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Genes in Autism Spectrum Disorder: A Literature Review

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ABSTRACT A regulated interaction between genes and environment helps to control a wide range of symptoms in complicated neurodevelopmental disorder, autism spectrum disorder (ASD). The knowledge of genetic variability, neurobiological changes helps one to better understand the processes behind ASD. A critical review of recent studies on the genetic foundation of ASD was carried out, with an emphasis on important genes including FOXP1, PARK2, SHANK2, DPP6, and SYNGAP1. The researchers looked at studies that used animal models, control models, and sophisticated diagnostic techniques like next-generation sequencing and variations of the polymerase chain reaction (PCR). Disruptions in neurotransmission, synaptic density and aberrant brain functions brought on by proapoptotic chromosomal changes that impact important brain areas are associated with genetic variability in ASD. Interplay between genetics and environment is highlighted by the rising incidence of ASD. There is hope for better management and results, thanks to cutting-edge diagnostic tools and creative therapies.

INTRODUCTION

ASD is a common and miscellaneous sort of neurodevelopmental disorders that place a heavy burden on those who are afflicted and those who provide care for them. Despite significant advancements in the grasping of the causes and neuropathology of ASD, as well as greater public awareness and more thorough study, no viable medications have been created to treat the most prominent and troublesome ASD symptoms. The incidence of autism increases yearly by about 1 percent but the reason for autism varies from person to person because it is caused by either hereditary (genetic) or due to environmental factors. Numerous experimental platforms, including genetic association studies, research using preclinical animal models, and investigations using patient samples, have already identified diverse mutations of core components and subsequent malfunctions of genes in ASD. Genetic causes like de novo deletion, duplications, inherited deletion, absent in controls occur in the genes. ASD is a multifaceted neurodevelopmental disorder stemming from intricate genomic-environmental interactions that disrupt typical brain maturation. Although there is no single, overarching cause of ASD yet, research is constantly improving the knowledge of potential etiological pathways. ASD is characterized by an extensive spectrum of rare de novo and inherited genetic variations spanning approximately 700 loci, thereby underscoring its status as one of the most genetically polygenic and heterogeneous entities within the domain of neuropsychiatric pathologies (Saxena and Chahrour 2017). Autism's molecular etiology is predominantly associated with alterations in the following genes, *FOXP1, DPP6, SCN4A, WNT3, WNT9B, CDH13,* 7q11.23, *COMMD1, CACNA2D4, SHANK2, SynGAP, DLGAP2, PTCHD1, PARK2, RFWD2, FBXO40, NLGN1, NRXN1, FLI16237, FHIT, SLC4A10,* etc. (Chaste and Leboyer 2012). In this systematic review, the researchers can elaborate the key genes that are responsible for the development of autism.

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Objectives

This study intends to analyse gene mutations like FOXP1, PARK2, SHANK2, DPP6 and SYNGAP1 that contribute to the aetiology of ASD by controlled illness models and animal experiments. The study intends to investigate the influence of proapoptotic gene mutations on synaptic density and neurotransmission by conducting in-depth analyses of brain regions impacted by gene abnormali-

ties, such as the pineal gland, hippocampus, amygdala, and frontal cortex.

MATERIAL AND METHODS

This systematic study focuses on identifying important genes linked to the development of Autism Spectrum Disorder (ASD). A thorough literature search was carried out utilising databases such as Cochrane, PubMed, Scopus and Web of Science, with publications published up to the knowledge cutoff date of January 2023. The terms included in the search technique included "Autism Spectrum Disorder", "ASD genetics", and "autism genes". Peer-reviewed publications, reviews, and meta-analyses that studied genetic factors contributing to ASD were eligible for inclusion.

The studies that were chosen underwent a rigorous quality review to ensure methodological rigour and relevance to the study aims. The identification of particular genes linked in ASD, included but not limited to FOXP1, DPP6, SCN4A, WNT3, WNT9B, CDH13, 7q11.23, COMMD1, CACNA2D4, SHANK2, SynGAP, DLGAP2, PTCHD1, PARK2, RFWD2, FBXO40 and NLGN1, was involved in data extraction.

The review summarises findings from genetic association studies, preclinical animal models, and patient-sample research. ASD exemplifies profound genetic heterogeneity, characterized by the involvement of nearly 700 genes harboring both de novo mutations and heritable variants. The goal is to provide a complete picture of the ASD genetic landscape, providing insights into putative etiological pathways and emphasising the most important genes involved in ASD development. The methodology used ensures a complete and methodical investigation, which aids in elucidating the intricate genomic foundations of ASD.

RESULTS AND DISCUSSION

p53

Studies on ASD pathogenesis in rat model by researchers has revealed that exposure to environmental contaminants like arsenic has led to an upregulation of hipk2 and p53 genes in the peripheral blood mononuclear cells This has resulted in mitochondrial dysfunction and aberrant DNA expression (Zhou et al. 2020). p53-dependent apoptosis and malformation of embryonic cerebral cortex was studied in a mouse model of ASD with CRM1 gene (Li et al. 2020). Significant ASD-like characteristics were observed in human beings and mice due to mutation in DNA-binding protein chromodomain helicase 8 (CHD8) (Nita et al. 2021). The development of ASD is influenced by abnormal CHD8 expression, which controls the p53-dependent genes mediating apoptosis, mitotic blockade, and sustained replicative ability of brain progenitor cells (Xiong et al. 2020). Neuron dendrite development and branching are regulated by the posttranslational alteration of p53. An additional murine model of ASD involving either deletion or truncation of the ANKRD11 gene demonstrated a downregulation of p53 acetylation, a critical regulator of pyramidal neuron migration and dendritic arborization during cortical development. The transcriptional activity of p53 was further linked to the modulation of specific microRNAs, including miR-19 b-1, miR-34c, miR-15a, and miR-23b, all of which have been implicated in the molecular etiology of ASD (Huang et al. 2021).

FOXP1

FOXP1 grades as one of the five highest risk genes (Satterstrom et al. 2020), and its inadequacy results in intellectual and specific linguistic impairment (Siper et al. 2017). A crucial regulator of cell development, Forkhead box protein 1 (FOXP1), mapped to chromosome 3p14.1, controls the expression of genes. Depending on the type of cell, the oncogene FOXP1 can start tumorigenicity. Whether or not autism is diagnosed, alterations in the FOXP1 gene may give rise to a spectrum of neurological and physical manifestations, including language deficits, cognitive and motor developmental delays, repetitive behavioral patterns, elevated activity levels, craniofacial anomalies, ocular misalignment, involuntary eye movements, and excessive weight gain. These clinical features tend to progress gradually over time but typically do not impact overall lifespan (Lin et al. 2021). Language development is delayed as a result of a lack of FOXP1 and FOXP2 (such as delayed vocal development, deficits in speech articulation, limited grammatical variation) (Pariani et al. 2009). However, FOXP2-related instances typically characterise facial muscle fine motor dysfunction with anomalies in language expression and receptivity, whereas FOXP1 tends to disrupt children's nerves and result in language retarda-

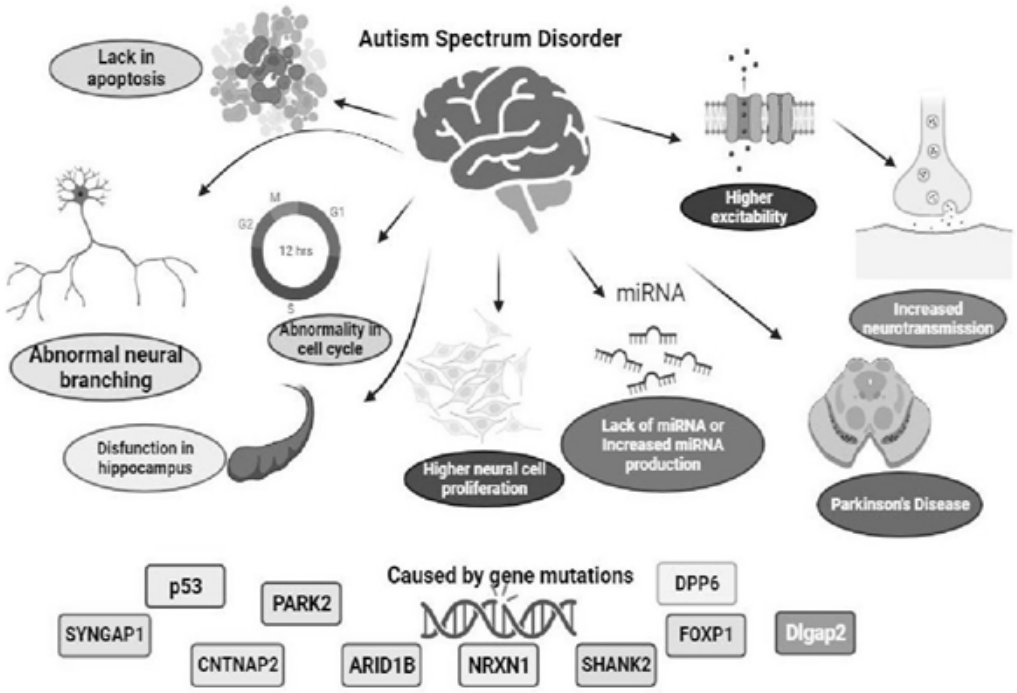
tion. FOXP1 plays a pivotal role in encoding memory, a process essential for transmitting behavioral patterns between generations. The introduction of short hairpin RNA constructs targeting FOXP1, delivered via adeno-associated viral vectors, led to reduced expression of this transcription factor within the pallial HVC domain—a critical nucleus in the avian brain associated with vocal learning. In forebrain neurons projecting to the striatum and exhibiting mirror-like properties, notable impairments in both structural integrity and synaptic adaptability were observed. Silencing FOXP1 within this neural pathway impeded juvenile birds from forming new auditory memories of adult songs, though it did not hinder their ability to reproduce vocalizations already acquired (Garcia-Oscos et al. 2021).

DPP6

Dipeptidyl aminopeptidase-like protein 6 (DPP6/DPPX/DPL1/BSPL/potassium channel accelerating factor, KAF) is a type II transmembrane serine peptidase that was initially discovered and cloned from brain tissue from rats and cows. Prokaryotes and eukaryotes depend on DPP6 for appropriate cell function (Malloy et al. 2022). This family includes the DPP4, DPP8, DPP9, and DPP10 proteins. A kind of inflammatory cell death is facilitated by both DPP8 and DPP9 (Okondo et al. 2017). The antigenic exopeptidase family members DPP4 and DPP6 have 32 and 50 percent sequence identity and similarity, respectively, in their protein structures. On chromosome 7q36.2, there is the gene for DPP6. The adult mouse brain has DPP6-S, DPP6-K, and DPP6-L, three isoforms of DPP6 with high levels of expression. In the CA1-CA3 areas of the hippocampal projection neurons, DPP6-S and DPP6-K and DPP6-L is restricted to the cerebellum and olfactory bulb (Nadal et al. 2006). It plays a role in modulating synaptic development and operates autonomously, while also contributing significantly to the regulation of neuronal responsiveness as a critical accessory component of transient voltage-dependent potassium channels. DPP6 reduces the hyperexcitability of neurons and the backpropagation of action potentials by increasing the conductance of the Kv4.2 channel. Further research has revealed DPP6 to encourage and sustain filopodial extension and stability (Lin et al. 2018). At least several hundred genes have uncommon spontaneous and familial copy number alterations, like deletion, duplication, translocation, and inversion, significantly contributing to ASD (Ruzzo et al. 2019). In 44 per cent of families with ASD, Marshall et al. (2008) discovered 277 imbalanced CNVs that were not present in controls. 7 and 2 percent of multifactorial populations with one or more siblings with ASD had de novo CNVs. Novel risk regions for ASD mapped to DPP6 and DPP10 were identified, with functions associated with postsynaptic density, intellectual disability, and gene expression dysregulation, which had either CNV increases or deletions that were initially reported at the same locus in unrelated individuals. All three genes, that is, SHANK3, NLGN4, and NRXN1-PSD, have been linked to intellectual disability, dysregulated gene expression, and postsynaptic density when other research on these genes is taken into account. Studies have identified DPP6 and DPP10 as risk genes for ASD, with Arg322Cys mutations in two children and paternal inheritance in their fathers and grandfathers. The modulation of potassium channels and the orchestration of axonal navigation are critical to neurodevelopment, as demonstrated by a combinatorial effect of variants in the DPP6 and LRRC4C genes. These insights may offer valuable implications for advancing the identification and therapeutic strategies for ASD (Bock et al. 2016; Maussion et al. 2017).

SHANK2

This gene produces a protein with protein-protein interaction motifs, featuring ankyrin repeat elements along with an SH3 domain, aligning it with the Shank group of synaptic architecture proteins. It serves as molecular scaffolding in excitatory synapses' postsynaptic density. Autism spectrum disease and other psychiatric disorders vulnerability may be linked to transcript variants, which are produced by alternative splicing in the SHANK gene (Zaslavsky et al. 2019). The SH3 and numerous ankyrin repeat domain proteins, which are post-synaptic scaffold proteins of excitatory synapses, are encoded by the SHANK genes (SHANK1, 2, and 3). Over 80 and 30 ASD-related mutations have been found in the SHANK3 and SHANK2 genes (Monteiro and Feng 2017). In those affected by ASD where genetic anomalies are present in the postsynaptic scaffold protein, Shank2 prevents osteoblastogenesis and thus increases risk of fracture due to low bone mass. This was proved by silencing of proteins, which interact with Shank2 (Ahmad et al. 2023).



Source: Author

The functional overlap of SHANK with other ASD-associated genes suggests synaptic dysfunction as a convergent mechanism of pathophysiology in ASD. Decreased mGluR1 expression, altered dendritic arborisation, and increased persistent depression in the striatum, but not in the hippocampus, were the causes of hyperactivity, increased locomotor activity, and repetitive behaviours in a recently created Transgenic rodent exhibiting a loss-of-function variant in the Shank2 locus. This Shank2 mutant rat also had clear variations in event-associated potentials and EEG spectral power, suggesting the presence of a specific hyper-motivation phenotype (Modi et al. 2018).

SYNGAP1

SYNGAP1 encodes a neuron-specific regulator of Ras GTPase activity localized at synaptic sites, a component of the NMDA receptor complex necessary for synaptic plasticity and function (Hamdan et al. 2011). The expression levels of NMDA and AMPA receptors within glutamatergic synaptic junctions are positively and negatively regulated by the SYNGAP1 gene. Researchers found that mice with heterozygous SYNGAP1 gene mutations (SYNGAP1-/+ animals) have behavioural and cognitive problems due to the alteration in excitatory/inhibitory balance in the cortex and hippocampus, thus speeding up the formation of glutamatergic synapses. This changes the synaptic plasticity necessary for the development of cognition and behaviour (Mignot et al. 2016). A SYNGAP1 mutation has been found in a 13-year-old male patient with mild ID, ASD, and epilepsy. CNVs including SHANK2, SYNGAP1, and ILRAPL1 genes are a key factor in the onset of autism spectrum conditions and cognitive disabilities. It is common to find genetic overlap and similarities between the two illnesses. Individuals who have a mutation in SYNGAP1 also experi-

ence mild to severe ID. The patient's clinical features are consistent with previous cases, and the mutation causes autistic symptoms, encephalopathy, and circuit-specific pathologies (Tezcan et al. 2020). De novo truncating mutations within the SYNGAP1 gene, which encodes a synapse-enriched GTPase-activating protein regulating RAS and RAP signaling pathways, have been implicated in the etiology of nonsyndromic intellectual disability (NSID). In their study, the investigators document the discovery of three previously unreported truncating variants—c.2184del [p.N729TfsX31], c.2212_2213del [p.S738X], and c.283dupC [p.H95PfsX5]—alongside the first identified pathogenic missense substitutions in SYNGAP1, namely c.1685C>T [p.P562L] and c.1084T>C [p.W362R], in individuals diagnosed with NSID. Moreover, a subset of individuals exhibited features such as autism, impaired motor coordination, and a distinct form of refractory generalized epilepsy. All variants emerged spontaneously, except c.283dupC, which was inherited from a father exhibiting somatic mosaicism. Biolistic delivery of wild-type SYNGAP1 into pyramidal neurons derived from cortical organotypic cultures led to a marked attenuation of activity-induced phosphorylation of ERK (pERK). On the other hand, pERK levels were not significantly impacted by plasmids encoding the mutant forms p.W362R, p.P562L, or the earlier documented variant p.R579X. According to these findings, SYNGAP1 lacks its function as a result of spontaneously arising amino acid–altering substitutions, p.R579X, and perhaps the entirety of other protein-truncating variants. Furthermore, the work offers new information on the epileptic symptoms linked to SYNGAP1 alteration while confirming the protein's role in autism (Berryer et al. 2013). Developmental encephalopathy with cognitive impairment, autism symptoms, and epilepsy is caused by SYNGAP1 mutations. While overexpression enhances learning and increases seizure latency, animals with diminished levels of SynGAP-α1/2 C-terminal splice variants exhibit severe abnormalities. Optimising cognitive abilities and reducing seizures could be accomplished via the upregulation of SynGAP-α expression (Kilinc et al. 2022).

DLGAP2

DLGAP2 (Disc large associated protein 2), also known as SAP90/PSD95-associated protein 2 (SAPAP2), is a protein that belongs to the DLGAP protein family. The DLGAP family proteins (DLGAP1-4) are postsynaptic scaffold proteins that are found in the excitatory synapses postsynaptic density (PSD) (Rasmussen et al. 2017). DLGAP proteins interact functionally with PSD95 and SHANK family members, forming an essential postsynaptic scaffolding network. This PSD95-DLGAP-SHANK assembly plays a critical role in orchestrating the localization of neurotransmitter receptors and intracellular signaling components at excitatory synaptic membranes (Vyas et al. 2021). DLGAP2 variants have reportedly been linked to ASD (Chien et al. 2013), schizophrenia (Li et al. 2014), and Alzheimer's disease (Ouellette et al. 2020). In a youngster with autism from Taiwan, loss of DLGAP2 is due to a microdeletion of about 2.4 Mb (mega base) in the 8p23 terminal region. Hippocampus phenotypes with decreased spatial memory in mice were more prominent in mutant DLGAP2 than in homozygous knockouts. BDNF, GluN2A, HOMER1, PSD95, GluR2, SHANK3, mGluR25, ARC, and mGluR1 post-synaptic protein expressions were altered in mutants. These mice demonstrated reduced mushroom-type and altered synaptic morphology whilst a higher spine density. Mice with DLGAP2 deficiency that exhibit intellectual impairment symptoms, may be a potential animal model that might help to better understand ASD in patients (Hsieh et al. 2023; Jiang-Xie et al. 2014). The Cre-loxP system, serial backcross, and recombination-based methods made it easier to create DLGAP2 mice to study the cognitive and physical traits, structure and function of synapses in the orbitofrontal cortex (OFC). In the resident-intruder task and the tube test, DLGAP2 mice showed worsened aggressive behaviours and increased social dominance. In DLGAP2/mice reduction in receptors and scaffold proteins in cortical synapses, decreased spine density, a smaller peak excitatory postsynaptic current amplitude, and Postsynaptic Density deficiencies in the OFC was noted.

NRXN1

A synaptic adhesion complex reliant on calcium signaling, formed between neurexin receptors and neuroligins, is essential for efficient synaptic transmission. The NRXN1 gene, situated at the 2p16.3 chromosomal locus, spans 7,505 base pairs and comprises 22 coding regions, translating into a protein

of 1,477 amino acids. The NRXN1 gene deletions, missense and nonsense mutations may contribute to the aetiology of ASD (Kim et al. 2008). A study on 30 non-syndromic autistic children and adolescents (ages 3-18) two known mutations were identified in the Neurexin 1 (NRXN1) gene that patients with autism tested heterozygous for S14L or L748I inherited from their father. Two NRXN1 gene mutations were found in 30 ASD patients. NRXN1 gene variants may increase non-syndromic ASD risk (Onay et al. 2017). Epilepsy and ASD co-occur 30 percent of the time, and epilepsy is linked to excessive neural activation. Several presynaptic neuron-adhesion proteins classified as NRXN1 are encoded by NRXN1. It was discovered that NRXN1 +/- cortical neurons had bigger sodium currents, higher action potential amplitudes, and quicker depolarisation times. The transcriptome alterations discovered by RNA Seq analysis showed a considerable upregulation of Ion channel subunits involved in membrane depolarization control, such as those encoded by GRIN1, GRIN3B, SLC17A6, CACNG3, CACNA1A, and SHANK1, which are potentially implicated in the heightened neuronal responsiveness observed in cortical cells with heterozygous NRXN1 deletions. Given that partial loss of NRXN1 isoforms modulates both intrinsic excitability and extra-synaptic activity, induced pluripotent stem cells derived from affected individuals may serve as a viable neurodevelopmental disorder model. These cellular systems can be leveraged to evaluate therapeutic interventions by monitoring calcium signaling dynamics and alterations in neuronal firing thresholds (Avazzadeh et al. 2021).

PARK2

Mitophagy regulating Parkin protein - PARK2 gene (OMIM*602544), is a cytosolic ubiquitin-E3-ligase. It collaborates with another locus associated with autosomal recessive Parkinsonian syndromes, PINK1 mitochondrial protein, to exert its effects (Konovalova et al. 2015). Event-related potential changes in people with early-onset Parkinson's disease, comparing those with and without PARK2 gene mutations, via degradation of phospho-BCL-2, enhance the mitochondrial route of apoptosis and antimicrotubule medicines chemosensitivity. The PARK2 gene in humans and mice encodes the 465-amino acid residue E3 ubiquitin ligase known as parkin, which is implicated in ASD. ASD affects one in 44 US children in neurodevelopmental issues. Parkin knockout mice exhibit autistic-like behaviours, reduced neuronal activity, and altered synapse density and hence are suggested as a model for autistic research (Huo et al. 2022). Out of the 863 references, the search turned up a total of eight clinical investigations, nine genomic analyses, and five documented case observations. Across all age demographics, those with ASD were more likely to have PD and Parkinsonian symptoms. 40 to 80 percent of Rett syndrome were frequently associated with Parkinsonian characteristics and hypokinetic behaviour. Bradykinesia, stiffness, hypomania, and gait freezing are frequently seen as Parkinsonian symptoms. More ASD cases than controls have changes in the copy number of the PD gene PARK2. While the evidence for other PD-associated genes (DRD2, GPCR37, the SLC gene family, and SMPD1) is less clear, it appears that RIT2 and CD157/BST1 are related to ASD and PD. Rare mutations like ATP13A2, CLN3, and WDR45 may cause autistic behaviour as well as concurrent Parkinsonism (Mai et al. 2023). The chromosomal locus 6q26 harbors a 157 kb intragenic microdeletion disrupting PARK2, identified in two male siblings diagnosed with autism spectrum disorder and exhibiting a syndromic presentation. Both individuals displayed distinct craniofacial anomalies, including full lips, elongated eyelashes, thick eyebrows, deep-set ocular features accompanied by pronounced lateral palpebral apertures, coarsened facial morphology, and mild osteological irregularities. The phenotypic divergence in autistic manifestations within the same family was evident; the elder brother demonstrated traits of autism with higher cognitive functioning and intact language abilities, whereas the younger one presented with severely limited speech capabilities and profound cognitive impairment. Real-time quantitative PCR delineated the PRKN gene within the deleted segment, and subsequent parental genotyping revealed a paternal origin of the structural variant, with the father exhibiting mild, subclinical autistic traits indicative of a broader autism phenotype (Barone et al. 2023). Furthermore, six genomic loci known to be associated with autism-related CNVs—including 1q21.1, 15q11.2-13.1, 15q13.3, 16p11.2, 22q11.21, and 22q13.33—encompassed 17 unique CNV regions observed among the cases studied. (Yin et al. 2016).

CNTNAP2

The *CNTNAP2* (Contactin-associated protein-like 2) encoded by the CNTNAP2 gene is downregulated in ASD patients. This longest gene in the human genome serves as a transmembrane anchoring protein and receptors in the neurofunctional system of vertebrates (O'Roak et al. 2011). The gene produces a protein called neurexin, which controls connections between neurons and glial cells, which function as neuron support cells, during brain development and aids in the formation of axon structures. CNTNAP2 gene occupies 1.5 percent of chromosome 7. Overall, neurexin 1 is a compelling candidate for participation in autism due to its role in the formation and operation of glutamatergic and GABAergic synapses, its interactions with neuroligins, and the induction of a behavioural impairment in knockout mice (Kim et al. 2008). This protein has laminin G domains, repetitions of the epidermal growth factor, PDZ binding site, discoidin/neuropilin motifs, fibrinogen-related globular modules, thrombospondin type-1 N-terminal segments, and coagulation factor V/VIII C-terminal–like structural units. This protein in the adjacent paranodal regions in myelin-coated nerve fibres promotes connections between neuroglial junctions and localises potassium channels within developing axons. Chromosomal rearrangements and deletions of CNTNAP2 have been linked with language delay and stuttering (Poot et al. 2010). CNTNAP2 gene's intron 1 is directly bound by FOXP2 and hence disruption in the latter is linked to developmental speech and language disorders (Peñagarikano and Geschwind 2012). CNTNAP2 deletion (KO) in mice had decreased neuronal density and impeded neuronal migration in the medial prefrontal cortex (mPFC), which showed aberrant behaviours that resemble key ASD characteristics. Alterations in synaptic plasticity and neural circuits were linked to CNTNAP2 KO mice (Lazaro et al. 2019). One of the prevalent biological traits in ASD is mitochondrial dysfunction (Citrigno et al. 2020). Jang et al. (2023) elucidated by integrative multi-omics analysis that mitochondrial proteins Mcu, Etfdh, Acaa2, Acadm, Acsbg1, Aldh7a1, and Acsf2 were altered in mouse and human ASD subjects. They observed that downregulation of MCU (Mitochondrial Calcium Uniporter) altered the mitochondrial membrane potential (MMP) (Yang et al. 2015). ETFDH (Electron Transfer Flavoprotein Dehydrogenase) regulates flavin-containing dehydrogenases on OXPHOS (oxidative phosphorylation system) complex II, impacting mitochondrial lipid oxidation and ETC system (Chokchaiwong et al. 2019). They consistently discovered elevated levels of lipid metabolic enzymes such Aldh7a1, Ascbg1, Acsf2, Acadm, and Acaa2 in both animal and human ASD patients. It is interesting to note that NDD (neurodegenerative disorder) individuals with typical ASD symptoms have ALDH7A1 mutations. One of the most well-known chemical disruptions in NDDs, including ASD, is synapse disruption (Coughlin et al. 2019). It was shown that some DEPs (Vamp2, Cntnap2, Erc2, Gad2, Nectin1, Rrab3a, Rab35, Chmp6, Chmp7, and Sept6) were downregulated in ASD individual and animal models and were connected to SV (synaptic vesicle) roles in excitatory neurons. Rab3a, a crucial SV docking protein, is downregulated, which suggests that vesicle transport was impacted in ASD (Schlüter et al. 2004). Downregulated Snap25 in ASD suggested a loss in binding efficiency. VAMP2 alters SV docking to syntaxin and SNAP25. Vesicle fusion problems in ASD have been linked to Vamp2 mutations. Moreover, Rab35 mutations affect endocytic recycling and SV pool leading to mental problems (Bhat et al. 2020). Axonal progression in the growth cone during neural development has been connected to ASD risk genes, according to a number of studies. (Accogli et al. 2020). Pak3 is downregulated in ASD cases, causing dysregulation of the actin cytoskeleton, impaired synaptic plasticity, and learning disability (Pavlowsky et al. 2012). JNK controls axon growth and neuronal polarity, and downregulation of Gap43 hinders axon structure, causing ASD symptoms and increased lipid metabolism (Corponi et al. 2019). Consequently, pathways governing neurotransmitter transport, cellular energy organelles, axonal insulation structures, and neural outgrowths exhibited aberrant modulation due to alterations in the Cntnap2 gene associated with autism spectrum conditions.

ARID1B

Numerous genetic variations, including missense/frame-shift/nonsense point mutations and protein-truncating intragenic deletions, are involved in AT-rich interaction domain 1B, also referred to as BAF250B, Haploinsufficiency of ARID1B. These variations have been linked to ASD, ID, and Coffin-Siris Syndrome, a genetic condition that causes a

range of developmental and cognitive delays. (Van der Sluijs et al. 2019). Another gene altered in ASD, ARID1B, likewise encodes a chromatin remodelling component (D'Gamma et al. 2015). One component (subunit) of several SWI/SNF (Switch /Sucrose Non-Fermentable) protein complexes is made by a functional protein translated from the ARID1B genomic sequence. Located on chromosome 6, SWI/SNF complexes control gene activity (expression) by chromatin remodelling (Bernier et al. 2014). Shibutani et al. (2017) examined abnormal gene expression and autism related behaviours in the ARID1B gene knockout mice model. Gene expression patterns and phenotypic alterations in ARID1B KO mice resemble those in ASD patients and Chd8-haploinsufficient mice. Also, it was discovered that the pattern of immature fast-spiking cells seen in autistic brains was similar to the pattern of gene expression in the Arid1b hKO mouse brain. Among eight ID individuals, NGS and microarray analysis revealed de novo translocations or deletions that each produced a shortened copy of the ARID1B gene. Five of these individuals had characteristics that were compatible with ASD (Halgren et al. 2012). Four individuals also had corpus callosum abnormalities, according to brain MRI results. Another investigation found that the ARID1B gene 44 transcript level is lower in ASD patients. ARID1B has been recognized as one of the top-tier autism-associated genes within the Simons Foundation Autism Research Initiative (SFARI) Gene repository, an extensive compendium cataloging genomic variants and structural alterations strongly implicated in ASD. (Moffat et al. 2022). The study discovered that Arid1b+/- mice had higher axonal and synaptic expression of genes and lower Arid1b mRNA and protein. These mice exhibited impaired ultrasonic vocalisations and developmental growth during neonatal development. Behaviourally, they showed low motor skills, learning and memory deficits in novel object recognition, and social deficits in social interactions. In contrast to earlier findings, the adult Arid1b+/- mice's brains had a larger hippocampus and corpus callosum and a smaller cerebellum (Ellegood et al. 2021). In both the juvenile and adult phases, Arid1b-happloinsufficient (Arid1b+/-) mice exhibit autistic-like behaviour along with permanent reductions in excitatory synapse density and transmission. To prevent synaptic and behavioural problems in adulthood, Arid1b+/- mice are chronically given the SSRI fluoxetine throughout the first three postnatal weeks. The mechanisms behind these rescues include overexpression of downstream expressions of FMRP and the re-establishment of regulatory mechanisms governing the gene expression of SynGAP1 and Arc, which is mediated by HDAC4/MEF2A. Their findings imply that transcriptional reprogramming protects synaptic and behavioural impairments in adult Arid1b+/- mice via persistent regulation of serotonergic receptors during crucial initial postnatal periods (Kim et al. 2022).

CONCLUSION

Autism Spectrum Disorder (ASD) patients have heightened inflammatory responses in both the brain and the peripheral regions, which may affect neuronal function, plasticity, and connection. These problems are caused by dysregulated local and systemic inflammation, which is predominantly caused by genetic changes that emerge during neurodevelopment. This emphasises the importance of autism as a neurodevelopmental disorder, with genetic factors accounting for 40-80 percent of ASD risk. These genetic variants, in conjunction with environmental factors, operate as causative agents. PTCHD1, HOX, FOXP2, CHD8, OXTR, and SHANK3 genes are important in the development of mental status, speech, nerve cell communication, and facial memory. Furthermore, chromosomal abnormalities such as duplications of 15q11-q13, 16p11.2, and 22q11.2, as well as deletions of 2q37, 22q11, 7q31, and 22q13.3, can contribute to autistic characteristics. While the actual cause is unknown owing to genetic heterogeneity, understanding these genetic factors may pave the way for innovative therapeutic options.

RECOMMENDATIONS

Further study should be directed towards clarifying the complex interplay between genetic variations and environmental variables in ASD. Comprehensive research into the particular methods by via PTCHD1, HOX, FOXP2, CHD8, OXTR, and SHANK3 genes regulate mental status, speech, neural transmission, and face memory is required. Furthermore, investigating the impact of chromosomal abnormalities such as duplications and deletions in regions such as 15q11-q13, 16p11.2, 22q11.2, 2q37, 7q31, and 22q13.3 can provide deeper insights into the genetic foundation of ASD. Integration of new genomic technologies and large-scale collabo-

rative initiatives will be critical for unravelling the complexity of genetic heterogeneity in ASD, paving the door for targeted and creative therapeutic strategies.

LIMITATIONS

The paper presents a thorough summary of ASD, emphasising genetic intricacies, research advances, and therapy options. However, there is a dearth of particular information on recent advances, specific nutraceuticals or therapeutic drugs investigated, and the level of advancement in focused genetic therapy. Furthermore, it briefly addresses limits in discovering autism genes and treating ASD but provides no clear data on these difficulties. The various strategies proposed, such as nutraceuticals and behavioural therapy in interaction with genes have received insufficient attention. Furthermore, it makes no mention of potential ethical concerns in genetic therapy or the societal implications of rising prevalence.

CONFLICT OF INTEREST

NIL

FINANCIAL AID

NIL

AUTHOR CONTRIBUTION

P. S. Yogitha: Article writing
M. R. Suchitra: Edited the article
Sampath P. Kumar: Alignment of the article

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