binding 8
AUTS2	Autism Susceptibility Candidate 2
RNA	Ribonucleic Acid
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
Cas9	CRISPR-associated Protein 9
DYRK1A	Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1
KMT2C	Lysine N-Methyltransferase 2C
OT	Oxytocin
AVP	Vasopressin
ZnT3	Zinc Transporter 3
FOXK1	Forkhead Box K1
KCNA7	Potassium Voltage-Gated Channel Subfamily A Member 7
NLGN3	Neuroligin-3

Author Contributions

Raneem Nabil Halaweh is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The author declares no conflicts of interest.

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