World Journal of
Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2024 September 9; 13(3): 98468

DOI: 10.5409/wjcp.v13.i3.98468

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Decoding the genetic landscape of autism: A comprehensive review

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Eman A Bediwy, Reem Elbeltagi

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Yagishita-Kyo N

Received: June 26, 2024
Revised: July 29, 2024
Accepted: August 1, 2024
Published online: September 9, 2024
Processing time: 64 Days and 8.4 Hours

Mohammed Al-Beltagi, Department of Pediatric, Faculty of Medicine, Tanta University, Alghrabia, Tanta 31511, Egypt

Mohammed Al-Beltagi, Department of Pediatric, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 12, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Irish Royal College of Surgeon, Muharraq, Busaiteen 15503, Bahrain

Adel Salah Bediwy, Department of Pulmonology, Faculty of Medicine, Tanta University, Alghrabia, Tanta 31527, Egypt

Adel Salah Bediwy, Department of Pulmonology, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Bahrain

Eman A Bediwy, Internal Medicine, Faculty of Medicine, Tanta University, Algharbia, Tanta 31527, Egypt

Reem Elbeltagi, Department of Medicine, The Royal College of Surgeons in Ireland-Bahrain, Muharraq, Busiateen 15503, Bahrain

Co-first authors: Mohammed Al-Beltagi and Nermin Kamal Saeed.

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, PhD, Academic Editor, Chairman, Full Professor, Research Scientist, Department of Pediatric, Faculty of Medicine, Tanta University, Al-Bahr Street, The Medical Complex, Alghrabia, Tanta 31511, Egypt. mbelrem@hotmail.com

Abstract

BACKGROUND
Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by heterogeneous symptoms and genetic underpinnings. Recent advancements in genetic and epigenetic research have provided insights into the intricate mechanisms contributing to ASD, influencing both diagnosis and therapeutic strategies.

AIM
To explore the genetic architecture of ASD, elucidate mechanistic insights into genetic mutations, and examine gene-environment interactions.

METHODS
A comprehensive systematic review was conducted, integrating findings from studies on genetic variations, epigenetic mechanisms (such as DNA methylation and histone modifications), and emerging technologies [including Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 and single-cell RNA sequencing]. Relevant articles were identified through systematic searches of databases such as PubMed and Google Scholar.

RESULTS
Genetic studies have identified numerous risk genes and mutations associated with ASD, yet many cases remain unexplained by known factors, suggesting undiscovered genetic components. Mechanistic insights into how these genetic mutations impact neural development and brain connectivity are still evolving. Epigenetic modifications, particularly DNA methylation and non-coding RNAs, also play significant roles in ASD pathogenesis. Emerging technologies like CRISPR-Cas9 and advanced bioinformatics are advancing our understanding by enabling precise genetic editing and analysis of complex genomic data.

CONCLUSION
Continued research into the genetic and epigenetic underpinnings of ASD is crucial for developing personalized and effective treatments. Collaborative efforts integrating multidisciplinary expertise and international collaborations are essential to address the complexity of ASD and translate genetic discoveries into clinical practice. Addressing unresolved questions and ethical considerations surrounding genetic research will pave the way for improved diagnostic tools and targeted therapies, ultimately enhancing outcomes for individuals affected by ASD.

Key Words: Autism spectrum disorder; Genetics; Epigenetics; Clustered Regularly Interspaced Short Palindromic Repeats-Cas9; Gene-environment interactions; Personalized medicine

Core Tip: This review synthesizes current knowledge on the genetic and epigenetic factors contributing to autism spectrum disorder (ASD). It highlights the complexity of ASD's genetic architecture and the role of epigenetic mechanisms such as DNA methylation and non-coding RNAs in disease pathogenesis. Emerging technologies like Clustered Regularly Interspaced Short Palindromic Repeats-Cas9 and advanced bioinformatics are pivotal for advancing our understanding of ASD. Collaborative research efforts are crucial for integrating diverse disciplines and international data, aiming to translate genetic insights into personalized therapies. Addressing unresolved questions and ethical considerations will be essential for maximizing the clinical utility of genetic discoveries in improving outcomes for individuals with ASD.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Bediwy EA, Elbeltagi R. Decoding the genetic landscape of autism: A comprehensive review. *World J Clin Pediatr* 2024; 13(3): 98468
URL: https://www.wjgnet.com/2219-2808/full/v13/i3/98468.htm
DOI: https://dx.doi.org/10.5409/wjcp.v13.i3.98468

INTRODUCTION

Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental condition marked by a heterogeneous array of symptoms that can significantly influence social interaction, communication, and behavioral patterns[1]. The term "spectrum" underscores the extensive variability in the severity and manifestation of symptoms among affected individuals. The cardinal features of ASD encompass deficits in social communication, engagement in repetitive behaviors, and a restricted range of interests. Specifically, individuals with ASD experience challenges in both verbal and non-verbal communication, have difficulty interpreting social cues, and encounter obstacles in forming and sustaining relationships[2]. They also display repetitive activities, stereotyped movements, adherence to specific routines, and intense preoccupations with particular topics or activities (Figure 1). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delineates the diagnostic criteria for ASD, emphasizing persistent deficits in social communication and interaction coupled with restrictive and repetitive behavioral patterns, interests, or activities[3].

Globally, ASD is estimated to affect approximately 1 in 100 children, though prevalence rates exhibit considerable variation across different countries and studies. In the United States, data from the Centers for Disease Control and Prevention indicate that about 1 in 36 children were diagnosed with ASD as of 2020[4]. This rising prevalence is likely attributable to enhanced awareness, expanded diagnostic criteria, and improved diagnostic methodologies. Epidemiological data also reveal a marked gender disparity, with ASD being approximately four times more prevalent in boys than in girls[5]. Emerging research, however, suggests that females with ASD may be underdiagnosed or diagnosed later, possibly due to distinct symptomatology that differs from their male counterparts[6].

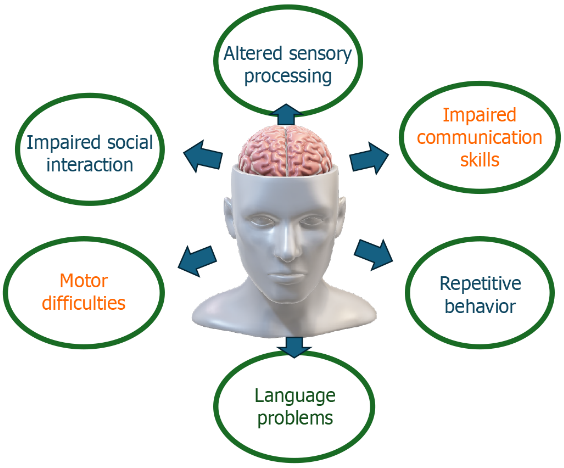

Figure 1 The main clinical manifestations of autism spectrum disorder.

ASD has profound implications for both affected individuals and their families. Children with ASD frequently exhibit developmental delays in speech, language, and motor skills. These children often necessitate individualized educational programs and support services to achieve academic success[7]. Social interaction difficulties can lead to social isolation and challenges in forming and maintaining peer relationships. Additionally, individuals with ASD have higher incidences of co-occurring medical and psychiatric conditions, such as anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), and other mental health disorders[8]. Adults with ASD face significant hurdles in securing and maintaining employment, with many experiencing underemployment or unemployment. A considerable number of adults with ASD require varying degrees of support to live independently, with some necessitating lifelong care. Families of individuals with ASD frequently endure high levels of stress, anxiety, and emotional strain[9]. The financial burden associated with therapies, medical care, special education, and supportive services can be substantial. Parents and caregivers often struggle to balance care responsibilities with professional and other family obligations, leading to reduced work hours or workforce withdrawal[10].

The economic impact of ASD is substantial, encompassing both direct costs, such as medical care and special education, and indirect costs, including lost productivity. In the United States, the lifetime cost of caring for an individual with ASD is estimated to range from $1.4 to $2.4 million[11]. The increasing prevalence of ASD imposes significant demands on healthcare systems to deliver diagnostic, therapeutic, and support services. Educational institutions require additional resources and specialized staff to address the unique needs of students with ASD. Furthermore, heightened awareness of ASD has spurred policy changes and advocacy efforts to enhance service provision, fund research initiatives, and promote inclusive practices[12].

This review aims to synthesize current research findings on the genetics of ASD. This comprehensive systematic analysis seeks to elucidate the intricate interplay between genetic factors, environmental influences, and phenotypic heterogeneity in ASD. By examining the latest advances in genomic technologies, such as whole-genome sequencing (WGS) and genome-wide association studies (GWAS), the review aims to identify and understand the genetic risk factors associated with ASD. Additionally, it explores emerging insights into gene-environment interactions, epigenetic mechanisms, and the role of rare and De novo mutations (DNMs) in the etiology of autism. This synthesis of research findings is intended to inform future research directions and therapeutic strategies, contributing to a deeper understanding of the genetic architecture of ASD and ultimately aiding in developing more effective interventions and support mechanisms for individuals affected by this complex disorder.

MATERIALS AND METHODS

This review utilized a systematic approach to synthesize and analyze existing literature on the genetic underpinnings of ASD. A systematic literature search was conducted using multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search spanned articles published till June 2024 to capture the most recent and relevant studies. Key search terms included "Autism Spectrum Disorder," "genetics," "whole-genome sequencing," "exome sequencing," "copy number variations," "epigenetics," "gene-environment interactions," "de novo mutations," and "genetic architecture." Boolean operators (AND, OR) were employed to refine and expand the search results. Specific inclusion and exclusion criteria were established to ensure the included studies' relevance and quality. Inclusion criteria ensured the studies were peer-reviewed, focused on human genetics in ASD, and published in English. We excluded non-peer-reviewed articles, animal studies, unavailable full texts, or articles not published in English.

Relevant data, including study objectives, methodologies, key findings, and conclusions, were extracted from the selected articles. The extracted data were organized into thematic categories to facilitate a structured synthesis of the information. These categories included advances in genomic technologies (*e.g.*, WGS, exome sequencing), the role of copy number variations (CNVs), gene-environment interactions, epigenetic mechanisms, therapeutic implications and personalized medicine, current and future therapies, research challenges, and future directions.

The quality of the included studies was assessed using standardized criteria adapted from the Critical Appraisal Skills Programme checklist. This evaluation considered factors such as study design, sample size, methodology robustness, and the relevance of findings to the research questions. Studies were rated as high, moderate, or low quality, and only high and moderate-quality studies were included in the final synthesis to ensure the reliability of the conclusions. As this study is a literature review, no primary data collection involving human subjects was conducted. Therefore, ethical approval was not required. However, ethical considerations were considered by ensuring the inclusion of ethically conducted studies and appropriately citing all sources.

RESULTS

The comprehensive systematic review identified 356 articles that met the inclusion criteria: 130 research articles, 202 review articles, 4 meta-analyses, 7 systematic reviews, 7 case reports, 2 editorials, and 4 commentaries (Figure 2). Our review of genetic research in ASD has elucidated key findings across several domains, highlighting the complexity and diversity of the disorder. Numerous risk genes have been identified, including *CHD8*, *SHANK3*, and *MECP2*, which play critical roles in synaptic function, neural development, and chromatin remodeling. Notably, studies have shown aberrant DNA methylation patterns, such as hypermethylation of the *MECP2* gene, linked to environmental influences like prenatal stress and toxins, contributing to neural anomalies in ASD. Histone modifications, including changes in acetylation and methylation states, disrupt chromatin structure and gene expression, particularly in genes associated with neural connectivity and plasticity. Additionally, dysregulation of non-coding RNAs, such as microRNAs, impacts the regulation of genes crucial for neural development and synaptic function, further contributing to ASD pathology.

These genetic insights are revolutionizing therapeutic strategies, shifting towards personalized medicine approaches. Tailoring behavioral interventions like Applied Behavior Analysis (ABA) and social skills training based on genetic profiles can address specific deficits more effectively. Pharmacological treatments, including antipsychotics and selective serotonin reuptake inhibitors (SSRIs), are increasingly guided by genetic profiling to enhance efficacy and minimize side effects. Nutritional interventions, such as gluten-free and casein-free diets, are also being personalized based on genetic predispositions related to metabolic processes, improving gastrointestinal and behavioral symptoms in individuals with ASD.

Future therapies are on the horizon, driven by genetic and epigenetic research advancements. Gene therapy targeting specific genetic abnormalities, such as *CHD8* or *SHANK3* mutations, holds promise for correcting or mitigating these genetic disruptions. Epigenetic therapies, including DNA methylation modulators and histone deacetylase inhibitors, aim to reverse abnormal chromatin states and restore normal gene expression patterns. Emerging technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 enable precise genetic modifications to study and potentially correct mutations, while advanced bioinformatics tools analyze extensive genomic data to identify novel genetic variants and risk genes. Single-cell RNA sequencing (scRNA-seq) provides insights into cellular heterogeneity in the brain, and brain organoids offer a model for studying the impact of genetic and environmental factors on neural development.

Collaborative research is crucial for advancing our understanding and treatment of ASD. Multidisciplinary collaborations integrate expertise from genetics, neuroscience, psychology, bioinformatics, and clinical medicine, enhancing research outcomes and facilitating the translation of findings into clinical practice. International collaborations and pooling resources and data from diverse populations enhance studies' statistical power and generalizability. Addressing ethical and practical considerations, such as the accessibility and privacy of genetic testing, is essential for integrating genetic insights into routine clinical care.

DISCUSSION

Overview of ASD

ASD is characterized by various symptoms affecting social interactions, communication, and behavior. Patients with ASD have verbal and nonverbal communication challenges, including difficulties in spoken language and nonverbal cues such as eye contact, facial expressions, and gestures[13]. They also have social reciprocity challenges, including difficulty engaging in reciprocal social interactions, sharing interests and emotions, and initiating or responding to social overtures. In addition, they have trouble developing, maintaining, and understanding relationships, including challenges in adapting behavior to suit various social contexts and forming friendships[14].

Patients with autism commonly suffer from repetitive behaviors and restricted interests. They engage in repetitive actions such as hand-flapping, rocking, or spinning. Additionally, they suffer from insistence on sameness, inflexible adherence to routines, or ritualized verbal or nonverbal behavior patterns[15]. They also have highly restricted, fixated interests with an intense focus on specific topics or objects, often abnormal in intensity or focus. They also have sensory sensitivities with over-reactivity to sensory input, such as an unusual interest in sensory aspects of the environment (*e.g.*, lights, sounds, textures)[16].

The DSM-5 outlines specific criteria for diagnosing ASD, divided into two main categories. The first category involves persistent deficits in social communication and social interaction. These deficits manifest in various ways: Social-emotional reciprocity issues, such as an abnormal social approach, failure of normal back-and-forth conversation,

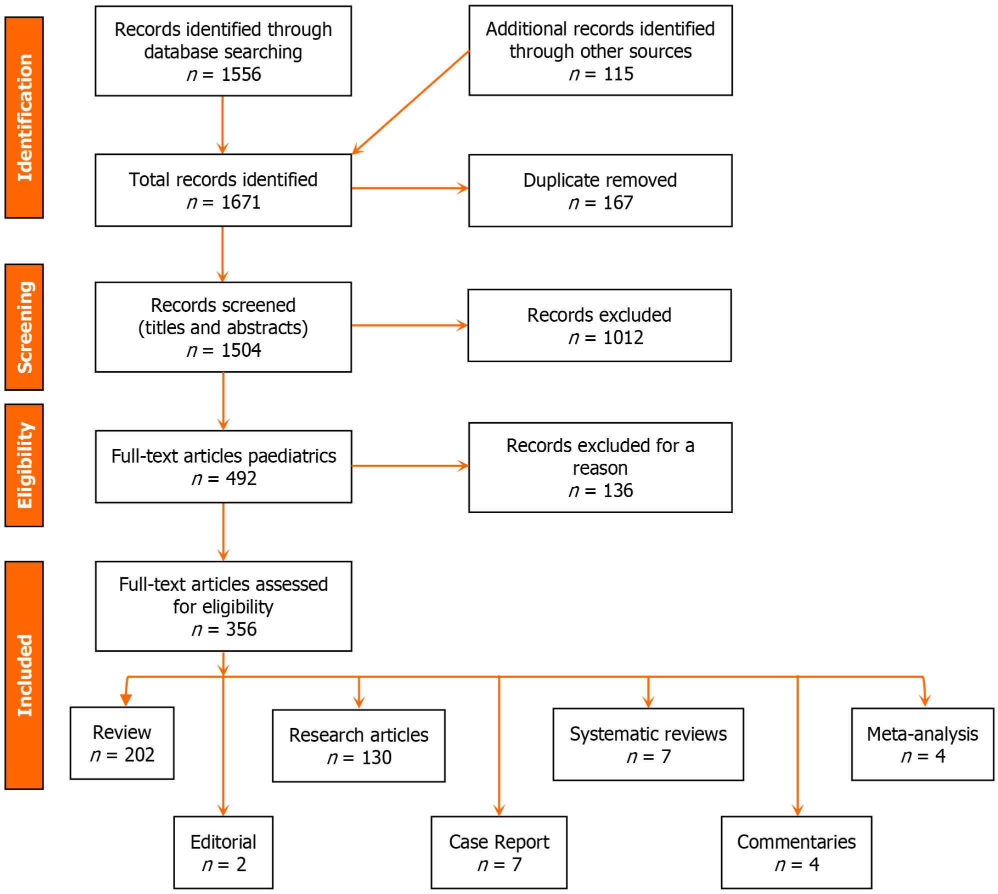

Figure 2 The study flow chart.

reduced sharing of interests or emotions, and failure to initiate or respond to social interactions[17]. There are also deficits in nonverbal communicative behaviors used for social interaction, including poorly integrated verbal and nonverbal communication, abnormalities in eye contact and body language, difficulties in understanding and using gestures, and a lack of facial expressions and nonverbal communication[18]. Lastly, there are deficits in developing, maintaining, and understanding relationships, including difficulty adjusting behavior to suit different social contexts, challenges in sharing imaginative play or making friends, and a general absence of interest in peers[19].

In addition to the core diagnostic criteria, the DSM-5 specifies that symptoms of ASD must be present in the early developmental period. However, they may not become fully apparent until social demands exceed the individual's limited capacities or may be masked by learned strategies later in life[20]. Furthermore, these symptoms must cause clinically significant impairment in social, occupational, or other important areas of current functioning. The disturbances observed should not be better explained by intellectual disability or global developmental delay. While intellectual disability and ASD often co-occur, a comorbid diagnosis requires that the social communication impairments be disproportionate to the general developmental level[21].

Overview and phenotypic heterogeneity of autism

ASD is marked by symptoms affecting social interactions, communication, and behavior. Patients face verbal and nonverbal communication challenges, including difficulties with spoken language, eye contact, facial expressions, and gestures. They struggle with social reciprocity, engaging in reciprocal interactions, sharing interests and emotions, and responding to social overtures. Additionally, they struggle to form and maintain relationships, adapt behavior to various social contexts, and form friendships[13,14]. Repetitive behaviors and restricted interests are common in autism. Patients engage in repetitive actions like hand-flapping and insist on sameness, adhering inflexibly to routines. They often have highly focused, intense interests in specific topics or objects and exhibit sensory sensitivities, reacting strongly to sensory inputs like lights, sounds, and textures[15,16].

The DSM-5 outlines two main diagnostic criteria categories for ASD: Deficits in social communication and social interaction and restricted repetitive behaviors and interests[17-19]. Social communication deficits include social-emotional reciprocity, nonverbal communication, and relationship development and maintenance[17-19]. Symptoms must be present early in development, cause significant impairment in functioning, and not be better explained by intellectual disability or global developmental delay. Intellectual disability and ASD often co-occur, but a comorbid diagnosis requires that social communication impairments exceed general developmental levels[20,21].

ASD isn't a one-size-fits-all condition. ASD is renowned for its phenotypic heterogeneity, which refers to the wide variability in the manifestation of symptoms and traits among individuals with the disorder. Variations in core symptoms, abilities, and motor skills, along with factors like sex and co-existing conditions, create a spectrum of experiences[22]. This heterogeneity encompasses a broad range of social, communicative, and behavioral challenges, making everyone's experience with autism unique. This phenotypic variability is due to the complex interplay of genetic, environmental, and biological factors[23]. Genetic factors include DNMs, inherited genetic variants, CNV, and epigenetic modifications. Environmental factors encompass prenatal exposures, perinatal events, and postnatal influences such as early childhood experiences and exposure to toxins[24]. Biological factors involve improper synaptic morphology and function, differences in brain structure and function, and imbalances in neurotransmitter systems. Co-occurring conditions, such as intellectual disability and other neurodevelopmental and psychiatric disorders, also contribute to variability in symptom presentation and severity[25]. Gender differences also play a role in phenotypic variability in patients with autism. Self-injurious behavior is more frequent in women than men with autism. Males with autism are more likely to have more severe language difficulties than females with autism[26].

Developmental trajectories, including the age of onset and progression of symptoms, along with the development of adaptive skills, further influence the heterogeneity of ASD[27]. Additionally, gene-environment interactions and epigenetic changes play crucial roles in shaping the manifestation of ASD traits. This clinical heterogeneity imposes a substantial challenge to the proper diagnosis and management of patients with autism. It also may reflect the genetic variability present in patients with ASD[28]. Individuals with ASD exhibit diverse levels of difficulty in engaging in reciprocal social interactions. Some may struggle with basic social conventions like making eye contact or recognizing social cues, while others might struggle to share interests or emotions. These challenges can include difficulties in initiating and sustaining conversations, understanding jokes or sarcasm, and recognizing social cues[29]. The ability to form and maintain relationships varies greatly. Some individuals may have profound difficulties in making and keeping friends, while others might develop meaningful relationships but find navigating the nuances of social interactions challenging. Problems with social reciprocity and forming relationships can lead to social isolation and challenges in peer interactions[30].

There is significant variability in verbal communication abilities among those with ASD. Some individuals may be nonverbal or have limited speech, while others may have extensive vocabulary but struggle with pragmatic language use, such as understanding idioms and metaphors or engaging in back-and-forth conversations[31]. Difficulties with nonverbal communication are common and can include challenges in understanding and using body language, facial expressions, and gestures. This can affect the ability to interpret others' emotions and intentions, leading to miscommunications and social misunderstandings. Patients with autism show variable behavioral challenges[32]. These behaviors manifest in various forms, including repetitive movements (*e.g.*, hand-flapping, rocking), ritualistic behaviors (*e.g.*, strict adherence to routines), and intense focus on specific interests (*e.g.*, deep knowledge about a particular subject). The intensity and nature of these behaviors can vary widely among individuals. These behaviors can be coping mechanisms or ways to express excitement, stress, or other emotions. While some individuals may exhibit mild repetitive behaviors, others may have behaviors that significantly interfere with daily activities[33].

Many individuals with ASD have atypical responses to sensory stimuli. This can include hyper-reactivity (*e.g.*, being overwhelmed by loud noises or bright lights) or hypo-reactivity (*e.g.*, seeming indifferent to pain or extreme temperatures). These sensory issues can significantly impact daily functioning and quality of life. Many individuals with ASD have a strong preference for routine and predictability[34]. Changes in routine can cause significant distress and anxiety. Higher rates of co-occurring conditions such as anxiety, depression, ADHD, epilepsy, and gastrointestinal issues are common in individuals with ASD. These conditions can compound the challenges faced by individuals with autism, adding to the complexity of managing their overall health and well-being[35].

Studying the phenotypic heterogeneity of ASD and its biological basis is crucial for several reasons. It helps to identify and understand genetic risk factors that specify specific pathways and mechanisms underlying the disorder's behavioral deficits. It also improves diagnostic accuracy by assisting clinicians to recognize and diagnose the disorder more precisely, thus ensuring that individuals receive the appropriate support and interventions[36]. This understanding enables the development of personalized treatment plans tailored to the unique social, communicative, and behavioral challenges faced by each individual with autism. Enhanced knowledge of phenotypic diversity also leads to better support systems in educational and workplace settings, creating more inclusive environments. Understanding this heterogeneity provides essential information for families and caregivers for practical support and advocacy, helping them manage daily challenges and set realistic expectations[37]. Additionally, research into the phenotypic variability of ASD informs public health policies and funding priorities, ensuring resources are allocated effectively to meet the diverse needs of the autism community. This research also provides insights into the underlying biological, genetic, and environmental factors contributing to ASD, potentially leading to early diagnosis and new therapeutic targets. Moreover, increasing awareness of ASD's diverse manifestations helps reduce stigma, fostering greater acceptance and inclusion in society[38].

Genetic architecture of autism

The genetic architecture of ASD is highly complex, with more than 100 genes implicated in its pathogenesis. ASD is considered a highly polygenic disorder, which is influenced by multiple genes, each contributing a small effect. The combined effect of many genetic variants, both common and rare, creates a cumulative risk of developing ASD[39]. This polygenic risk model helps explain the broad spectrum of ASD phenotypes and the variability in symptom severity and presentation. Genetic susceptibility to ASD refers to the increased likelihood of developing the disorder based on an individual's genetic makeup[40]. This susceptibility is influenced by various genetic factors (Figure 3), including common genetic variants with small effects, rare genetic variants with large effects, DNMs, and CNVs augmented with the gene-

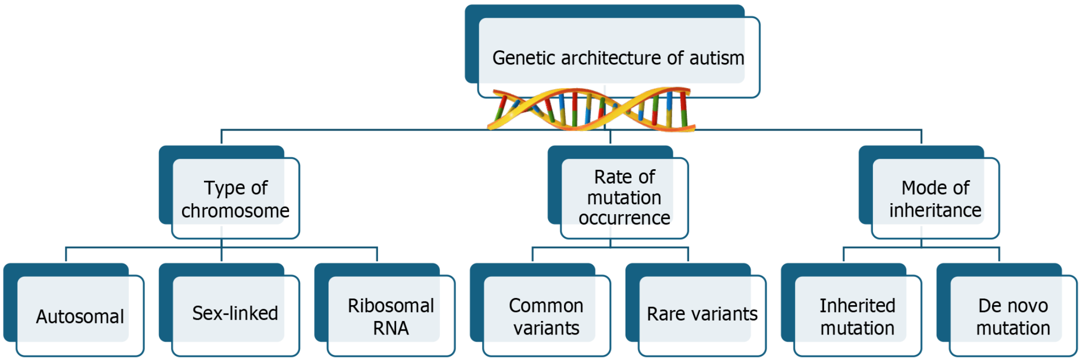

Figure 3 Simple diagrammatic presentation of the genetic architecture of autism.

environment interactions and epigenetic factors effects, which can contribute to the risk of ASD either individually or through complex interactions[41].

Common genetic variants: These genetic variants are relatively frequent variations in the DNA sequence frequently found in the general population and contribute modestly to the risk of developing ASD. Each common variant typically has a small effect on ASD risk, but collectively, they can significantly contribute to genetic susceptibility[42]. These variants are often single nucleotide polymorphisms (SNPs) identified through GWAS. These studies involve scanning the genomes of many individuals to find genetic markers associated with ASD[43]. These studies have identified several SNPs that are more common in individuals with autism compared to those without the disorder. In addition, risk alleles are specific versions of genetic variants that increase the likelihood of developing ASD. While each risk allele contributes only slightly to ASD risk, the presence of multiple risk alleles can have a substantial impact[44].

A polygenic score, also known as a polygenic risk score, is a measure that aggregates the effects of many genetic variants to estimate an individual's genetic predisposition to a particular trait or disorder, such as ASD. This score is calculated based on the presence of numerous common genetic variants, each contributing a small effect to the overall risk[45]. The polygenic score is derived from GWAS, which identifies SNPs associated with ASD. Each SNP is assigned a weight based on its association with ASD, and the polygenic score is the sum of these weighted SNPs present in an individual’s genome. The polygenic score estimates how frequent genetic variations in the population contribute to the development of autism[46]. A higher polygenic score indicates a greater genetic predisposition to ASD and a higher probability of being diagnosed with autism. However, it is important to note that a polygenic score is not deterministic; it only provides a risk estimate based on genetic factors[47]. Environmental influences and gene-environment interactions also play significant roles in the development of ASD. Polygenic scores can be used in research to understand the genetic architecture of ASD and to identify individuals at higher genetic risk[48]. These scores might eventually aid in early detection and personalized intervention strategies in clinical settings, although their use in routine clinical practice is still under research and debate. Individuals can be stratified based on their polygenic scores into different risk categories. This stratification can help identify those who might benefit from more intensive monitoring or early intervention[49]. Several common variants have been associated with ASD, though each variant's individual contribution to the disorder is small.

Rare genetic variants: The genetic architecture of ASD is highly heterogeneous, involving a combination of common and rare genetic variants. While common variants each contribute a small effect size, rare genetic variants can have a substantial impact on the risk of developing ASD[39]. These rare variants often exhibit high penetrance, meaning they significantly increase the risk of ASD in carriers. Examples of such mutations include those found in genes like *CHD8*, *SHANK3*, and *MECP2*[50]. These mutations are frequently associated with severe forms of ASD and comorbid conditions such as intellectual disability, epilepsy, and specific syndromic features. The presence of rare genetic variants contributes to the phenotypic variability seen in ASD. Different mutations can lead to diverse clinical presentations, even within the same gene. For instance, mutations in *SHANK3* can result in a range of phenotypes from severe intellectual disability to milder social deficits[51]. Additionally, rare variants can interact with environmental factors, influencing the onset and severity of ASD symptoms. This highlights the importance of considering both genetic predisposition and environmental exposures in understanding ASD[52].

Many rare genetic variants implicated in ASD affect synaptic proteins, which are crucial for synapse formation, function, and plasticity[53]. Genes like *SHANK3*, *NRXN1*, and *NLGN4* are essential in synaptic signaling and neuronal connectivity. Genetic variations such as *CHD8* and *MECP2* affect chromatin remodeling and gene expression regulation, which are critical for proper neuronal development and function[54]. Rare variants also impact neurotransmitter systems, including glutamatergic, GABAergic, dopaminergic, and serotonergic pathways, which are vital for maintaining the balance of excitatory and inhibitory signals in the brain[55]. Advances in sequencing technologies have facilitated the identification of rare genetic variants in individuals with ASD. Whole-exome sequencing (WES) and WGS are instrumental in discovering novel mutations and understanding their functional consequences[56]. Experimental approaches, including animal models and cellular assays, are used to characterize the functional impact of rare variants. These studies help elucidate the biological pathways affected by these mutations and their role in ASD pathology[57].

The identification of rare genetic variants can inform genetic testing and diagnosis, enabling personalized approaches to managing ASD. Genetic counseling can also provide valuable insights to families regarding the inheritance patterns and risks of ASD[58]. Understanding the specific genetic and molecular mechanisms underlying ASD can lead to the development of targeted therapies. For example, drugs modulating synaptic function or neurotransmitter systems may offer potential treatment options for individuals with specific genetic mutations[59].

DNMs: DNM are mutations found in the genomes of autistic or non-autistic children but not in the genomes of their parents. DNMs are new genetic changes that arise spontaneously in the germ cells of parents or early in embryonic development and are not inherited from either parent. They play a significant role among the genetic contributors to ASD [60]. DNMs are particularly important in the context of ASD for several reasons. They are often found in genes critical for brain development and function. Studies have shown that individuals with ASD have a higher burden of DNMs compared to their unaffected siblings. These mutations can occur in coding regions of the genome, disrupting the structure and function of proteins involved in neural development, synaptic signaling, and other key processes[61,62]. One of the key aspects of DNMs is their high impact on the risk of developing ASD. Unlike common variants that contribute small incremental risks, DNMs can have large effects[63]. For instance, mutations in genes such as *CHD8*, *SCN2A*, and *SYNGAP1* have been identified as high-confidence ASD risk genes due to the significant disruptions they cause in neurodevelopmental processes. These genes are involved in critical pathways, including chromatin remodeling, synaptic function, and ion channel activity, highlighting the diverse biological mechanisms through which DNMs can influence ASD[64].

The identification of DNMs has been facilitated by advances in next-generation sequencing technologies, such as WES and WGS[65]. These technologies allow for the comprehensive analysis of the entire genome coding sequence, uncovering rare and potentially pathogenic mutations that may not be detected through traditional genetic testing methods[66]. Research has identified hundreds of genes that harbor DNMs associated with ASD, underscoring the genetic complexity of the disorder. In terms of phenotypic consequences, DNMs are often associated with more severe forms of ASD[67]. Children with DNMs may exhibit profound intellectual disabilities, severe communication deficits, and a higher incidence of comorbid conditions such as epilepsy. This contrasts with ASD cases linked to common genetic variants, which may present with milder symptoms[68].

Furthermore, DNMs provide insights into the genetic architecture of sporadic ASD cases-those without a family history of the disorder. Since these mutations are new and not inherited, they can explain the occurrence of ASD in families with no previous instances, helping to understand the sporadic nature of many ASD cases[69]. This also has implications for genetic counseling, as the recurrence risk of ASD due to DNMs in subsequent pregnancies is generally low, although slightly elevated compared to the general population. Understanding the role of DNMs in ASD has significant implications for both research and clinical practice. It highlights the importance of early genetic screening and diagnosis, which can lead to timely interventions and personalized treatment strategies[70]. Additionally, ongoing research into the functional impact of specific DNMs can identify potential therapeutic targets, paving the way for developing novel treatments to mitigate the effects of these genetic alterations[71].

Some of the well-studied genetic mutations observed in patients with ASD

This section highlights some of the well-studied genetic mutations observed in patients with ASD. Table 1 shows some notable loci, including *CHD8*, *CNTNAP2*, and *SHANK3*. Figure 4 shows some of the important genes liable for mutations in ASD: Their functions and localization of representative molecules.

***CHD8*:** A vital chromatin regulator enzyme during fetal development) gene is a significant genetic factor associated with ASD, located at chromosome 14q11.2, and encoding a protein crucial for chromatin remodeling and gene expression regulation[72]. *CHD8* influences neurodevelopment, neuronal differentiation, and synaptic function, and its disruption can lead to widespread effects on brain structure and function pertinent to ASD. DNMs in *CHD8*, which arise spontaneously and are not inherited, are strongly linked to ASD[25]. These mutations often result in macrocephaly, gastrointestinal issues, specific facial dysmorphisms, and core ASD symptoms such as deficits in social communication and repetitive behaviors[73]. Additionally, *CHD8* mutations are associated with intellectual disability or cognitive impairments, particularly in language and motor skills. Studies have shown that *CHD8* regulates a large network of genes implicated in ASD, and its mutations can disrupt multiple neurodevelopmental pathways[74]. Animal models with *CHD8* mutations exhibit similar features to humans, providing insights into the mechanisms contributing to ASD. Research also explores gene-environment interactions involving *CHD8* to identify intervention periods and therapeutic targets[75]. Potential therapies could involve modulating disrupted pathways, emphasizing the importance of genetic testing and personalized medicine. Understanding *CHD8* mutations helps tailor interventions and support services to individual needs, advancing the development of targeted therapies to mitigate the impact of these genetic mutations.

***CNTNAP2*:** Gene variant is a significant genetic factor implicated in ASD, playing a crucial role in the development and function of the nervous system, particularly in cortical areas related to language, cognition, and social behavior[76]. The *CNTNAP2* gene is the largest gene in the human genome, located at chromosome 7q35, and one of the few known human genes essential for language development. *CNTNAP2* encodes a protein involved in brain cell adhesion and neuronal communication, which is essential for synapse formation, nerve signal transmission, interactions between neurons and between neurons and glial cells, and the clustering of potassium channels[77]. Variants in *CNTNAP2*, including both common and rare mutations, have been linked to ASD and associated with core symptoms such as social communication deficits, repetitive behaviors, language delays, and intellectual disability[78]. Gandhi *et al*[79] showed that disruptions in *CNTNAP2* Lead to altered neural connectivity and signaling, contributing to ASD pathogenesis. Animal models with *CNTNAP2* mutations exhibit behaviors analogous to human ASD, providing valuable insights. Studies also explore how

Table 1 Genes implicated in autism spectrum disorder

No.	Gene symbol	Full gene name	Location	Function	Implication in ASD	Frequency in ASD patients
1	*CHD8*	Chromodomain helicase DNA binding protein 8	Chr. 14q11.	Crucial for chromatin remodeling and gene expression regulation	Regulates network of genes in ASD pathways. Disruption is linked to ASD, macrocephaly, gastrointestinal issues, facial dysmorphisms, social deficits, repetitive behaviors, and intellectual disability	0.2%-0.3%
2	*CNTNAP2*	Contactin-associated protein 2	Chr. 7q35	Essential for brain cell adhesion, synapse formation, and nerve signal transmission. Key role in language and cognition	Altered neural connectivity, language delays, social communication deficits, repetitive behaviors, intellectual disability	0.5%-1%
3	*SHANK* family	SH3 and multiple ankyrin repeat domains protein	SHANK: Chr. 19, SHANK: Chr. 11, *SHANK3*: Chr. 22q13.3	Postsynaptic scaffolding proteins are critical for glutamatergic synapse function. Mutations linked to ASD	Synaptic dysfunction affects the structural integrity of synapses, causing social deficits, repetitive behaviors, and intellectual disability	1%-2%
4	*AVPR1A*	Arginine vasopressin receptor 1A	Chr. 12q14-15	Regulates social behavior and communication	Variants linked to ASD impair social recognition, bonding, social cognition deficits, and repetitive behaviors	0.10%
5	*OXTR*	Oxytocin receptor	Chr. 3p26.2	Key in social cognition and emotional regulation	SNPs and deletions impact receptor function. Variations affect oxytocin binding, which is linked to ASD social deficits	0.1%-0.2%
6	*DRD1*, *DRD2*	Dopamine receptors D1 (DRD1), D2 (DRD2)	DRD1: Chr. 5q35.2, DRD2: Chr. 11q22-23	Crucial for reward processing, motivation, and social behaviors	Impact on synaptic transmission, neural circuits in social interaction. Repetitive behaviors, social deficits, and altered dopaminergic pathways	0.10%
7	*DRD3*	Dopamine receptor D3	Chr. 3q13	Modulates neural circuits related to movement, emotion, and cognition	Variants and CNVs impact dopamine signaling, potentially contributing to ASD features	0.10%
8	*MECP2*	Methyl-CpG-binding protein 2	Chr. Xq28	Regulates gene expression critical for neuronal development	Mutations associated with Rett syndrome and some cases of ASD	1%-2% in females with Rett syndrome
9	*NRXN1*	Neurexin 1	Chr. 2p16.3	Presynaptic cell adhesion molecule crucial for synapse formation	Mutations associated with social communication deficits and cognitive impairments in ASD	0.3%-1%
10	*NRXN2*	Neurexin 2	Chr. 11q13.1	Presynaptic cell adhesion molecule involved in synaptic transmission	Mutations associated with social communication difficulties and ASD traits	Rare, precise frequency unknown
11	*NLGN4X*	Neuroligin 4X	Chr. Xp22.32-p22.31	Postsynaptic cell adhesion protein is involved in synaptic function	Mutations associated with synaptic connectivity disruptions and ASD features	0.5% in males
12	*NLGN4Y*	Neuroligin 4Y	Chr. Yq11.221	Homolog of *NLGN4X* on the Y chromosome	Mutations contribute to synaptic dysfunction and ASD traits in males	Rare, precise frequency unknown
13	*PTCHD1*	Patched domain-containing protein 1	Chr. Xp22.11	Protein is crucial for brain neuronal development and synaptic function	Mutations associated with deficits in social communication, repetitive behaviors, and cognitive flexibility in ASD	0.5% in males
14	*SLC6A4*	Serotonin transporter	Chr. 17q11.2	Regulates serotonin levels in the brain	Variations linked to alterations in social behavior, repetitive behaviors, and sensory processing in ASD	0.1%-0.2%
15	*DLG4*	Discs large homolog 4	Chr. 17p13.1	Scaffolding protein is essential for organizing neurotransmitter receptors at synapses	Mutations associated with synaptic plasticity deficits and behavioral symptoms in ASD	Rare, precise frequency unknown
16	*GABRG2*	Gamma-2 subunit of GABA(A) receptor	Chr. 5q34	Mediates inhibitory neurotrans-mission in the CNS	Mutations associated with synaptic excitation/inhibition imbalance and ASD symptoms	0.10%
17	*GRM7*	Metabotropic glutamate receptor 7	Chr. 3p26.1	Modulates synaptic transmission and plasticity	Mutations associated with altered glutamatergic signaling and ASD traits	Rare, precise frequency unknown

18	*BDNF*	Brain-derived neurotrophic factor	Chr. 11p14.1	Promotes neuronal growth, survival, and synaptic plasticity	Mutations associated with cognitive and behavioral symptoms of ASD	Rare, precise frequency unknown
19	*NRCAM*	Neuronal cell adhesion molecule	Chr. 7q31.1	Involved in synaptic plasticity and neural connectivity	Mutations associated with altered neural circuitry and behavioral traits in ASD	Rare, precise frequency unknown
20	*HTR2A*	Serotonin receptor 2A	Chr. 13q14.2	Regulates serotonin signaling pathways in the brain	Mutations associated with social behavior deficits and cognitive impairments in ASD	Rare, precise frequency unknown
21	*CX3CR1*	Chemokine receptor 1	Chr. 3p22.2	Involved in brain immune response and neuroinflammatory processes	Variants associated with microglial dysfunction and synaptic connectivity issues in ASD	Rare, precise frequency unknown
22	*CHRNA7*	Alpha-7 nicotinic acetylcholine receptor	Chr. 15q13.3	Integral to cholinergic signaling in the CNS	Mutations associated with cognitive deficits, social impairments, and ASD symptoms	Rare, precise frequency unknown
23	*GRIN2A*	GluN2A subunit of NMDA receptor	Chr. 16p13.2	Essential for synaptic plasticity and learning	Mutations associated with cognitive impairments, seizures, and ASD features	Rare, precise frequency unknown
24	*PTGS2*	Prostaglandin-endoperoxide synthase 2	Chr. 1q31.1	Synthesizes prostaglandins involved in inflammation and immune responses	Potential role in immune dysregulation related to ASD; further research needed	Rare, precise frequency unknown
25	REELN	Reelin	Chr. 7q22	Guides neuronal migration and synaptic plasticity during brain development	Rare mutations associated with altered neuronal migration and synaptic connectivity in ASD	0.1%-0.2%
26	*FOXP2*	Forkhead box P2	Chr. 7q31.1	Important for language development and speech production	Rare mutations linked to speech and language deficits in individuals with ASD	Rare, precise frequency unknown
27	*SNAP25*	Synaptosome associated protein 25	Chr. 20p12.2	Facilitates neurotransmitter release at synapses	Rare genetic variants implicated in synaptic dysregulation in ASD	Rare, precise frequency unknown
28	*CACNA1G*	Calcium voltage-gated channel subunit alpha1 G	Chr. 17q21.33	Part of voltage-gated calcium channels regulating neuronal excitability and synaptic plasticity	Rare mutations associated with altered neural connectivity and behavior in ASD	Rare, precise frequency unknown
29	*GABRA5*	Gamma-aminobutyric acid type A receptor alpha5 subunit	Chr. 15q12	Subunit of GABA-A receptor critical for inhibitory neurotransmission	Rare variants linked to disrupted GABAergic signaling in ASD	Rare, precise frequency unknown
30	*GRIN2B*	Glutamate ionotropic receptor NMDA type subunit 2B	Chr. 12p13.1	It is a subunit of NMDA receptor involved in synaptic plasticity and excitatory neurotransmission	Rare mutations associated with altered synaptic signaling pathways in ASD	Rare, precise frequency unknown
31	*GRIK2*	Glutamate ionotropic receptor kainate type subunit 2	Chr. 6q16.3	Subunit of kainate receptor modulating synaptic transmission and plasticity	Rare genetic variants implicated in synaptic dysfunction and behavioral traits of ASD	Rare, precise frequency unknown
32	*HOMER1*	Homer protein homolog 1	Chr. 5q14.1	Postsynaptic density protein is involved in synaptic signaling and plasticity	Rare mutations linked to synaptic dysfunction and behavioral traits of ASD	Rare, precise frequency unknown

The frequency values provided are approximate and can vary depending on the specific study or population examined. Some genes have "Rare, precise frequency unknown," indicating that while they are implicated in autism spectrum disorder, their mutation frequency is less clearly defined. ASD: Autism spectrum disorder; CNS: Central nervous system; CNV: Copy number variation; NMDA receptor: N-methyl-D-aspartate receptor; SNPs: Single nucleotide polymorphisms.

CNTNAP2 variants interact with environmental factors, which could identify critical intervention periods and therapeutic targets[80]. These findings underscore the importance of genetic testing and personalized medicine, as understanding *CNTNAP2* mutations allows for tailored interventions and support mechanisms, advancing the development of more effective treatments for individuals with ASD.

***SHANK*:** Several large-scale genomic studies have established a strong association between ASD and mutations in the *SHANK* family of genes, specifically *SHANK1*, *SHANK2*, and *SHANK3*[81]. These genes encode a family of postsynaptic scaffolding proteins that are critical for the proper functioning of glutamatergic synapses in the central nervous system (CNS). The SHANK proteins play pivotal roles in synaptic structure and signaling, ensuring the stability and efficiency of

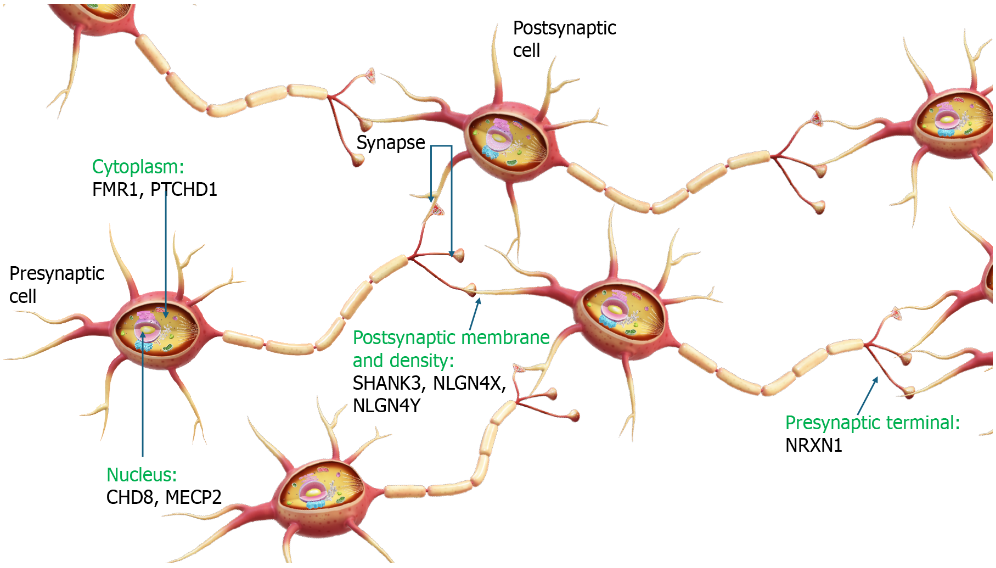

Figure 4 Genetic mutations in autism spectrum disorder: Functions and localizations of representative molecules. This figure provides an overview of representative molecules and their roles in synaptic function, focusing on the structure of a synapse, including the presynaptic terminal (containing neurotransmitter vesicles), the postsynaptic density (containing receptors and signaling proteins), and the synaptic cleft (space between presynaptic and postsynaptic terminals). Key molecules include *CHD8* (chromatin remodeling, gene expression regulation; nucleus; mutations disrupt gene expression, affecting synaptic development), *SHANK3* (postsynaptic scaffold protein; postsynaptic density; mutations affect synaptic signaling and plasticity), *MECP2* (DNA methylation regulation, transcriptional repression; nucleus; mutations affect neuronal function), FMR1 (regulates synaptic protein synthesis; cytoplasm, dendrites; mutations affect synaptic strength and plasticity), NRXN1 (cell adhesion, synaptic transmission; presynaptic terminal; mutations impair synaptic adhesion and neurotransmitter release), *NLGN4X* (cell adhesion molecule; postsynaptic membrane; mutations disrupt synaptic signaling and connectivity, especially in males), *NLGN4Y* [similar to *NLGN4X*; postsynaptic membrane; variations contribute to sex differences in autism spectrum disorder (ASD)], and *PTCHD1* (involved in the Hedgehog signaling pathway; cell membrane and cytoplasm; mutations linked to ASD and intellectual disabilities, more pronounced in males). The synaptic diagram illustrates the overall structure with labeled components, and molecule annotations place symbols representing each molecule at their respective localizations within the synapse, using arrows or lines to indicate their functional roles and the impact of mutations. Additional notes include color coding for different molecules to distinguish their roles and localizations and a legend explaining the symbols, colors, and impact of mutations. This figure underscores the importance of synaptic proteins and pathways in maintaining proper signaling and plasticity, with genetic mutations leading to impaired synaptic function central to ASD pathology.

synaptic connections, which are essential for learning, memory, and overall cognitive function[82].

Mutations in the *SHANK1* gene have been linked to ASD, particularly in males. *SHANK1* encodes a protein contributing to glutamatergic synapses' postsynaptic density (PSD), influencing synaptic strength and plasticity. Individuals with *SHANK1* mutations may exhibit milder ASD symptoms compared to mutations in *SHANK2* and *SHANK3*, but they still present with notable social communication deficits and repetitive behaviors[83]. Mutations in the *SHANK2* gene are associated with a range of neurodevelopmental disorders, including ASD. The SHANK2 protein plays a role in synaptic signaling and the structural integrity of synapses. Variants in *SHANK2* can lead to significant disruptions in synaptic function, resulting in the core symptoms of ASD, such as social communication challenges, repetitive behaviors, and sometimes intellectual disability[84]. Studies have shown that both inherited and DNMs in SHANK2 can contribute to the development of ASD[85].

The *SHANK3* gene is a significant genetic factor associated with ASD, encoding a protein crucial for the development and function of synapses, which are essential for neuronal communication. This protein, also known as ProSAP2, acts as a scaffolding protein in the PSD of excitatory synapses, ensuring synaptic connections' structural and functional integrity [86]. Mutations in *SHANK3* are strongly linked to ASD, particularly in cases related to Phelan-McDermid syndrome, which results from deletions or mutations on chromosome 22q13, where *SHANK3* is located[87]. Individuals with *SHANK3* mutations often exhibit severe expressive language delays, intellectual disability, and significant social communication and behavioral deficits, hallmark features of ASD. These mutations, which can be de novo or inherited, include point mutations, deletions, and duplications that disrupt SHANK3 protein function[88]. Zhou *et al*[89] indicate that *SHANK3* mutations lead to synaptic dysfunction, impairing neuronal communication and resulting in the neurological and behavioral manifestations observed in ASD. Animal models with *SHANK3* mutations exhibit behaviors similar to human ASD symptoms, such as social deficits, repetitive behaviors, and anxiety, offering valuable insights for studying underlying mechanisms and potential interventions[90]. The role of *SHANK3* in synaptic function makes it a critical target for therapeutic research, with efforts underway to develop treatments that can compensate for the loss of *SHANK3* function or restore its normal activity through gene therapy, small molecule drugs, and other innovative approaches[91]. Understanding *SHANK3* mutations in ASD not only aids in diagnosing and managing individuals with these specific genetic alterations but also provides broader insights into the synaptic and neurobiological mechanisms underlying ASD, essential for developing targeted therapies to improve the quality of life for those affected.

***AVPR1A*:** The *AVPR1A* gene, encoding the arginine vasopressin receptor 1A, has been implicated in ASD due to its critical role in regulating social behavior. This receptor, part of the vasopressin-oxytocin signaling system, influences social bonding, communication, and various social behaviors by initiating signaling cascades essential for neuronal activity and synaptic plasticity[92]. Studies have identified several polymorphisms, such as *RS3* in the *AVPR1A* gene, linked to ASD, as well as rare CNVs affecting gene dosage and receptor function[93]. Variations in *AVPR1A* can lead to significant differences in social behavior, including deficits in social recognition, reduced ability to form social bonds, and impaired communication, which are core aspects of ASD[94]. Animal models have shown that altered *AVPR1A* expression results in notable changes in social interaction, providing insights into similar human behaviors[95]. Clinical studies have associated specific *AVPR1A* alleles with social cognition deficits and repetitive behaviors, highlighting the gene's role in ASD susceptibility[96]. Understanding *AVPR1A*'s impact on ASD opens potential therapeutic avenues targeting the vasopressin-oxytocin pathway and suggests that genetic variants in *AVPR1A* could serve as biomarkers for personalized interventions, enhancing social functioning in individuals with autism.

OXTR: *OXTR* gene mutations have been scrutinized for their potential involvement in ASD, given the pivotal role of oxytocin in social behavior and bonding, processes often disrupted in individuals with ASD. The *OXTR* gene on chromosome 3 encodes the oxytocin receptor protein primarily expressed in brain regions crucial for social cognition, emotional regulation, and reward processing[97]. Various mutations in *OXTR*, including SNPs, insertions, deletions, and structural variants, can alter oxytocin receptor function. These mutations may impair oxytocin binding affinity and downstream signaling pathways, influencing social behavior and communication skills relevant to ASD[98]. While specific *OXTR* mutations have not been conclusively linked to ASD, genetic studies suggest associations between *OXTR* variations and susceptibility to social deficits characteristic of ASD. Regulatory variations in *OXTR*, affecting gene expression levels in brain regions critical for social functioning, further contribute to ASD risk[99].

Dopamine receptor: Dopamine receptors D1 (*DRD1*) and D2 (*DRD2*) are integral components of the dopamine system, crucial for regulating various neurological functions such as reward processing, motivation, and motor control. Mutations or variations in the genes encoding these receptors have been implicated in ASD, suggesting a role in the disorder's neurobiological underpinnings[100]. *DRD1*, the predominant dopamine receptor in the CNS, influences neuronal growth, cognitive flexibility, and social behaviors, all of which are commonly impaired in individuals with ASD. Genetic variants affecting *DRD1* expression or function may disrupt dopaminergic pathways, contributing to ASD symptoms like repetitive behaviors and social deficits[101]. Similarly, *DRD2*, involved in modulating synaptic transmission and reward mechanisms, has also been linked to ASD. Variants in the *DRD2* gene may alter dopamine signaling, impacting neural circuits crucial for social interaction and communication[102]. Animal studies support these findings, demonstrating that changes in *DRD1* and *DRD2* expression can lead to behaviors resembling those seen in ASD, providing insights into potential therapeutic strategies targeting dopamine receptors to mitigate symptoms associated with autism[103].

The *DRD3* gene encodes the dopamine receptor D3, which is crucial in modulating neural circuits related to movement, emotion, and cognition. Variants in the *DRD3* gene have been explored for their association with ASD due to dopamine's significant role in social behavior, reward processing, and executive function[104]. Specific polymorphisms, such as the Ser9Gly variant, and CNVs in *DRD3* can affect receptor function and dopamine signaling, potentially contributing to ASD's behavioral and cognitive features. Alterations in dopamine signaling through *DRD3* receptors can influence social behaviors, affecting social motivation, reward processing, and social interactions[105]. Animal studies have shown that manipulating *DRD3* expression impacts social behavior, repetitive behaviors, and cognitive flexibility relevant to ASD symptoms[106]. Human studies have found mixed results regarding the association between *DRD3* variants and ASD, with some suggesting a link to increased risk of autism and specific traits like repetitive behaviors and social communication difficulties[107].

***MECP2*:** The *MECP2* gene encodes the methyl-CpG-binding protein 2, a critical regulator of gene expression in the brain, playing a crucial role in neuronal development and synaptic plasticity. Mutations in *MECP2* are primarily associated with Rett syndrome, a severe neurodevelopmental disorder, but are also implicated in some cases of ASD. These mutations can include missense, nonsense, insertions, deletions, and duplications, leading to a loss or abnormal function of the MECP2 protein[108,109]. Clinically, individuals with *MECP2* mutations may exhibit impaired social interaction, communication difficulties, and repetitive behaviors, overlapping with core ASD features. The phenotypic effects of *MECP2* mutations can vary widely, contributing to a spectrum of neurodevelopmental conditions[110]. Research has identified *MECP2* mutations in a subset of individuals with ASD, highlighting the gene's contribution to the genetic heterogeneity of autism[111]. Animal models with *MECP2* mutations exhibit similar neurological and behavioral traits to humans, providing insights into these disorders' underlying mechanisms[112].

***NRXN1* and *NRXN2*:** Mutations in *NRXN1* and *NRXN2* genes, which encode neurexins, are implicated in ASD and other neurodevelopmental disorders. Neurexins are presynaptic cell adhesion molecules crucial for synapse formation, synaptic transmission, and neural circuit development. *NRXN1* mutations include deletions, duplications, and point mutations, often resulting in a loss of function[113]. Individuals with *NRXN1* mutations frequently exhibit ASD features such as social communication deficits, repetitive behaviors, and restricted interests. These mutations are also linked to intellectual disability, schizophrenia, and epilepsy. Although *NRXN1* deletions are relatively rare, they are significant genetic risk factors for ASD[114]. *NRXN2* mutations, involving similar types of genetic alterations, are associated with social communication difficulties, cognitive impairments, and repetitive behaviors, also contributing to the genetic heterogeneity of ASD. Both *NRXN1* and *NRXN2* mutations impair synaptic transmission and plasticity, leading to deficits in learning, memory, and behavior[115]. Research on these genes underscores their importance in synaptic function and highlights potential therapeutic targets. Large-scale genomic studies and animal models have further elucidated the impact of these mutations, suggesting that restoring normal synaptic function could mitigate the effects of these genetic disruptions and improve outcomes for individuals with ASD[116].

***NLGN4X* and *NLGN4Y*:** Mutations in the *NLGN4X* and *NLGN4Y* genes, which encode neuroligin (NLGNs)-4 proteins crucial for synaptic function, have been implicated in ASD. *NLGN4X*, located on the X chromosome, and *NLGN4Y*, its Y chromosome homolog, play essential roles in synaptic organization and neurotransmission[117]. Mutations in *NLGN4X*, including missense mutations and deletions, disrupt synaptic connectivity and function, contributing to ASD features such as impaired social communication, repetitive behaviors, and intellectual disability[118]. These mutations are primarily inherited in an X-linked recessive manner, affecting males more severely due to the lack of *NLGN4Y* compensation on the Y chromosome. *NLGN4Y* mutations, although less studied, similarly affect synaptic function and may contribute to ASD and other neurodevelopmental disorders in males[119].

***PTCHD1*:** *PTCHD1* gene mutations have garnered attention in ASD research due to their implications for neurodevelopmental processes. Located on the X chromosome, the *PTCHD1* gene encodes a protein crucial for brain neuronal development and synaptic function[120]. Various mutations in *PTCHD1*, including deletions, duplications, and missense mutations, disrupt its normal function, potentially affecting synaptic plasticity and neurotransmitter signaling pathways. These disruptions are implicated in the pathophysiology of ASD, contributing to deficits in social communication, repetitive behaviors, and cognitive flexibility observed in affected individuals[121]. *PTCHD1* mutations are more prevalent in males due to their X-linked inheritance pattern. Research into *PTCHD1* aims to elucidate how these mutations alter neuronal connectivity and synaptic transmission, providing insights into ASD's genetic mechanisms[122].

***SLC6A4*:** *SLC6A4* (also known as the serotonin transporter) gene plays a critical role in regulating serotonin levels in the brain by facilitating serotonin reuptake from the synaptic cleft back into presynaptic neurons[123]. Serotonin is a neurotransmitter involved in various physiological processes, including mood regulation, emotional processing, and social behavior, all of which are implicated in ASD[124]. Mutations in *SLC6A4*, encompassing various forms such as SNPs and structural variants, can impact serotonin transporter function and serotonin reuptake efficiency. These genetic alterations may disrupt serotonin signaling pathways, influencing neuronal development, synaptic plasticity, and the formation of neural circuits essential for social cognition and emotional processing[125]. While specific *SLC6A4* mutations have not been definitively linked to ASD, variations in the gene have been associated with alterations in social behavior, repetitive behaviors, and sensory processing observed in individuals with ASD[126].

***DLG4*:** *DLG4* gene (also known as Discs Large Homolog 4 or PSD-95) is a critical gene involved in synaptic function and neuronal development. It encodes a scaffolding protein essential for organizing and stabilizing neurotransmitter receptors and signaling proteins at excitatory synapses, particularly those involved in glutamatergic transmission in the CNS[127]. Mutations in *DLG4* can disrupt its function, affecting synaptic plasticity, neurotransmitter signaling, and neuronal circuitry, potentially contributing to the cognitive and behavioral symptoms observed in individuals with ASD [128]. These genetic changes, which may include missense mutations, deletions, or other structural variants, can lead to deficits in synaptic plasticity and an altered excitatory/inhibitory balance in the brain, associated with impairments in social communication, repetitive behaviors, and sensory processing in ASD[129]. Research into *DLG4* underscores the importance of synaptic proteins in ASD pathophysiology, providing insights into the molecular mechanisms underlying synaptic dysfunction and neuronal connectivity deficits[130].

GABRG2: The *GABRG2* gene, which encodes the gamma-2 subunit of the GABA(A) receptor, is critical in mediating inhibitory neurotransmission in the CNS. Mutations in *GABRG2* have been implicated in several neurological and developmental disorders, including ASD. GABA(A) receptors are pivotal in maintaining the balance between excitation and inhibition in the brain, which is essential for normal cognitive and behavioral functions[131]. In the context of autism, mutations in *GABRG2* can disrupt the function of GABA(A) receptors, leading to an imbalance in synaptic excitation and inhibition. This disruption can contribute to the core symptoms of ASD, such as social communication difficulties, repetitive behaviors, and restricted interests. Individuals with *GABRG2* mutations may exhibit a range of phenotypic manifestations, reflecting the gene's role in the broader neurodevelopmental landscape[132]. Studies have shown that *GABRG2* mutations can result in altered receptor function, affecting synaptic transmission and plasticity and leading to hyperexcitability of neural circuits, which is often observed in individuals with ASD[133]. Additionally, *GABRG2* mutations have been linked to co-occurring conditions frequently seen in autism, such as epilepsy, intellectual disability, and anxiety disorders, further complicating the clinical presentation and management of ASD[134].

***GRM7*:** *GRM7* gene, which encodes the metabotropic glutamate receptor 7 (mGluR7), modulates synaptic transmission and plasticity in the brain. Mutations or variations in *GRM7* have been associated with ASD, highlighting the gene's significance in neurodevelopmental processes. mGluR7 plays a crucial role in inhibitory neurotransmission by regulating the release of neurotransmitters at presynaptic terminals[135]. Dysregulation of glutamatergic signaling due to *GRM7* mutations can contribute to ASD symptoms, including social communication deficits, repetitive behaviors, and restricted interests[136]. Animal model studies have shown that *GRM7* expression or function alterations can result in autism-relevant behaviors, such as impaired social interactions and increased repetitive actions[137]. Genetic studies in human populations have identified associations between SNPs in *GRM7* and an increased risk of developing ASD. This suggests that genetic variation in this receptor may influence susceptibility to the disorder[138]. The involvement of *GRM7* in ASD points to potential therapeutic targets, with current research exploring the development of mGluR7 agonists or antagonists to restore normal glutamatergic signaling and mitigate autism symptoms[139]. Overall, *GRM7* mutations and their impact on glutamatergic signaling represent a significant area of interest for understanding the genetic and molecular basis of autism and for developing new therapeutic approaches.

***BDNF*:** *BDNF* is a crucial protein involved in neurons' growth, maintenance, and survival, playing a significant role in synaptic plasticity essential for learning and memory. Mutations or variations in the *BDNF* gene have been implicated in ASD, suggesting that *BDNF* dysfunction may contribute to the neurodevelopmental abnormalities characteristic of autism [140]. *BDNF* influences several aspects of neuronal function, including dendritic growth, synapse formation, and neurotransmitter release, which are vital for proper brain development and function[141]. In individuals with ASD, alterations in *BDNF* levels or activity can disrupt these processes, leading to deficits in social communication, repetitive behaviors, and restricted interests typical of the disorder[142]. Studies have shown that individuals with ASD often have altered *BDNF* expression levels, with some research indicating that lower levels of *BDNF* may be associated with more severe autism symptoms[143]. Specific SNPs in the *BDNF* gene have been linked to an increased risk of developing ASD, as these genetic variations can affect *BDNF* production or function, contributing to the pathophysiology of autism[144]. Animal models have been instrumental in elucidating the role of *BDNF* in ASD, with mice exhibiting altered *BDNF* expression showing behaviors reminiscent of autism, such as impaired social interactions and increased repetitive behaviors[145]. These models provide valuable insights into the mechanisms by which *BDNF* dysfunction may lead to ASD symptoms and offer a platform for testing potential therapeutic interventions. The link between *BDNF* and ASD also opens up potential therapeutic avenues, as strategies aimed at modulating *BDNF* levels or enhancing its activity could potentially alleviate some of the symptoms associated with autism. For instance, certain pharmacological agents, physical exercise, and dietary interventions have been shown to increase *BDNF* levels and may hold promise as adjunct therapies for ASD[146,147].

***NRCAM*:** *NRCAM* is a crucial protein involved in the development and function of the nervous system, particularly in the formation and maintenance of synapses[148]. Mutations or variations in the *NRCAM* gene have been associated with ASD, highlighting its potential role in the disorder's pathogenesis. *NRCAM* belongs to the immunoglobulin superfamily of cell adhesion molecules and plays a significant role in axonal guidance, synaptic plasticity, and neural connectivity, all of which are critical for proper brain function and development[149]. In individuals with ASD, *NRCAM* mutations may lead to altered neural circuitry and connectivity issues, which are common neuropathological features of the disorder. Studies have shown that *NRCAM* is involved in processes such as dendritic spine development and the regulation of synaptic strength, both of which are essential for cognitive functions like learning and memory. Disruptions in these processes can contribute to the core symptoms of ASD, including social communication deficits and repetitive behaviors [150]. Research has indicated that *NRCAM* interacts with other synaptic proteins and receptors, influencing neurons' structural and functional plasticity. For instance, *NRCAM*'s interaction with the L1 family of cell adhesion molecules is vital for neurite outgrowth and axonal pathfinding, which are often disrupted in ASD[151,152]. Additionally, animal models with *NRCAM* gene knockouts exhibit behavioral phenotypes reminiscent of ASD, such as social interaction impairments and increased anxiety-like behaviors, further supporting the gene's involvement in autism[130]. Overall, the association between *NRCAM* mutations and ASD underscores the importance of cell adhesion molecules in neurodevelopment and synaptic function.

***HTR2A*:** The *HTR2A* gene encodes the 5-hydroxytryptamine (serotonin) receptor 2A, a critical receptor in the brain involved in neurotransmission pathways. Mutations or variations in the *HTR2A* gene have been linked to ASD, suggesting that disruptions in serotonin signaling could play a role in the disorder's pathophysiology[153]. Serotonin is essential for regulating mood, anxiety, and social behavior, and abnormalities in serotonin signaling have been implicated in various psychiatric conditions, including autism. Studies indicate individuals with ASD often exhibit altered serotonin levels in the brain and peripheral tissues[124]. The *HTR2A* receptor is distributed in brain regions associated with cognitive functions, such as the prefrontal cortex and hippocampus. Mutations in the *HTR2A* gene can change the receptor's expression or function, disrupting serotonergic signaling crucial for social behavior and cognitive processing [154]. Genetic studies have identified polymorphisms in the *HTR2A* gene associated with increased ASD risk, where certain SNPs in the promoter region can affect gene expression levels[155]. Functional studies in animal models demonstrate that alterations in *HTR2A* signaling can affect social behavior and anxiety, mirroring ASD symptoms. The *HTR2A* receptor also plays a role in neurodevelopmental processes, including synaptogenesis and neural differentiation, with disruptions potentially leading to brain development and connectivity abnormalities characteristic of ASD[156].

***CX3CR1*:** The *CX3CR1* gene encodes the chemokine receptor 1, which is involved in the brain's immune response and neuroinflammatory processes[157]. Mutations or polymorphisms in *CX3CR1* have been implicated in ASD, suggesting that disruptions in immune signaling pathways may contribute to ASD pathogenesis. *CX3CR1* is expressed in microglia, the brain's resident immune cells, which are crucial for synaptic pruning, neuronal connectivity, and neuroinflammation [158]. Proper microglial function is essential for normal brain development and neural circuit maintenance. Research indicates that *CX3CR1* variants can alter microglial function, impairing synaptic pruning and increasing neuroinflammation, resulting in abnormal synaptic connectivity and contributing to the neurological deficits seen in ASD[159]. Studies show that certain *CX3CR1* polymorphisms are linked to increased microglial activation and exaggerated brain inflammatory responses, disrupting neuronal communication and plasticity, which are key to cognitive and social behaviors[160]. Animal models with *CX3CR1* mutations exhibit ASD-like behaviors, such as social interaction deficits and repetitive behaviors, providing insights into the gene's impact on brain development and function[161]. Genetic studies in humans have identified associations between specific *CX3CR1* variants and increased ASD susceptibility, highlighting the potential role of immune dysregulation in the disorder[162].

***CHRNA7*:** The *CHRNA7* gene encodes the alpha-7 nicotinic acetylcholine receptor (α7nAChR), a key component of cholinergic signaling in the CNS. This receptor is crucial for neurodevelopmental processes such as synaptic plasticity, neurotransmitter release, and cognitive function[163]. Mutations or polymorphisms in *CHRNA7* have been linked to ASD, suggesting that disruptions in cholinergic signaling may play a role in autism's pathophysiology. The α7nAChR is highly expressed in brain regions involved in cognition, memory, and social behavior, including the hippocampus, cortex, and amygdala, and it modulates the release of neurotransmitters like glutamate, GABA, and dopamine[164]. Research indicates that *CHRNA7* mutations can reduce receptor function or expression, impairing cholinergic signaling and affecting synaptic formation, neuronal differentiation, and network connectivity. This can result in cognitive and social deficits typical of ASD[165]. Studies have found associations between *CHRNA7* gene variants and autism, including CNVs causing partial deletions or duplications of the gene, which disrupt α7nAChR function[166]. Animal models with *CHRNA7* mutations exhibit autism-like behaviors, reinforcing the gene's role in neurodevelopment and autism. Additionally, α7nAChR regulates brain anti-inflammatory responses, and its impaired signaling may increase neuroinflammation, which is implicated in ASD etiology[167].

***GRIN2A*:** The *GRIN2A* gene encodes the GluN2A subunit of the NMDA (N-methyl-D-aspartate) receptor, which is essential for synaptic plasticity, learning, and memory. Mutations in *GRIN2A* are linked to various neurodevelopmental disorders, including ASD, epilepsy, and intellectual disability[168]. These mutations can lead to either a gain or loss of NMDA receptor function, disrupting synaptic signaling and neural circuitry[169]. Individuals with *GRIN2A* mutations often exhibit language deficits, intellectual disability, seizures, and autistic behaviors, highlighting the gene's complex role in brain development and function[170]. Research using animal models has shown that disruptions in NMDA receptor signaling due to *GRIN2A* mutations affect the development of neural circuits involved in social behavior, communication, and cognition[171]. Potential therapeutic approaches include pharmacological agents that modulate NMDA receptor activity and genetic therapies to correct specific mutations.

***PTGS2*:** *PTGS2* gene, also known as COX-2, plays a pivotal role in synthesizing prostaglandins, which are important mediators of inflammation and immune responses in the body[172]. While *PTGS2* mutations have been extensively studied in relation to inflammatory diseases and cancer, their direct association with ASD is not well-established in the current research literature. Studies exploring the role of immune dysregulation and inflammation in ASD have suggested potential links between immune system abnormalities and the development of autistic symptoms[173]. Prostaglandins, synthesized by *PTGS2*, are involved in regulating immune responses that could impact neurodevelopmental processes [174]. However, specific evidence directly implicating *PTGS2* mutations in ASD pathogenesis remains limited. Further research is necessary to determine whether variations in *PTGS2* influence inflammatory pathways that might contribute to the development or severity of ASD traits in affected individuals.

***Reelin* (*RELN*):** *Reelin* (*RELN*) is a pivotal protein in brain development, crucial for guiding the migration and positioning of neurons during the early stages of development[175]. Located on chromosome 7q22, the *RELN* gene encodes an extracellular matrix protein that interacts with receptors like VLDLR and ApoER2 to regulate neuronal migration and synaptic plasticity. Mutations in *RELN* have been implicated in various neurodevelopmental disorders, including ASD [176]. Research indicates that disruptions in *RELN* expression or function can lead to altered neuronal migration patterns and abnormal synaptic connectivity, potentially contributing to the cognitive and behavioral impairments seen in ASD [177]. While rare mutations in *RELN* have been identified in some individuals with ASD, they are not universally present across all cases. Animal models with *RELN* mutations exhibit behavioral deficits akin to autism, supporting its role in neurodevelopmental processes[75]. Understanding how *RELN* mutations impact brain development and function is crucial for developing targeted therapies and interventions for ASD, highlighting the need for further research into its specific mechanisms and therapeutic implications.

***FOXP2*:** *FOXP2*, located on chromosome 7q31, is a gene crucial for language development and speech production. Mutations in *FOXP2* are associated with speech and language disorders, particularly developmental verbal dyspraxia, which affects speech coordination[178]. Beyond its role in language, *FOXP2* mutations have also been studied in relation to ASD. While rare, mutations in *FOXP2* have been identified in individuals with ASD, suggesting a potential link between *FOXP2* dysfunction and the broader ASD phenotype, particularly affecting language and communication skills [179]. Animal studies and genetic research indicate that *FOXP2* mutations may disrupt neural circuits involved in language processing and social communication, contributing to ASD symptoms[180]. Further investigation is needed to elucidate the precise role of *FOXP2* in ASD pathogenesis and to explore its implications for developing targeted therapies aimed at improving language abilities and social communication skills in individuals with ASD.

***SNAP25*:** *SNAP25* is a gene located on chromosome 20p12.2 that plays a pivotal role in neurotransmitter release at synapses, essential for efficient neuronal communication[181]. Mutations and variations in *SNAP25* have been implicated in various neurodevelopmental and neuropsychiatric conditions, including ASD[182]. Research indicates that alterations in *SNAP25* function can disrupt synaptic transmission, impacting neural circuitry and potentially contributing to the development of ASD symptoms. While *SNAP25* mutations in ASD are less common compared to other disorders like ADHD or schizophrenia, studies have identified rare genetic variations in individuals with ASD[183]. Animal models with *SNAP25* mutations exhibit behaviors relevant to ASD, such as impaired social interactions and repetitive behaviors, reflecting its importance in neural development and behavior regulation[184]. Further investigation into how *SNAP25* disruptions specifically influence ASD pathophysiology could provide insights into underlying mechanisms and potential targets for therapeutic interventions tailored to ASD-related synaptic dysregulation.

***CACNA1G*:** *CACNA1G* is a gene that encodes a subunit of the voltage-gated calcium channels, which are crucial for regulating calcium ion influx into neurons. These channels play a vital role in neurotransmitter release, neuronal excitability, and synaptic plasticity in the brain[185]. Mutations or variations in *CACNA1G* have been implicated in various neurological and neuropsychiatric disorders, including ASD[186]. Studies have identified rare genetic variants in *CACNA1G* among individuals with ASD, suggesting a potential link between *CACNA1G* dysfunction and ASD susceptibility[187]. Animal models with *CACNA1G* mutations display behavioral traits relevant to ASD, such as altered social interaction, repetitive behaviors, and impaired communication skills. These findings indicate that disruptions in *CACNA1G* function may contribute to ASD pathophysiology by affecting neuronal excitability and synaptic transmission [188]. Further research is needed to elucidate the specific mechanisms by which *CACNA1G* mutations impact ASD risk and to explore potential therapeutic targets aimed at modulating calcium channel activity to mitigate ASD-related symptoms.

***GABRA5*:** *GABRA5* is a gene that encodes a subunit of the GABA-A receptor, which is integral to inhibitory neurotransmission in the brain. GABAergic signaling regulates neuronal excitability and maintains the balance between excitation and inhibition within neural circuits[189]. Mutations or variations in *GABRA5* have been implicated in several neurological and psychiatric disorders, including ASD[190]. Studies have identified rare genetic variants in *GABRA5* among individuals with ASD, suggesting a potential link between *GABRA5* dysfunction and ASD susceptibility[132]. Animal models with *GABRA5* mutations exhibit behavioral characteristics associated with ASD, such as altered social behaviors, repetitive behaviors, and impaired communication skills[191]. These findings suggest that disruptions in *GABRA5*-mediated inhibitory neurotransmission may contribute to the neurodevelopmental abnormalities observed in ASD.

***GRIN2B*:** *GRIN2B* is a gene that encodes a subunit of the NMDA receptor, a critical receptor involved in excitatory neurotransmission and synaptic plasticity in the brain[192]. Mutations or variations in *GRIN2B* have been associated with various neurodevelopmental and neuropsychiatric disorders, including ASD[193]. Studies have identified rare genetic variants in *GRIN2B* among individuals with ASD, suggesting a potential link between *GRIN2B* dysfunction and ASD susceptibility[194]. Animal models with *GRIN2B* mutations exhibit behavioral characteristics relevant to ASD, such as altered social interactions, repetitive behaviors, and impaired cognitive functions[195]. These findings underscore the importance of NMDA receptor function in neurodevelopment and the potential role of *GRIN2B* mutations in disrupting synaptic signaling pathways implicated in ASD pathophysiology.

***GRIK2*:** *GRIK2* is a gene that codes for a subunit of the kainate receptor, which is involved in synaptic transmission and plasticity in the brain. Kainate receptors are a type of ionotropic glutamate receptor that modulates excitatory neurotransmission and plays a role in regulating synaptic development and function[196]. Stolz *et al*[197] showed that mutations or variations in *GRIK2* have been implicated in several neurodevelopmental disorders, including ASD. Studies have identified rare genetic variants in *GRIK2* among individuals with ASD, suggesting a potential link between *GRIK2* dysfunction and ASD susceptibility[198]. Animal models with *GRIK2* mutations exhibit behavioral traits associated with ASD, such as altered social interactions, repetitive behaviors, and cognitive impairments[199]. These findings highlight the significance of kainate receptor-mediated synaptic signaling in neurodevelopment and underscore *GRIK2* as a candidate gene contributing to the genetic complexity of ASD.

***HOMER1*:** *HOMER1* is a gene that encodes a family of PSD proteins involved in synaptic signaling and neuronal plasticity in the brain. These proteins play a crucial role in regulating the structure and function of synapses, particularly at glutamatergic synapses, where they interact with various neurotransmitter receptors and signaling molecules[200]. Mutations or variations in *HOMER1* have been implicated in several neuropsychiatric and neurodevelopmental disorders, including ASD. Studies have identified rare genetic variants in *HOMER1* among individuals with ASD, suggesting a potential role in ASD susceptibility[201]. Animal models with *HOMER1* mutations exhibit behavioral characteristics relevant to ASD, such as altered social interactions, repetitive behaviors, and cognitive deficits[202]. These findings underscore the importance of *HOMER1*-mediated synaptic function in neurodevelopment and synaptic plasticity, implicating *HOMER1* as a candidate gene contributing to the genetic underpinnings of ASD.

Chromosomal disorders in patients with autism

ASD is characterized by a wide range of genetic etiologies, including various chromosomal disorders. These chromosomal abnormalities, which involve alterations in chromosome number or structure, can significantly impact neurodevelopment and contribute to the manifestation of ASD symptoms. While less frequent than DNMs, chromosomal disorders represent another critical genetic piece of the puzzle in understanding ASD[203]. There are two main categories of chromosomal disorders observed in patients with ASD: Numerical abnormalities and structural abnormalities. Numerical abnormalities involve having an atypical number of chromosomes, such as Down syndrome (extra chromosome 21) or Turner syndrome (missing X chromosome). Structural abnormalities refer to changes in chromosome structure, like deletions, duplications, or translocations[204]. Studies suggest that chromosomal abnormalities are present in around 7.4% of individuals with ASD, a higher percentage compared to the general population. These abnormalities can sometimes contribute to more severe forms of ASD, particularly when intellectual disability and developmental delays are also present[205]. Individuals with ASD and chromosomal abnormalities may also experience a higher prevalence of co-occurring conditions like epilepsy and behavioral issues[8].

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and is often associated with ASD. FXS results from a mutation in the *FMR1* gene located on the X chromosome, which leads to the silencing of the gene and a deficiency in the fragile X mental retardation protein[206]. Approximately 30%-50% of individuals with FXS meet the criteria for ASD, exhibiting symptoms such as social anxiety, repetitive behaviors, and language impairments [207]. Duplications of the 15q11-13 region, often referred to as Dup15q syndrome, are among the most common chromosomal abnormalities linked to ASD. This region contains several genes critical for brain development, including *UBE3A*[208]. Individuals with Dup15q syndrome typically exhibit severe developmental delays, intellectual disability, epilepsy, and a high prevalence of ASD, with features such as social communication deficits and repetitive behaviors [209].

22q11.2 deletion syndrome, also known as DiGeorge Syndrome or Velocardiofacial Syndrome, involves deleting a small piece of chromosome 22. This syndrome is associated with a broad spectrum of clinical manifestations, including congenital heart defects, palatal abnormalities, immune deficiencies, and neuropsychiatric disorders[210]. Approximately 20%-40% of individuals with 22q11.2 deletion syndrome exhibit ASD-like behaviors, including social communication challenges and restricted interests[211]. Turner syndrome affects females and is characterized by the complete or partial absence of one X chromosome (45, X karyotype). While Turner syndrome is primarily associated with physical features such as short stature and gonadal dysgenesis, there is also an increased prevalence of neurodevelopmental disorders, including ASD. Girls with Turner syndrome may exhibit social difficulties, attention deficits, and learning disabilities[212, 213].

Klinefelter syndrome (47, XXY) is a chromosomal disorder that affects males and is characterized by the presence of an extra X chromosome. Individuals with Klinefelter Syndrome often have mild cognitive impairments, speech and language delays, and social difficulties[214]. There is an elevated risk of ASD in males with Klinefelter Syndrome, with symptoms such as social communication deficits and repetitive behaviors[215]. Down syndrome, caused by the presence of an extra chromosome 21 (trisomy 21), is the most common chromosomal disorder associated with intellectual disability. Although not typically classified under ASD, a significant proportion of individuals with Down syndrome exhibit autistic traits, including social interaction challenges and repetitive behaviors[216]. The co-occurrence of ASD and Down syndrome highlights the overlap between different neurodevelopmental conditions[217]. Various other chromosomal abnormalities, such as duplications, deletions, and translocations, can also contribute to the development of ASD. For instance, abnormalities in chromosomes 1q21.1, 16p11.2, and 17q12 have been implicated in ASD, with each region harboring multiple genes involved in neurodevelopmental processes[218].

Identifying a chromosomal disorder can be achieved through karyotyping, a standard genetic test that analyzes chromosomes for abnormalities. Early diagnosis of a chromosomal disorder can lead to earlier diagnosis of ASD and the implementation of appropriate therapies and support systems[219]. Additionally, understanding the specific chromosomal abnormality can inform genetic counseling for families, providing information about potential recurrence risk in future pregnancies[220]. The identification of chromosomal disorders in patients with ASD has significant implications for diagnosis, management, and genetic counseling. Chromosomal microarray analysis and other advanced genetic testing methods have become crucial tools in identifying these abnormalities, enabling early diagnosis and tailored interventions[221]. Understanding the role of chromosomal disorders in ASD provides valuable insights into the genetic architecture of the disorder and underscores the importance of comprehensive genetic evaluations for individuals with ASD[222]. This knowledge not only aids in developing targeted therapies but also enhances our ability to provide personalized care and support for affected individuals and their families. However, it is crucial to recognize that chromosomal disorders are just one contributing factor to ASD in a subset of individuals. Most ASD cases have a more complex genetic architecture involving a combination of genetic and environmental factors[223].

Gender differences in autism symptomology: Sex chromosome effects?

ASD shows notable sex differences in its prevalence and symptomatology, with males being more frequently diagnosed than females. The reported male-to-female ratios vary from 1.33:1 to 15.7:1. Despite the general severity of autism not differing significantly between genders, notable differences exist in how ASD manifests, particularly when comorbid features are present[224]. Males with ASD often exhibit more externalizing behaviors, such as aggression, repetitive movements, and hyperactivity. In contrast, females are more prone to internalizing behaviors, including anxiety and depression. Furthermore, females with ASD tend to have more pronounced cognitive impairments, with the male-to-female ratio nearing 1:1 among those with severe intellectual disabilities[225]. These observations raise the question of whether these gender differences in ASD are due to distinct biological mechanisms or diagnostic biases influenced by the patient's presentation. Typically, ASD is diagnosed as a categorical condition rather than a continuum, which may significantly interact with behavioral and cognitive differences between males and females[26]. For instance, the less disruptive and less overt behaviors in girls with ASD might mean that only those with severe impairment are brought to diagnostic attention[226]. Recognizing these differences is crucial for clinical management, including screening for specific comorbidities and therapeutically targeting the most debilitating symptoms.

Some researchers believe that regardless of diagnostic biases, certain sex-specific biological mechanisms contribute to the gender disparity in ASD[227]. The female-protective effect (FPE) is a leading theory in this regard, suggesting that specific factors protect females from developing ASD, thereby requiring them to have a higher threshold to reach clinical impairment[228]. Evidence supporting this hypothesis includes studies indicating a greater genetic load related to ASD in females compared to males and in clinically unaffected female relatives compared to unaffected male relatives of individuals with ASD[229]. For example, a study of dizygotic twins by Attermann *et al*[229] using the Childhood Autism Spectrum Test and the Autism-Tics, Attention Deficit Hyperactivity Disorder, and Other Comorbidities inventory found higher autism symptom scores in siblings of female probands compared to those of male probands[230]. Similar findings were observed in another large-scale study by Van't Westeinde *et al*[231], which focused on repetitive and restricted behavior differences between male and female dizygotic twins. Females used more compensation and masking camouflage strategies than males. A related argument supporting the FPE is that males are more likely to meet clinical criteria for ASD than females, given the same genetic risk[232]. For instance, individuals with a *SHANK1* microdeletion were rigorously assessed, revealing that males more frequently met the clinical criteria for ASD, while females with the same mutation exhibited anxiety but not ASD[83].

The FPE mechanisms likely involve genes on the sex chromosomes and sex hormones. Although ASD is not linked to the X chromosome, it is suggested that the Y chromosome may pose a risk or that a second X chromosome may offer protection, as indicated by higher ASD rates in Turner syndrome (XO) and 47, XYY syndrome[233]. The role of sex chromosomes and related molecules has been increasingly recognized in contributing to these differences. Understanding these molecular mechanisms is crucial for developing sex-specific diagnostic and therapeutic approaches. The *MECP2* gene on the X chromosome is a well-known player in neurodevelopmental disorders. Mutations in *MECP2* are primarily associated with Rett syndrome, a condition that predominantly affects females and shares some phenotypic overlap with ASD. *MECP2* is involved in the regulation of gene expression through binding to methylated DNA. Its dysfunction can lead to widespread gene expression changes and neural development abnormalities[234]. Since males have only one X chromosome, mutations in *MECP2* can have more severe consequences, potentially explaining some of the observed sex differences in ASD prevalence and severity. NLGNs are a family of postsynaptic cell adhesion molecules critical for synapse formation and function[25]. *NLGN4X* and *NLGN4Y* are located on the X and Y chromosomes, respectively. Mutations in *NLGN4X* have been linked to ASD, with affected individuals showing impairments in synaptic function and neural connectivity[117]. The presence of *NLGN4X* on the X chromosome means that females with two X chromosomes may have a protective effect if one copy is mutated, whereas males with only one X chromosome are more vulnerable. *NLGN4Y*, on the Y chromosome, has a similar but not identical function to *NLGN4X*, and its role in ASD is less clear. However, variations in these genes can contribute to the differences in ASD manifestation between males and females [118]. *PTCHD1* is another gene of interest located on the X chromosome, which encodes a protein involved in the Hedgehog signaling pathway, essential for brain development. Mutations or deletions in *PTCHD1* have been implicated in ASD, intellectual disability, and other neurodevelopmental disorders. Like *MECP2* and *NLGN4X*, *PTCHD1* mutations may have more pronounced effects in males due to the lack of a second X chromosome that could compensate for the defective gene[120]. The inclusion of sex chromosome-related molecules in the study of ASD is vital for uncovering the nuances of sex differences in the disorder. By investigating the roles of *MECP2*, *NLGN4X*, *NLGN4Y*, and *PTCHD1*, researchers can better understand the genetic and molecular basis of these differences. This knowledge will pave the way for more tailored and effective therapeutic strategies that account for sex-specific variations in ASD presentation and progression[235].

Hormonal differences between males and females may also play a role. The differences in the vasopressinergic system in males and females might explain the male prevalence of ASD[94]. The role of sex hormones, particularly testosterone, in early brain development in children with ASD has garnered considerable interest. Several studies have found correlations between fetal testosterone levels, systematizing traits, social impairments, and reduced empathy[236]. Additionally, adults with ASD have been found to have higher levels of testosterone metabolites compared to unaffected individuals[226]. Future research should focus on developing gender-specific measures to better understand the influence of gender-specific factors on diagnosis and treatment. To date, no treatment studies have specifically targeted females with ASD based on hypothesis-driven approaches. Understanding these gender differences is vital for creating more effective and personalized interventions for individuals with ASD. Table 2 summarizes these gender differences in patients with ASD.

Advances in genomic technologies

Recent advances in genomic technologies have significantly enhanced our ability to diagnose ASD. High-throughput sequencing methods, such as WGS and WES, have enabled the identification of numerous genetic variants associated with ASD[237]. These technologies allow for a comprehensive analysis of the entire genome or the coding regions, respectively, providing insights into both common and rare genetic factors contributing to the disorder. Additionally, microarray-based comparative genomic hybridization (aCGH) has facilitated the detection of chromosomal abnormalities, such as CNVs, which are often implicated in ASD[238]. Integrating these advanced genomic tools into clinical practice holds promise for earlier and more accurate diagnosis, personalized treatment strategies, and a deeper understanding of the genetic architecture underlying ASD[239].

WES: Exome sequencing has made significant contributions to identifying risk genes in patients with ASD. This technology focuses on sequencing the exonic regions of the genome, representing about 1%-2% of the entire genome but containing the vast majority of known disease-related genetic variations[240]. By concentrating on these regions, exome sequencing provides a more cost-effective and efficient means of uncovering the genetic underpinnings of ASD[241]. One of the major contributions of exome sequencing to ASD research is the identification of DNMs-mutations that are not inherited from either parent but occur spontaneously. These mutations have been found to play a critical role in the development of ASD[242]. Studies utilizing exome sequencing have revealed that a significant proportion of individuals with ASD have unique DNMs in various genes, which might not have been identified through traditional genetic testing methods. These discoveries have expanded our understanding of the genetic diversity and complexity of ASD[243].

Exome sequencing has also facilitated the discovery of rare, high-impact variants contributing to the disorder. By analyzing the exomes of large cohorts of individuals with ASD and comparing them to control groups, researchers have identified numerous rare variants in genes that are crucial for brain development and function[244]. These findings have highlighted the importance of genes involved in synaptic function, neuronal communication, and other neurodevelopmental processes in the etiology of ASD. Furthermore, exome sequencing has identified several novel ASD risk genes. For instance, genes such as *CHD8*, SCN2A, and *SYNGAP1* have been implicated in ASD through exome sequencing studies [245]. These genes are involved in critical biological pathways, including chromatin remodeling, ion channel function, and synaptic signaling. Identifying these risk genes has provided new insights into the molecular mechanisms underlying

Table 2 The differences in autism symptomology and related factors between males and females

Aspect	Males with ASD	Females with ASD
Prevalence	Higher prevalence, male-to-female ratio 1.33:1 to 15.7:1	Lower prevalence
Behavioral manifestation	More externalizing behaviors (aggression, repetitive movements, hyperactivity)	More internalizing behaviors (anxiety, depression)
Cognitive impairments	Less pronounced cognitive impairments	More pronounced cognitive impairments, with a male-to-female ratio nearing 1:1 among those with severe intellectual disabilities
Diagnostic bias	More likely to be diagnosed due to overt behaviors	Less likely to be diagnosed unless severe impairment is present due to less disruptive behaviors
Genetic load	Lower genetic load	Higher genetic load in affected females and unaffected female relatives compared to males
Compensation and masking strategies	Less frequent use	More frequent use
Clinical criteria meeting	More likely to meet clinical criteria for ASD given the same genetic risk	Less likely to meet clinical criteria, may exhibit related issues such as anxiety
Sex chromosome influence	Y chromosome may pose a risk	The second X chromosome may offer protection, as indicated by higher ASD rates in Turner syndrome (XO) and 47, XYY syndrome
Hormonal influence	Differences in the vasopressinergic system, higher fetal testosterone levels associated with ASD traits	Potential protection from the second X chromosome, hormonal influences not as clearly defined
Camouflage strategies	Less frequent use	More frequent use to mask symptoms
Research and treatment	Focused mainly on males	Lack of hypothesis-driven treatment studies targeting females

This table highlights the key differences in the manifestation, diagnosis, and underlying biological mechanisms of autism spectrum disorder between males and females. Understanding these differences is essential for improving diagnostic criteria and developing gender-specific treatments. ASD: Autism spectrum disorder.

ASD and has opened up potential avenues for targeted therapeutic interventions[246].

Another significant advantage of exome sequencing is its ability to uncover gene-disrupting mutations in individuals with ASD who do not have a family history of the disorder. This capability is crucial for understanding sporadic cases of ASD, where the genetic basis might be less apparent[247]. By pinpointing specific genetic mutations in these cases, exome sequencing helps to clarify the genetic contributions to ASD in a broader population. Moreover, exome sequencing has proven valuable in studying the genetic architecture of ASD in diverse populations. It allows researchers to explore the genetic variations and mutations that may be more prevalent in certain ethnic or geographic groups, contributing to a more comprehensive understanding of the global genetic landscape of ASD[248].

WGS: WGS has revolutionized the field of genetics by comprehensively analyzing an individual's entire genome, encompassing both coding and non-coding regions. This technology has significantly advanced our understanding of the genetic basis of ASD in several keyways[249]. First, WGS has facilitated the discovery of rare genetic variants that were previously undetectable with older methods. These rare variants often have a large effect size and can be crucial in understanding the genetic underpinnings of ASD[250]. By analyzing the entire genome, WGS can identify mutations in non-coding regions that may regulate gene expression, adding a new layer of complexity to our understanding of ASD genetics[251].

Second, unlike targeted sequencing or WES, which focus only on specific parts of the genome, WGS provides a complete picture. This includes single nucleotide variants, insertions, deletions, CNVs, and structural variants. The ability to detect a wide range of mutation types helps identify novel genetic contributors to ASD[252]. Third, a significant portion of the human genome is non-coding, and mutations in these regions can affect gene regulation and expression. WGS allows researchers to investigate these regions and understand how they may contribute to ASD. For instance, mutations in regulatory elements, enhancers, and promoters can disrupt normal gene function and lead to ASD[253]. Moreover, through WGS, researchers have identified numerous new genes associated with ASD that were not previously linked to the disorder. These discoveries expand the list of potential targets for therapeutic intervention and provide new insights into the biological pathways involved in ASD[254]. ASD is known for its genetic heterogeneity, meaning many different genetic factors can contribute to it. WGS helps elucidate this complexity by identifying the diverse genetic mutations across different individuals with ASD. This understanding can lead to more personalized approaches to diagnosis and treatment[54].

Additionally, WGS enables large-scale genomic studies and the creation of extensive databases of genetic information. By comparing the genomes of thousands of individuals with and without ASD, researchers can identify patterns and commonalities that provide deeper insights into the genetic architecture of the disorder[243]. WGS is particularly useful in family-based studies, where the genomes of affected individuals and their relatives are sequenced. This approach can identify inherited mutations and DNMs (new mutations do not present in the parents) that contribute to ASD, helping to pinpoint specific genetic risk factors[255]. Overall, WGS has dramatically advanced our understanding of the genetic basis of ASD by providing a detailed and comprehensive view of the genome. This technology continues to uncover new genetic insights, paving the way for better diagnostic tools, personalized treatments, and a deeper understanding of the complex genetic landscape of ASD[256].

CNVs: CNVs have a substantial impact on the risk of developing ASD. CNVs refer to structural changes in the genome that result in the duplication or deletion of large segments of DNA. These variations can encompass one or multiple genes and significantly alter gene dosage, disrupting normal cellular functions[257]. One of the key contributions of studying CNVs to our understanding of ASD is the identification of specific genomic regions where duplications or deletions are associated with increased risk for the disorder[258]. For example, deletions and duplications at the 16p11.2 Locus have been repeatedly implicated in ASD. Individuals with deletions in this region often exhibit neurodevelopmental issues, including ASD, intellectual disability, and language impairments[259]. Conversely, duplications at the same locus are also associated with ASD but may present with differing clinical features, underscoring the complex relationship between gene dosage and neurodevelopmental outcomes[260].

The presence of CNVs can disrupt the function of multiple genes simultaneously, leading to widespread effects on brain development and function. This is particularly relevant for genes involved in synaptic connectivity, neuronal communication, and brain signaling pathways[261]. CNVs that affect these genes can lead to abnormalities in the formation and maintenance of synapses, which are critical for proper brain function and development[262]. For instance, CNVs affecting the *NRXN1* gene, which encodes a protein essential for synaptic function, have been associated with ASD, highlighting the importance of synaptic integrity in the disorder. Furthermore, the study of CNVs has revealed that individuals with ASD often carry a higher burden of rare, large CNVs compared to the general population[263]. These rare CNVs can significantly affect gene function and are often de novo, meaning they are not inherited from the parents but arise spontaneously. The identification of such de novo CNVs in individuals with ASD supports the idea that these structural variations are critical contributors to the genetic architecture of the disorder[264].

Research has also shown that certain CNVs are more prevalent in individuals with ASD who also exhibit additional comorbid conditions, such as intellectual disability or epilepsy[265]. This suggests that CNVs not only contribute to ASD risk but may also influence the broader clinical phenotype, leading to a range of neurodevelopmental outcomes depending on the specific genes and pathways affected. The impact of CNVs on ASD risk is further highlighted by their contribution to the genetic heterogeneity of the disorder[266]. ASD is known for its diverse genetic landscape, and CNVs add another layer of complexity by introducing large-scale genomic changes that can vary widely among affected individuals. This genetic diversity underscores the need for personalized approaches to diagnosis and treatment, as the specific CNVs present in an individual can influence the manifestation and severity of ASD symptoms[267].

Gene-environment interactions and their effects on autism development

Gene-environment interactions play a crucial role in the development of ASD. This concept refers to the dynamic interplay between genetic predispositions and environmental factors, where the combined effects can influence the onset and progression of ASD. Understanding these interactions is essential for unraveling the complex etiology of autism and developing more effective prevention and intervention strategies[268]. Certain genetic variations can increase an individual's susceptibility to ASD, but these variations alone may not be sufficient to cause the disorder. For instance, mutations in genes such as *CHD8*, SCN2A, and *SHANK3* have been identified in individuals with ASD, highlighting a genetic predisposition[223]. However, not all individuals with these mutations develop ASD, suggesting that other factors, including environmental influences, play a role in triggering or exacerbating the condition[52].

Environmental influences, particularly those occurring during prenatal and perinatal periods, have been increasingly recognized as significant factors that may interact with genetic predispositions to influence the risk of developing ASD [269]. Numerous studies have explored how various environmental exposures can contribute to ASD, offering insights into the complex etiology of the disorder. Several studies have established a link between maternal infections during pregnancy and an increased risk of ASD in offspring[270]. For example, a study by Atladóttir *et al*[271] found that maternal infection during the first trimester was associated with a higher risk of ASD. The proposed mechanism involves the maternal immune response, which can produce inflammatory cytokines that cross the placenta and potentially disrupt fetal brain development. The use of certain medications during pregnancy has been linked to an increased risk of ASD. For instance, Christensen *et al*[272] reported that maternal use of valproate, an antiepileptic drug, was associated with a significantly increased risk of ASD and other neurodevelopmental disorders. The study suggests that valproate can alter neurodevelopment through its effects on folate metabolism and histone deacetylase inhibition.

Prenatal exposure to environmental toxins, such as pesticides and heavy metals, has been implicated in the development of ASD. Research by Roberts *et al*[273] indicated that living near agricultural areas where pesticides are used during pregnancy was associated with a higher risk of having a child with ASD. These toxins can disrupt neural development by interfering with signaling pathways critical for brain development. Maternal nutrition, particularly the intake of essential nutrients like folic acid, has been shown to influence ASD risk. A study by Schmidt *et al*[274] found that adequate maternal folic acid intake around conception was associated with a reduced risk of ASD. Folic acid is crucial for DNA methylation and neural tube development, and its deficiency during critical periods can adversely affect fetal brain development.

Perinatal complications such as preterm birth, low birth weight, and hypoxia have been associated with an increased risk of ASD. A meta-analysis by Gardener *et al*[275] found that several perinatal factors, including low birth weight and preterm birth, were significantly associated with ASD. These complications can result in hypoxic-ischemic injury to the developing brain, leading to neurodevelopmental disorders. Advanced parental age, particularly paternal age, has been linked to an increased risk of ASD. Reichenberg *et al*[276] demonstrated that children of older fathers had a higher risk of

ASD, potentially due to the accumulation of DNMs in the sperm of older men. These genetic mutations can interact with environmental factors, increasing the likelihood of ASD development.

Environmental factors can interact with genetic vulnerabilities to influence ASD risk. For example, individuals with certain genetic mutations may be more susceptible to environmental insults. Kinney *et al*[277] found that prenatal exposure to severe maternal stress was associated with a higher risk of ASD in children with a familial history of the disorder. This suggests that genetic susceptibility and environmental stressors can act synergistically to increase ASD risk. Environmental exposures can lead to epigenetic changes that affect gene expression without altering the DNA sequence. These modifications can influence the development of ASD. Dutheil *et al*[278] showed that prenatal exposure to air pollution was associated with changes in DNA methylation patterns in genes related to neurodevelopment, suggesting a potential mechanism for how environmental factors can impact ASD risk. Gene-environment interaction models provide valuable frameworks for understanding how genetic predispositions and environmental factors jointly influence the risk of developing ASD. These models illustrate the complexity of ASD etiology, emphasizing that neither genetic nor environmental factors alone can fully explain the disorder. Several models have been proposed to elucidate these interactions[41].

The diathesis-stress model: The diathesis-stress model is one of the most widely recognized frameworks for understanding gene-environment interactions in ASD. This model posits that individuals inherit genetic vulnerabilities (diatheses) that predispose them to ASD[279]. However, the expression of these genetic vulnerabilities depends on the presence of environmental stressors. For example, a child with a genetic predisposition to ASD may only develop the disorder if exposed to certain environmental factors such as prenatal stress, maternal infections, or exposure to toxins during critical periods of neurodevelopment. This model highlights the interplay between inherent genetic risks and environmental triggers in the manifestation of ASD[280].

The differential susceptibility model: The differential susceptibility model suggests that some individuals are more susceptible to environmental influences, both positive and negative, due to their genetic makeup. In this model, certain genetic variants make individuals more responsive to environmental conditions[281]. For instance, a child with specific genetic variants may be more adversely affected by prenatal exposure to toxins or maternal stress, increasing their risk of developing ASD[282]. Conversely, the same genetic variants might make the child more responsive to positive environmental interventions, such as enriched early learning environments or supportive caregiving, potentially mitigating ASD symptoms or improving developmental outcomes[283].

The biological sensitivity to context model: Similar to the differential susceptibility model, the biological sensitivity to context model proposes that genetic variations influence an individual's sensitivity to environmental contexts. This model focuses on the idea that some individuals are biologically more reactive to environmental stimuli due to their genetic makeup. In the context of ASD, this model suggests that children with certain genetic profiles may have heightened biological responses to environmental stressors or toxins, which could disrupt neurodevelopment and increase the risk of ASD. Alternatively, these children may also benefit more from positive environmental influences, highlighting the importance of supportive and enriched environments for at-risk individuals[284,285].

The gene-environment correlation model: The gene-environment correlation model explores how genetic and environmental factors can be correlated, meaning that genetic predispositions can influence an individual's exposure to certain environments. There are three types of gene-environment correlations: Passive, evocative, and active[286]. In the passive correlation, parents provide both the genes and the environment, such as a parent with ASD traits creating an environment that influences the child's development[287]. Evocative correlation occurs when an individual's genetic traits elicit specific responses from the environment, such as a child's social difficulties leading to social isolation[288]. Active correlation involves individuals seeking out environments that complement their genetic predispositions, such as a child with sensory sensitivities avoiding noisy settings[289]. These correlations can help explain how genetic predispositions and environmental exposures jointly contribute to the development of ASD.

Epigenetic models: Epigenetic models emphasize the role of environmental factors in modifying gene expression through epigenetic mechanisms such as DNA methylation and histone modification. These changes do not alter the DNA sequence but can profoundly affect gene expression and neurodevelopment[290]. Environmental factors such as prenatal nutrition, exposure to toxins, and maternal stress can induce epigenetic modifications that influence the risk of ASD[291]. For example, prenatal exposure to air pollution has been associated with changes in DNA methylation patterns in genes involved in neurodevelopment, suggesting a potential mechanism for how environmental exposures can impact ASD risk [292]. Epigenetic models underscore the dynamic interplay between genes and the environment in shaping developmental outcomes[293].

Integrative models: Integrative models combine elements from multiple frameworks to comprehensively understand gene-environment interactions in ASD. These models recognize that genetic predispositions, environmental exposures, and epigenetic mechanisms all contribute to the risk of ASD and interact in complex ways[294,295]. Integrative models often incorporate neurobiology, developmental psychology, and epidemiology insights to create a holistic view of ASD etiology. For example, an integrative model might consider how genetic vulnerabilities to neuroinflammation interact with prenatal exposure to maternal infections, leading to epigenetic changes that disrupt brain development and increase ASD risk[296].

These gene-environment interaction models (Table 3) offer valuable insights into the multifaceted nature of ASD. These models emphasize that the development of ASD is not solely determined by genetic or environmental factors but by their complex interplay. Understanding these interactions is crucial for identifying at-risk individuals, developing targeted

Table 3 Comparison between the different gene-environment interaction models in the context of autism spectrum disorder

Model	Key concept	Description	Examples
Diathesis-stress model	Genetic vulnerability plus environmental stressors trigger ASD	Inherited genetic predispositions (diatheses) interact with environmental stressors to manifest ASD	Prenatal stress, maternal infections, or toxin exposure in genetically predisposed individuals lead to the development of ASD
Differential susceptibility model	Genetic variants make individuals more responsive to environmental influences, both positive and negative	Certain genetic profiles heighten sensitivity to environmental conditions, affecting ASD risk and response to interventions	Genetically susceptible children may develop ASD with prenatal toxin exposure but show improvement with enriched early learning environments
Biological sensitivity to context model	Genetic variations influence sensitivity to environmental contexts	Some individuals have heightened biological reactivity to environmental stimuli due to their genetic makeup, impacting neurodevelopment and ASD risk	Children with specific genetic profiles may have increased stress responses to environmental toxins or benefit more from supportive caregiving
Gene-environment correlation model	Genetic predispositions influence exposure to certain environments	Genetic factors shape individuals' environments, through passive, evocative, or active correlations	Parents with ASD traits create environments affecting child development (passive); a child's social difficulties lead to isolation (evocative); a child avoids noisy places (active)
Epigenetic models	Environmental factors modify gene expression through epigenetic mechanisms	Environmental influences like nutrition, toxins, or stress-induced changes in gene expression *via* DNA methylation or histone modification affect neurodevelopment and ASD risk	Prenatal air pollution exposure causes DNA methylation changes in neurodevelopmental genes, influencing ASD risk
Integrative models	Combines genetic, environ-mental, and epigenetic factors for a holistic understanding of ASD risk	Integrates multiple frameworks, considering genetic vulnerabilities, environmental exposures, and epigenetic mechanisms in ASD development	Interaction of genetic neuroinflammation susceptibility with prenatal maternal infections leads to epigenetic changes and increased ASD risk

This table provides a comparative overview of the key concepts, descriptions, and examples of how each model explains the interaction between genetic and environmental factors in autism spectrum disorder development. ASD: Autism spectrum disorder.

interventions, and informing preventive strategies.

Epigenetic mechanisms

Epigenetic modifications play a crucial role in regulating gene expression without altering the underlying DNA sequence, significantly contributing to the development of ASD. These mechanisms include DNA methylation, histone modification, and non-coding RNA molecules, which can either activate or silence genes, thereby influencing neural development and function[297,298].

DNA methylation typically suppresses gene expression and can be influenced by environmental factors such as prenatal stress, toxins, or nutritional deficiencies. In ASD, aberrant DNA methylation patterns have been observed in genes associated with synaptic function and neurodevelopment[299]. For example, hypermethylation of the *MECP2* gene, critical for brain development and associated with Rett syndrome (an ASD-related disorder), has been identified in some individuals with ASD[300].

Histone modifications alter the chromatin structure and gene accessibility, playing a critical role in gene expression regulation. These modifications can be influenced by external factors such as maternal diet or exposure to pollutants, potentially leading to atypical neural circuitry linked to ASD[301]. Studies have shown that individuals with ASD often exhibit altered histone acetylation and methylation states, disrupting chromatin structure and gene expression, particularly in genes implicated in neural connectivity and plasticity[302].

Non-coding RNAs, including microRNAs, regulate gene expression post-transcriptionally and have been implicated in modulating genes involved in neural connectivity and plasticity. Dysregulation of specific microRNAs that regulate neural development and synaptic function has been found in individuals with ASD, leading to the misregulation of critical brain function genes[303].

Research on epigenetic changes in individuals with ASD has uncovered several key findings. Perini *et al*[304] revealed abnormal DNA methylation patterns in genes involved in synaptic function and neural development, suggesting that epigenetic dysregulation contributes to the neural anomalies observed in ASD. Another study highlighted that individuals with ASD often exhibit altered histone acetylation and methylation states, disrupting chromatin structure and gene expression[305]. Additionally, research into non-coding RNAs, such as microRNAs, has emphasized their role in ASD. Dysregulation of microRNAs that regulate neural development and synaptic function leads to misregulating crucial brain function genes[306]. These studies underscore the importance of epigenetic mechanisms in ASD and suggest that both inherited and environmentally induced epigenetic changes can significantly impact gene expression, contributing to the disorder's pathogenesis[291]. Understanding the interplay between genetic predispositions and epigenetic modifications offers valuable insights into the complex etiology of ASD and highlights potential avenues for early intervention and therapeutic strategies. These findings pave the way for further exploration into epigenetic therapies that could potentially reverse or mitigate some of the effects of these epigenetic alterations in ASD.

Therapeutic implications

The growing understanding of the genetic underpinnings of ASD is revolutionizing therapeutic strategies, moving towards more personalized and targeted approaches. Traditional treatments for ASD have been mainly one-size-fits-all. Still, as we uncover more about the genetic diversity and complexity of ASD, it becomes clear that a more individualized approach is essential[307]. This section explores how these genetic findings are being translated into personalized treatment modalities, offering hope for more effective management and improved outcomes for individuals with ASD.

Personalized medicine: Advancements in genetic research are transforming the treatment landscape for ASD by enabling personalized medicine approaches. Personalized medicine involves tailoring medical treatment to the individual characteristics of each patient, particularly their genetic profile[308]. This approach is highly promising for ASD and is known for its complexity and heterogeneity. Discoveries in genetics have pinpointed numerous genes and genetic variations linked to ASD. These insights allow for the development of targeted therapies that address specific biological pathways disrupted in different individuals[309]. For example, mutations in the *CHD8* gene, associated with certain ASD cases, suggest that therapies modulating chromatin remodeling and gene expression, *e.g.*, using Baf53b, could be beneficial [310]. Similarly, therapies targeting synaptic function may be developed for individuals with *SHANK3* gene disruptions [311].

Pharmacogenomics, which studies how genes affect an individual's drug response, is a critical aspect of personalized medicine. By analyzing a patient's genetic profile, clinicians can predict which medications will be most effective and which might cause adverse reactions[312]. In the context of ASD, this could mean more precise management of co-occurring conditions like anxiety, depression, and ADHD, as well as core autism symptoms. For instance, variations in the serotonin transporter gene (*SLC6A4*) may inform the choice of antidepressants, leading to more effective and tailored treatment plans. Identifying biomarkers-measurable indicators of a biological state or condition-can greatly aid in the early diagnosis and personalized treatment of ASD[313]. Genetic and epigenetic biomarkers provide insights into the severity and specific characteristics of ASD in an individual, guiding personalized intervention strategies. Specific DNA methylation patterns or histone modifications, for example, might serve as biomarkers for particular ASD subtypes, helping to effectively tailor therapeutic approaches[314].

Personalized medicine also extends to non-pharmacological interventions, such as behavioral therapies, dietary adjustments, and environmental modifications. Genetic insights can inform the selection of behavioral therapies that are more likely to be effective[315]. For instance, individuals with mutations in genes affecting social cognition may benefit more from social skills training and interventions focusing on enhancing social interactions[316]. While the promise of personalized medicine is substantial, there are challenges to overcome. The genetic architecture of ASD is highly intricate, involving numerous genes and environmental factors[317]. Comprehensive genetic testing and sophisticated interpretation are necessary to implement personalized approaches effectively[318]. Additionally, ethical considerations, such as genetic privacy and potential discrimination, must be carefully addressed[319]. Future research should aim further to clarify the genetic and epigenetic landscape of ASD, develop advanced tools for genetic testing, and design targeted therapies based on these findings. Collaboration among geneticists, clinicians, and researchers is crucial to translating genetic discoveries into practical, personalized treatment strategies that improve outcomes for individuals with ASD[320].

Current and future therapies: Exploring the genetic underpinnings of ASD is paving the way for innovative therapies that could significantly enhance treatment efficacy. Current therapies for ASD include behavioral interventions, pharmacological treatments, and nutritional strategies[321]. ABA is a widely used behavioral therapy that focuses on improving specific behaviors such as communication, social skills, and adaptive learning skills. Genetic insights can help tailor ABA programs to target specific deficits associated with particular genetic profiles[322]. Social skills training interventions are also essential, especially for individuals with ASD-related genetic variations affecting social cognition[323]. Pharmacological treatments such as antipsychotics and SSRIs are commonly used to manage irritability, aggression, anxiety, and depression in individuals with ASD[324]. Genetic research helps identify those who might benefit most from these medications while minimizing side effects. Nutritional and dietary interventions, such as gluten-free and casein-free diets, are used by some individuals with ASD[325]. Genetic predispositions related to metabolic processes can inform nutritional adjustments to improve gastrointestinal and behavioral symptoms[326].

Future therapies, including gene therapy and epigenetic interventions, hold exciting possibilities. Targeted genetic interventions could potentially correct or mitigate the effects of specific genetic abnormalities, such as those in the *CHD8* or *SHANK3* genes[327]. Epigenetic therapies, such as DNA methylation modulators and histone deacetylase inhibitors, could correct epigenetic dysregulation observed in ASD, potentially reversing abnormal chromatin states and restoring normal gene expression patterns[297]. Pharmacogenomics promises highly personalized medication regimens that maximize efficacy and minimize adverse effects. Understanding variations in the serotonin transporter gene can guide the use of SSRIs and other psychotropic medications[328]. Non-coding RNA-based therapies, such as microRNA modulation, could correct dysregulation in neural development and synaptic function associated with ASD[329].

Recent genetic studies suggest a link between neuroinflammation and ASD. Targeting inflammatory pathways genetically associated with ASD could offer new therapeutic avenues to reduce neuroinflammation and improve neurological outcomes[330]. Stem cell therapy is a burgeoning field with the potential to regenerate or repair neural tissue affected by genetic mutations associated with ASD. Research is ongoing to determine the feasibility and safety of using stem cells to address neurodevelopmental deficits in ASD[331]. Continued research is essential to translate genetic findings into practical therapies. This includes clinical trials to evaluate the efficacy and safety of new genetic and epigenetic therapies, biomarker discovery to track treatment responses and tailor interventions, and interdisciplinary collaboration between geneticists, neuroscientists, and clinicians to integrate genetic data into therapeutic practices[332].

Genetic research is driving significant advancements in the treatment of ASD, offering hope for more effective and personalized therapies. Current treatments informed by genetic insights are already improving outcomes, while future interventions hold the promise of addressing the underlying genetic causes of ASD[283]. As research progresses, these innovative therapies will continue to evolve, providing more targeted and individualized care for individuals with ASD.

Future directions and research challenges

Unresolved questions: Despite significant advances in understanding the genetic basis of ASD, many questions remain unresolved, highlighting crucial areas for future research. Identifying these gaps is essential for guiding ongoing and future studies to deepen our understanding of ASD and improve diagnostic and therapeutic strategies. One key question revolves around the full spectrum of genetic variations contributing to ASD. While numerous risk genes and mutations have been identified, many cases of ASD cannot be explained by known genetic factors alone. This suggests that there are still undiscovered genetic components, possibly rare variants or non-coding regions, that play a critical role in ASD[42]. WGS and advanced bioinformatics tools are needed to uncover these hidden genetic elements.

Another significant gap is the lack of understanding of the precise mechanisms by which identified genetic mutations lead to ASD. Although specific genes and pathways have been implicated, the detailed biological processes linking these genetic changes to ASD symptoms remain unclear. This includes elucidating how genetic mutations affect neural development, synaptic function, and brain connectivity. Advanced imaging techniques and animal models can provide valuable insights into these mechanisms[333]. Another area requiring further exploration is the interaction between genetic and environmental factors in ASD development. While studies have shown that environmental factors such as prenatal stress, exposure to toxins, and nutritional deficiencies can influence ASD risk, the exact nature of these interactions is not well understood[334]. Longitudinal studies and integrative approaches combining genetic, epigenetic, and environmental data are needed to clarify these complex relationships.

Additionally, there is a need to investigate the heterogeneity of ASD. ASD is a highly variable condition with a wide range of symptoms and severities. Understanding the genetic basis of this heterogeneity is crucial for developing personalized treatment approaches. Research should focus on identifying genetic and epigenetic markers that can predict symptom profiles and treatment responses in individuals with ASD[19]. The role of epigenetic modifications in ASD is an emerging field with many unanswered questions. While aberrant DNA methylation, histone modifications, and non-coding RNAs have been linked to ASD, more research is needed to understand how these epigenetic changes are regulated and interact with genetic predispositions[298]. Identifying specific epigenetic alterations associated with different ASD subtypes can provide new targets for therapeutic interventions.

Finally, translating genetic research into clinical practice poses significant challenges. While genetic testing can identify risk factors and guide personalized treatments, the accessibility and cost of such tests remain barriers. Developing affordable and widely available genetic tests is essential for integrating genetic insights into routine clinical care[36]. Moreover, ethical considerations related to genetic testing, such as privacy, consent, and the potential for genetic discrimination, must be addressed[335]. Future research must address these unresolved questions and gaps in knowledge to advance our understanding of ASD. Collaborative efforts integrating genomics, neuroscience, environmental sciences, and clinical research are crucial for unraveling the complex etiology of ASD and improving outcomes for individuals with the disorder[307].

Emerging technologies

Emerging technologies such as CRISPR and advanced bioinformatics tools hold immense potential to address the existing gaps in ASD research and pave the way for groundbreaking discoveries and treatments. These innovative approaches can help unravel the complexities of ASD, offering new insights and therapeutic opportunities[336].

CRISPR-Cas9, a powerful genome-editing tool, enables precise modification of DNA sequences, allowing researchers to investigate the functional consequences of specific genetic mutations associated with ASD[337]. By creating animal models or cell lines with targeted genetic alterations, scientists can study the resulting phenotypic changes and understand how these mutations contribute to ASD[338]. This technology can also be used to correct genetic defects *in vitro*, providing a potential pathway for developing gene therapy approaches for ASD. Additionally, CRISPR can be employed to explore the role of non-coding regions of the genome, which are often overlooked but may contain regulatory elements crucial for neural development and function[339].

Advanced bioinformatics tools are essential for analyzing the vast amounts of genomic data generated by next-generation sequencing techniques such as WGS and WES[340]. These tools can identify novel genetic variants and potential risk genes associated with ASD by integrating and comparing data from multiple studies. Machine learning algorithms and artificial intelligence can enhance the interpretation of complex genetic data, uncovering patterns and correlations that may be missed by traditional analysis methods[341]. Bioinformatics approaches can also facilitate the study of gene-environment interactions by integrating genomic, epigenomic, and environmental datasets, providing a comprehensive understanding of the multifactorial nature of ASD[342].

scRNA-seq is another emerging technology that offers insights into the brain's cellular heterogeneity. Researchers can identify specific cell types and states affected by ASD-associated genetic mutations by analyzing gene expression at the single-cell level. This technology can reveal how different cell populations contribute to the pathology of ASD and highlight potential cellular targets for therapeutic interventions[343]. Furthermore, developing organoids (three-dimensional cultures derived from stem cells) allows for the modeling of human brain development *in vitro*. Brain organoids can mimic the early stages of neural development, providing a platform to study the effects of genetic and environmental factors on brain formation and function[344]. These models can be used to screen potential drugs and evaluate their effects on neural development, offering a promising avenue for preclinical testing of new treatments for ASD.

In addition to these technologies, advancements in neuroimaging techniques, such as functional magnetic resonance imaging and diffusion tensor imaging, can enhance our understanding of the structural and functional connectivity in the brains of individuals with ASD[345]. Combining genetic data with neuroimaging findings can elucidate how genetic variations impact brain structure and function, leading to the identification of biomarkers for early diagnosis and targeted interventions[346]. Integrating these emerging technologies into ASD research promises to address key gaps in our knowledge and transform our approach to understanding and treating ASD. By leveraging CRISPR, advanced bioinformatics, single-cell analysis, organoids, and neuroimaging, researchers can unravel the intricate genetic and biological underpinnings of ASD, ultimately leading to more effective and personalized therapies for individuals affected by this complex disorder[347].

Collaborative research: Advancing our understanding of ASD and developing effective treatments necessitate a concerted effort that spans multiple disciplines and countries. The complexity of ASD's genetic underpinnings and its interaction with environmental factors demand a collaborative research approach, bringing together diverse expertise and resources[348]. The necessity of multidisciplinary collaborations in ASD research cannot be overstated, as they allow for integrating knowledge from various fields such as genetics, neuroscience, psychology, bioinformatics, and clinical medicine. Geneticists and molecular biologists can identify and characterize genetic mutations associated with ASD, while neuroscientists can study how these mutations affect brain development and function[349]. Psychologists and psychiatrists can provide insights into the behavioral and cognitive aspects of ASD, helping to link genetic findings with clinical presentations. Bioinformaticians and data scientists can manage and analyze large datasets, revealing patterns and correlations that are critical for understanding the genetic architecture of ASD[350]. Clinicians can translate these findings into diagnostic tools and therapeutic interventions, ensuring that research outcomes benefit patients directly. The necessity of this collaborative effort is clear, and it is through such integration that we can truly advance our understanding and treatment of ASD.

International collaborations are equally important, enabling researchers to access larger and more diverse populations. Genetic studies require extensive data to identify rare variants and to ensure findings are applicable across different ethnic and genetic backgrounds. International consortia, such as the Autism Genome Project, have already made significant strides by pooling resources and data from research groups worldwide[351]. These collaborations can enhance the statistical power of genetic studies and lead to more robust and generalizable findings. Moreover, sharing data and methodologies across borders can accelerate the pace of discovery and avoid duplication of efforts[243]. Collaborative research also facilitates the sharing of advanced technologies and expertise. Institutions in different countries may have unique strengths and capabilities, and pooling these resources can lead to more comprehensive and innovative approaches to ASD research. For example, a research group with expertise in CRISPR technology can partner with a team skilled in neuroimaging to investigate the effects of specific genetic mutations on brain structure and function[352]. Similarly, collaborations with pharmaceutical companies can help translate genetic discoveries into new treatments, leveraging their expertise in drug development and clinical trials[353].

Furthermore, collaborative efforts can address the ethical, legal, and social implications of genetic research on ASD. Multidisciplinary teams can work together to ensure that research practices are ethical and that findings are communicated responsibly to the public. International collaborations can help harmonize regulatory standards and ensure that advances in genetic research benefit individuals with ASD globally[354]. To facilitate these collaborations, funding agencies and research institutions must prioritize and support initiatives that promote teamwork and data sharing[355]. Grant programs encouraging multidisciplinary and international projects can provide researchers with the necessary resources and incentives to work together. Establishing centralized databases and biobanks accessible to the global research community can also enhance collaboration and data integration[356].

Study limitations

This review, while comprehensive in its scope, has several limitations that must be acknowledged. Firstly, the rapid pace of advancements in genetic and epigenetic research means that some of the findings and technologies discussed may quickly become outdated as new discoveries emerge. Additionally, the review relies heavily on studies with varying methodologies, sample sizes, and population demographics, potentially leading to inconsistencies in the reported findings. The complexity and heterogeneity of ASD also pose significant challenges; the review attempts to cover a wide range of genetic and epigenetic factors, but this breadth may come at the expense of depth in some areas. Furthermore, the review predominantly focuses on genetic and epigenetic aspects, potentially underrepresenting other crucial factors such as environmental influences and their interactions with genetic predispositions. While efforts have been made to include various aspects of ASD research, selecting studies and sources might have introduced a bias, potentially overlooking relevant findings from smaller or less-publicized research efforts. The review also touches upon emerging therapies and personalized medicine. Still, the practical implementation and accessibility of these advancements are not fully addressed, which could limit the applicability of the discussed interventions in real-world settings. Finally, while mentioned, ethical considerations surrounding genetic testing and personalized medicine are not explored in depth. Issues such as genetic privacy, consent, and the potential for discrimination require more comprehensive discussion to ensure the responsible application of genetic insights. In conclusion, while this review provides a broad overview of the genetic and epigenetic underpinnings of ASD and their therapeutic implications, it is constrained by the rapidly evolving nature of the field, potential methodological biases, and the need for a more in-depth exploration of certain areas and ethical considerations.

CONCLUSION

This systematic review highlights significant advancements in understanding the genetic and epigenetic underpinnings of ASD and their therapeutic implications. Genetic discoveries, such as mutations in *CHD8* and *SHANK3*, and epigenetic factors like DNA methylation and non-coding RNAs, reveal the complex mechanisms contributing to ASD. These insights pave the way for personalized medicine, enhancing the precision of current treatments and informing future therapies like gene editing and epigenetic modulation. Emerging technologies, including CRISPR and advanced bioinformatics, accelerate research, offering deeper insights into genetic mutations. Collaborative efforts across disciplines and countries are crucial for advancing our understanding and translating findings into clinical practice. Despite these advancements, challenges remain, including the complexity of ASD's genetic architecture, gene-environment interactions, and ethical considerations of genetic testing. Continued research and collaboration promise more effective, personalized, and comprehensive approaches to managing ASD, improving outcomes and quality of life for those affected.

FOOTNOTES

Author contributions: Al-Biltagi M coordinated the project, contributed to the design, supervised the literature search, and ensured data integrity; Saeed NK was involved in the methodology, literature screening, data extraction, and manuscript writing; Bediwy AS participated in the literature search, data extraction, preliminary analyses, and manuscript drafting; Bediwy EA oversaw technical aspects, quality control, and statistical analysis and contributed to the manuscript, particularly in the analysis sections; Elbeltagi R addressed ethical considerations, contributed to the literature search and data extraction, and provided insights during data synthesis. All authors critically revised the manuscript and approved the final version, agreeing to be accountable for all aspects of the work. Al-Biltagi M and Saeed NK contributed equally to this work as co-first authors.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Egypt

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010; Reem Elbeltagi 0000-0001-9969-5970.

S-Editor: Qu XL
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Hodges H**, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. *Transl Pediatr* 2020; **9**: S55-S65 [PMID: 32206584 DOI: 10.21037/tp.2019.09.09]

2 **Frye RE**. Social Skills Deficits in Autism Spectrum Disorder: Potential Biological Origins and Progress in Developing Therapeutic Agents. *CNS Drugs* 2018; **32**: 713-734 [PMID: 30105528 DOI: 10.1007/s40263-018-0556-y]

3 **Posar A**, Resca F, Visconti P. Autism according to diagnostic and statistical manual of mental disorders 5(th) edition: The need for further improvements. *J Pediatr Neurosci* 2015; **10**: 146-148 [PMID: 26167220 DOI: 10.4103/1817-1745.159195]

4 **Talantseva OI**, Romanova RS, Shurdova EM, Dolgorukova TA, Sologub PS, Titova OS, Kleeva DF, Grigorenko EL. The global prevalence of autism spectrum disorder: A three-level meta-analysis. *Front Psychiatry* 2023; **14**: 1071181 [PMID: 36846240 DOI: 10.3389/fpsyt.2023.1071181]

5 **Neggers YH**. Increasing prevalence, changes in diagnostic criteria, and nutritional risk factors for autism spectrum disorders. *ISRN Nutr* 2014; **2014**: 514026 [PMID: 24967269 DOI: 10.1155/2014/514026]

6 **Ratto AB**, Kenworthy L, Yerys BE, Bascom J, Wieckowski AT, White SW, Wallace GL, Pugliese C, Schultz RT, Ollendick TH, Scarpa A, Seese S, Register-Brown K, Martin A, Anthony LG. What About the Girls? Sex-Based Differences in Autistic Traits and Adaptive Skills. *J Autism Dev Disord* 2018; **48**: 1698-1711 [PMID: 29204929 DOI: 10.1007/s10803-017-3413-9]

7 **Alrehaili RA**, ElKady RM, Alrehaili JA, Alreefi RM. Exploring Early Childhood Autism Spectrum Disorders: A Comprehensive Review of Diagnostic Approaches in Young Children. *Cureus* 2023; **15**: e50111 [PMID: 38186518 DOI: 10.7759/cureus.50111]

8 **Al-Beltagi M**. Autism medical comorbidities. *World J Clin Pediatr* 2021; **10**: 15-28 [PMID: 33972922 DOI: 10.5409/wjcp.v10.i3.15]

9 **Picardi A**, Gigantesco A, Tarolla E, Stoppioni V, Cerbo R, Cremonte M, Alessandri G, Lega I, Nardocci F. Parental Burden and its Correlates in Families of Children with Autism Spectrum Disorder: A Multicentre Study with Two Comparison Groups. *Clin Pract Epidemiol Ment Health* 2018; **14**: 143-176 [PMID: 30158998 DOI: 10.2174/1745017901814010143]

10 **Tathgur MK**, Kang HK. Challenges of the Caregivers in Managing a Child with Autism Spectrum Disorder- A Qualitative Analysis. *Indian J Psychol Med* 2021; **43**: 416-421 [PMID: 34584307 DOI: 10.1177/02537176211000769]

11 **Buescher AV**, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr* 2014; **168**: 721-728 [PMID: 24911948 DOI: 10.1001/jamapediatrics.2014.210]

12 **Hasson L**, Keville S, Gallagher J, Onagbesan D, Ludlow AK. Inclusivity in education for autism spectrum disorders: Experiences of support from the perspective of parent/carers, school teaching staff and young people on the autism spectrum. *Int J Dev Disabil* 2024; **70**: 201-212 [PMID: 38481460 DOI: 10.1080/20473869.2022.2070418]

13 **Vogindroukas I**, Stankova M, Chelas EN, Proedrou A. Language and Speech Characteristics in Autism. *Neuropsychiatr Dis Treat* 2022; **18**: 2367-2377 [PMID: 36268264 DOI: 10.2147/NDT.S331987]

14 **LaGasse AB**. Social outcomes in children with autism spectrum disorder: a review of music therapy outcomes. *Patient Relat Outcome Meas* 2017; **8**: 23-32 [PMID: 28260959 DOI: 10.2147/PROM.S106267]

15 **Tian J**, Gao X, Yang L. Repetitive Restricted Behaviors in Autism Spectrum Disorder: From Mechanism to Development of Therapeutics. *Front Neurosci* 2022; **16**: 780407 [PMID: 35310097 DOI: 10.3389/fnins.2022.780407]

16 **Grapel JN**, Cicchetti DV, Volkmar FR. Sensory features as diagnostic criteria for autism: sensory features in autism. *Yale J Biol Med* 2015; **88**: 69-71 [PMID: 25745375]

17 **Wiggins LD**, Rice CE, Barger B, Soke GN, Lee LC, Moody E, Edmondson-Pretzel R, Levy SE. DSM-5 criteria for autism spectrum disorder maximizes diagnostic sensitivity and specificity in preschool children. *Soc Psychiatry Psychiatr Epidemiol* 2019; **54**: 693-701 [PMID: 30850887 DOI: 10.1007/s00127-019-01674-1]

18 **Elbeltagi R**, Al-Beltagi M, Saeed NK, Alhawamdeh R. Play therapy in children with autism: Its role, implications, and limitations. *World J Clin Pediatr* 2023; **12**: 1-22 [PMID: 36685315 DOI: 10.5409/wjcp.v12.i1.1]

19 **Masi A**, DeMayo MM, Glozier N, Guastella AJ. An Overview of Autism Spectrum Disorder, Heterogeneity and Treatment Options. *Neurosci Bull* 2017; **33**: 183-193 [PMID: 28213805 DOI: 10.1007/s12264-017-0100-y]

20 **Lord C**, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. *Lancet* 2018; **392**: 508-520 [PMID: 30078460 DOI: 10.1016/S0140-6736(18)31129-2]

21 **Hus Y**, Segal O. Challenges Surrounding the Diagnosis of Autism in Children. *Neuropsychiatr Dis Treat* 2021; **17**: 3509-3529 [PMID: 34898983 DOI: 10.2147/NDT.S282569]

22 **Georgiades S**, Szatmari P, Boyle M, Hanna S, Duku E, Zwaigenbaum L, Bryson S, Fombonne E, Volden J, Mirenda P, Smith I, Roberts W, Vaillancourt T, Waddell C, Bennett T, Thompson A; Pathways in ASD Study Team. Investigating phenotypic heterogeneity in children with autism spectrum disorder: a factor mixture modeling approach. *J Child Psychol Psychiatry* 2013; **54**: 206-215 [PMID: 22862778 DOI: 10.1111/j.1469-7610.2012.02588.x]

23 **Almandil NB**, Alkuroud DN, AbdulAzeez S, AlSulaiman A, Elaissari A, Borgio JF. Environmental and Genetic Factors in Autism Spectrum Disorders: Special Emphasis on Data from Arabian Studies. *Int J Environ Res Public Health* 2019; **16** [PMID: 30813406 DOI: 10.3390/ijerph16040658]

24 **Zhang Y**, Liu X, Guo R, Xu W, Guo Q, Hao C, Ni X, Li W. Biological implications of genetic variations in autism spectrum disorders from genomics studies. *Biosci Rep* 2021; **41** [PMID: 34240107 DOI: 10.1042/BSR20210593]

25 **Jiang CC**, Lin LS, Long S, Ke XY, Fukunaga K, Lu YM, Han F. Signalling pathways in autism spectrum disorder: mechanisms and therapeutic implications. *Signal Transduct Target Ther* 2022; **7**: 229 [PMID: 35817793 DOI: 10.1038/s41392-022-01081-0]

26 **Napolitano A**, Schiavi S, La Rosa P, Rossi-Espagnet MC, Petrillo S, Bottino F, Tagliente E, Longo D, Lupi E, Casula L, Valeri G, Piemonte F, Trezza V, Vicari S. Sex Differences in Autism Spectrum Disorder: Diagnostic, Neurobiological, and Behavioral Features. *Front Psychiatry* 2022; **13**: 889636 [PMID: 35633791 DOI: 10.3389/fpsyt.2022.889636]

27 **Shen MD**, Piven J. Brain and behavior development in autism from birth through infancy. *Dialogues Clin Neurosci* 2017; **19**: 325-333 [PMID: 29398928 DOI: 10.31887/DCNS.2017.19.4/mshen]

28 **Khogeer AA**, AboMansour IS, Mohammed DA. The Role of Genetics, Epigenetics, and the Environment in ASD: A Mini Review. *Epigenomes* 2022; **6** [PMID: 35735472 DOI: 10.3390/epigenomes6020015]

29 **Thye MD**, Bednarz HM, Herringshaw AJ, Sartin EB, Kana RK. The impact of atypical sensory processing on social impairments in autism spectrum disorder. *Dev Cogn Neurosci* 2018; **29**: 151-167 [PMID: 28545994 DOI: 10.1016/j.dcn.2017.04.010]

30 **Chan DV**, Doran JD, Galobardi OD. Beyond Friendship: The Spectrum of Social Participation of Autistic Adults. *J Autism Dev Disord* 2023; **53**: 424-437 [PMID: 35079929 DOI: 10.1007/s10803-022-05441-1]

31 **Pelzl MA**, Travers-Podmaniczky G, Brück C, Jacob H, Hoffmann J, Martinelli A, Hölz L, Wabersich-Flad D, Wildgruber D. Reduced impact of nonverbal cues during integration of verbal and nonverbal emotional information in adults with high-functioning autism. *Front Psychiatry* 2022; **13**: 1069028 [PMID: 36699473 DOI: 10.3389/fpsyt.2022.1069028]

32 **Ibrahimagic A**, Patkovic N, Radic B, Hadzic S. Communication and Language Skills of Autistic Spectrum Disorders in Children and Their Parents' Emotions. *Mater Sociomed* 2021; **33**: 250-256 [PMID: 35210946 DOI: 10.5455/msm.2021.33.250-256]

33 **Okoye C**, Obialo-Ibeawuchi CM, Obajeun OA, Sarwar S, Tawfik C, Waleed MS, Wasim AU, Mohamoud I, Afolayan AY, Mbaezue RN. Early Diagnosis of Autism Spectrum Disorder: A Review and Analysis of the Risks and Benefits. *Cureus* 2023; **15**: e43226 [PMID: 37692637 DOI: 10.7759/cureus.43226]

34 **Balasco L**, Provenzano G, Bozzi Y. Sensory Abnormalities in Autism Spectrum Disorders: A Focus on the Tactile Domain, From Genetic Mouse Models to the Clinic. *Front Psychiatry* 2019; **10**: 1016 [PMID: 32047448 DOI: 10.3389/fpsyt.2019.01016]

35 **Mosner MG**, Kinard JL, Shah JS, McWeeny S, Greene RK, Lowery SC, Mazefsky CA, Dichter GS. Rates of Co-occurring Psychiatric Disorders in Autism Spectrum Disorder Using the Mini International Neuropsychiatric Interview. *J Autism Dev Disord* 2019; **49**: 3819-3832 [PMID: 31175504 DOI: 10.1007/s10803-019-04090-1]

36 **Genovese A**, Butler MG. Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). *Int J Mol Sci* 2020; **21** [PMID: 32630718 DOI: 10.3390/ijms21134726]

37 **Evans K**, Whitehouse AJO, D'Arcy E, Hayden-Evans M, Wallace K, Kuzminski R, Thorpe R, Girdler S, Milbourn B, Bölte S, Chamberlain A. Perceived Support Needs of School-Aged Young People on the Autism Spectrum and Their Caregivers. *Int J Environ Res Public Health* 2022; **19** [PMID: 36497683 DOI: 10.3390/ijerph192315605]

38 **Turnock A**, Langley K, Jones CRG. Understanding Stigma in Autism: A Narrative Review and Theoretical Model. *Autism Adulthood* 2022; **4**: 76-91 [PMID: 36605561 DOI: 10.1089/aut.2021.0005]

39 **Cirnigliaro M**, Chang TS, Arteaga SA, Pérez-Cano L, Ruzzo EK, Gordon A, Bicks LK, Jung JY, Lowe JK, Wall DP, Geschwind DH. The contributions of rare inherited and polygenic risk to ASD in multiplex families. *Proc Natl Acad Sci U S A* 2023; **120**: e2215632120 [PMID: 37506195 DOI: 10.1073/pnas.2215632120]

40 **Wendt FR**, Carvalho CM, Pathak GA, Gelernter J, Polimanti R. Polygenic risk for autism spectrum disorder associates with anger recognition in a neurodevelopment-focused phenome-wide scan of unaffected youths from a population-based cohort. *PLoS Genet* 2020; **16**: e1009036 [PMID: 32941431 DOI: 10.1371/journal.pgen.1009036]

41 **Tordjman S**, Somogyi E, Coulon N, Kermarrec S, Cohen D, Bronsard G, Bonnot O, Weismann-Arcache C, Botbol M, Lauth B, Ginchat V, Roubertoux P, Barburoth M, Kovess V, Geoffray MM, Xavier J. Gene × Environment interactions in autism spectrum disorders: role of epigenetic mechanisms. *Front Psychiatry* 2014; **5**: 53 [PMID: 25136320 DOI: 10.3389/fpsyt.2014.00053]

42 **Havdahl A**, Niarchou M, Starnawska A, Uddin M, van der Merwe C, Warrier V. Genetic contributions to autism spectrum disorder. *Psychol Med* 2021; **51**: 2260-2273 [PMID: 33634770 DOI: 10.1017/S0033291721000192]

43 **Al-Sarraj Y**, Al-Dous E, Taha RZ, Ahram D, Alshaban F, Tolfat M, El-Shanti H, Albagha OME. Family-Based Genome-Wide Association Study of Autism Spectrum Disorder in Middle Eastern Families. *Genes (Basel)* 2021; **12** [PMID: 34069769 DOI: 10.3390/genes12050761]

44 **El-Fishawy P**, State MW. The genetics of autism: key issues, recent findings, and clinical implications. *Psychiatr Clin North Am* 2010; **33**: 83-105 [PMID: 20159341 DOI: 10.1016/j.psc.2009.12.002]

45 **Lewis CM**, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med* 2020; **12**: 44 [PMID: 32423490 DOI: 10.1186/s13073-020-00742-5]

46 **Jansen AG**, Dieleman GC, Jansen PR, Verhulst FC, Posthuma D, Polderman TJC. Psychiatric Polygenic Risk Scores as Predictor for Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in a Clinical Child and Adolescent Sample. *Behav Genet* 2020; **50**: 203-212 [PMID: 31346826 DOI: 10.1007/s10519-019-09965-8]

47 **Li D**, Choque-Olsson N, Jiao H, Norgren N, Jonsson U, Bölte S, Tammimies K. The influence of common polygenic risk and gene sets on social skills group training response in autism spectrum disorder. *NPJ Genom Med* 2020; **5**: 45 [PMID: 33083014 DOI: 10.1038/s41525-020-00152-x]

48 **Chaste P**, Leboyer M. Autism risk factors: genes, environment, and gene-environment interactions. *Dialogues Clin Neurosci* 2012; **14**: 281-292 [PMID: 23226953 DOI: 10.31887/DCNS.2012.14.3/pchaste]

49 **Constantino JN**, Charman T, Jones EJH. Clinical and Translational Implications of an Emerging Developmental Substructure for Autism. *Annu Rev Clin Psychol* 2021; **17**: 365-389 [PMID: 33577349 DOI: 10.1146/annurev-clinpsy-081219-110503]

50 **Apte M**, Kumar A. Correlation of mutated gene and signalling pathways in ASD. *IBRO Neurosci Rep* 2023; **14**: 384-392 [PMID: 37101819 DOI: 10.1016/j.ibneur.2023.03.011]

51 **Gamsiz ED**, Sciarra LN, Maguire AM, Pescosolido MF, van Dyck LI, Morrow EM. Discovery of Rare Mutations in Autism: Elucidating Neurodevelopmental Mechanisms. *Neurotherapeutics* 2015; **12**: 553-571 [PMID: 26105128 DOI: 10.1007/s13311-015-0363-9]

52 **Bölte S**, Girdler S, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cell Mol Life Sci* 2019; **76**: 1275-1297 [PMID: 30570672 DOI: 10.1007/s00018-018-2988-4]

53 **Chen J**, Yu S, Fu Y, Li X. Synaptic proteins and receptors defects in autism spectrum disorders. *Front Cell Neurosci* 2014; **8**: 276 [PMID: 25309321 DOI: 10.3389/fncel.2014.00276]

54 **Rylaarsdam L**, Guemez-Gamboa A. Genetic Causes and Modifiers of Autism Spectrum Disorder. *Front Cell Neurosci* 2019; **13**: 385 [PMID: 31481879 DOI: 10.3389/fncel.2019.00385]

55 **Teleanu RI**, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters-Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. *Int J Mol Sci* 2022; **23** [PMID: 35682631 DOI: 10.3390/ijms23115954]

56 **Sener EF**, Canatan H, Ozkul Y. Recent Advances in Autism Spectrum Disorders: Applications of Whole Exome Sequencing Technology. *Psychiatry Investig* 2016; **13**: 255-264 [PMID: 27247591 DOI: 10.4306/pi.2016.13.3.255]

57 **Pensado-López A**, Veiga-Rúa S, Carracedo Á, Allegue C, Sánchez L. Experimental Models to Study Autism Spectrum Disorders: hiPSCs, Rodents and Zebrafish. *Genes (Basel)* 2020; **11** [PMID: 33233737 DOI: 10.3390/genes11111376]

58 **Jiang YH**, Yuen RK, Jin X, Wang M, Chen N, Wu X, Ju J, Mei J, Shi Y, He M, Wang G, Liang J, Wang Z, Cao D, Carter MT, Chrysler C, Drmic IE, Howe JL, Lau L, Marshall CR, Merico D, Nalpathamkalam T, Thiruvahindrapuram B, Thompson A, Uddin M, Walker S, Luo J, Anagnostou E, Zwaigenbaum L, Ring RH, Wang J, Lajonchere C, Wang J, Shih A, Szatmari P, Yang H, Dawson G, Li Y, Scherer SW. Detection of clinically relevant genetic variants in autism spectrum disorder by whole-genome sequencing. *Am J Hum Genet* 2013; **93**: 249-263 [PMID: 23849776 DOI: 10.1016/j.ajhg.2013.06.012]

59 **de la Torre-Ubieta L**, Won H, Stein JL, Geschwind DH. Advancing the understanding of autism disease mechanisms through genetics. *Nat Med* 2016; **22**: 345-361 [PMID: 27050589 DOI: 10.1038/nm.4071]

60 **Alonso-Gonzalez A**, Rodriguez-Fontenla C, Carracedo A. De novo Mutations (DNMs) in Autism Spectrum Disorder (ASD): Pathway and Network Analysis. *Front Genet* 2018; **9**: 406 [PMID: 30298087 DOI: 10.3389/fgene.2018.00406]

61 **Wilfert AB**, Sulovari A, Turner TN, Coe BP, Eichler EE. Recurrent de novo mutations in neurodevelopmental disorders: properties and clinical implications. *Genome Med* 2017; **9**: 101 [PMID: 29179772 DOI: 10.1186/s13073-017-0498-x]

62 **Yuen RK**, Merico D, Cao H, Pellecchia G, Alipanahi B, Thiruvahindrapuram B, Tong X, Sun Y, Cao D, Zhang T, Wu X, Jin X, Zhou Z, Liu X, Nalpathamkalam T, Walker S, Howe JL, Wang Z, MacDonald JR, Chan A, D'Abate L, Deneault E, Siu MT, Tammimies K, Uddin M, Zarrei M, Wang M, Li Y, Wang J, Wang J, Yang H, Bookman M, Bingham J, Gross SS, Loy D, Pletcher M, Marshall CR, Anagnostou E, Zwaigenbaum L, Weksberg R, Fernandez BA, Roberts W, Szatmari P, Glazer D, Frey BJ, Ring RH, Xu X, Scherer SW. Genome-wide characteristics of de novo mutations in autism. *NPJ Genom Med* 2016; **1**: 160271-1602710 [PMID: 27525107 DOI: 10.1038/npjgenmed.2016.27]

63 **Antaki D**, Guevara J, Maihofer AX, Klein M, Gujral M, Grove J, Carey CE, Hong O, Arranz MJ, Hervas A, Corsello C, Vaux KK, Muotri AR, Iakoucheva LM, Courchesne E, Pierce K, Gleeson JG, Robinson EB, Nievergelt CM, Sebat J. A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex. *Nat Genet* 2022; **54**: 1284-1292 [PMID: 35654974 DOI: 10.1038/s41588-022-01064-5]

64 **Gill PS**, Clothier JL, Veerapandiyan A, Dweep H, Porter-Gill PA, Schaefer GB. Molecular Dysregulation in Autism Spectrum Disorder. *J Pers Med* 2021; **11** [PMID: 34575625 DOI: 10.3390/jpm11090848]

65 **Koboldt DC**, Steinberg KM, Larson DE, Wilson RK, Mardis ER. The next-generation sequencing revolution and its impact on genomics. *Cell* 2013; **155**: 27-38 [PMID: 24074859 DOI: 10.1016/j.cell.2013.09.006]

66 **Katsanis SH**, Katsanis N. Molecular genetic testing and the future of clinical genomics. *Nat Rev Genet* 2013; **14**: 415-426 [PMID: 23681062 DOI: 10.1038/nrg3493]

67 **Tammimies K**. Genetic mechanisms of regression in autism spectrum disorder. *Neurosci Biobehav Rev* 2019; **102**: 208-220 [PMID: 31059729 DOI: 10.1016/j.neubiorev.2019.04.022]

68 **Jeste SS**, Tuchman R. Autism Spectrum Disorder and Epilepsy: Two Sides of the Same Coin? *J Child Neurol* 2015; **30**: 1963-1971 [PMID: 26374786 DOI: 10.1177/0883073815601501]

69 **Fu JM**, Satterstrom FK, Peng M, Brand H, Collins RL, Dong S, Wamsley B, Klei L, Wang L, Hao SP, Stevens CR, Cusick C, Babadi M, Banks E, Collins B, Dodge S, Gabriel SB, Gauthier L, Lee SK, Liang L, Ljungdahl A, Mahjani B, Sloofman L, Smirnov AN, Barbosa M, Betancur C, Brusco A, Chung BHY, Cook EH, Cuccaro ML, Domenici E, Ferrero GB, Gargus JJ, Herman GE, Hertz-Picciotto I, Maciel P, Manoach DS, Passos-Bueno MR, Persico AM, Renieri A, Sutcliffe JS, Tassone F, Trabetti E, Campos G, Cardaropoli S, Carli D, Chan MCY, Fallerini C, Giorgio E, Girardi AC, Hansen-Kiss E, Lee SL, Lintas C, Ludena Y, Nguyen R, Pavinato L, Pericak-Vance M, Pessah IN, Schmidt RJ, Smith M, Costa CIS, Trajkova S, Wang JYT, Yu MHC; Autism Sequencing Consortium (ASC); Broad Institute Center for Common Disease Genomics (Broad-CCDG); iPSYCH-BROAD Consortium, Cutler DJ, De Rubeis S, Buxbaum JD, Daly MJ, Devlin B, Roeder K, Sanders SJ, Talkowski ME. Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nat Genet* 2022; **54**: 1320-1331 [PMID: 35982160 DOI: 10.1038/s41588-022-01104-0]

70 **Ozonoff S**, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobkins K, Hutman T, Iverson JM, Landa R, Rogers SJ, Sigman M, Stone WL. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics* 2011; **128**: e488-e495 [PMID: 21844053 DOI: 10.1542/peds.2010-2825]

71 **Asher D**, Dai D, Klimchak AC, Sedita LE, Gooch KL, Rodino-Klapac L. Paving the way for future gene therapies: A case study of scientific spillover from delandistrogene moxeparvovec. *Mol Ther Methods Clin Dev* 2023; **30**: 474-483 [PMID: 37674905 DOI: 10.1016/j.omtm.2023.08.002]

72 **Weissberg O**, Elliott E. The Mechanisms of *CHD8* in Neurodevelopment and Autism Spectrum Disorders. *Genes (Basel)* 2021; **12** [PMID: 34440307 DOI: 10.3390/genes12081133]

73 **Beighley JS**, Hudac CM, Arnett AB, Peterson JL, Gerdts J, Wallace AS, Mefford HC, Hoekzema K, Turner TN, O'Roak BJ, Eichler EE, Bernier RA. Clinical Phenotypes of Carriers of Mutations in *CHD8* or Its Conserved Target Genes. *Biol Psychiatry* 2020; **87**: 123-131 [PMID: 31526516 DOI: 10.1016/j.biopsych.2019.07.020]

74 **Hoffmann A**, Spengler D. Chromatin Remodeler *CHD8* in Autism and Brain Development. *J Clin Med* 2021; **10** [PMID: 33477995 DOI: 10.3390/jcm10020366]

75 **Li Z**, Zhu YX, Gu LJ, Cheng Y. Understanding autism spectrum disorders with animal models: applications, insights, and perspectives. *Zool Res* 2021; **42**: 800-824 [PMID: 34755500 DOI: 10.24272/j.issn.2095-8137.2021.251]

76 **St George-Hyslop F**, Kivisild T, Livesey FJ. The role of contactin-associated protein-like 2 in neurodevelopmental disease and human cerebral cortex evolution. *Front Mol Neurosci* 2022; **15**: 1017144 [PMID: 36340692 DOI: 10.3389/fnmol.2022.1017144]

77 **D'Onofrio G**, Accogli A, Severino M, Caliskan H, Kokotović T, Blazekovic A, Jercic KG, Markovic S, Zigman T, Goran K, Barišić N, Duranovic V, Ban A, Borovecki F, Ramadža DP, Barić I, Fazeli W, Herkenrath P, Marini C, Vittorini R, Gowda V, Bouman A, Rocca C, Alkhawaja IA, Murtaza BN, Rehman MMU, Al Alam C, Nader G, Mancardi MM, Giacomini T, Srivastava S, Alvi JR, Tomoum H, Matricardi S, Iacomino M, Riva A, Scala M, Madia F, Pistorio A, Salpietro V, Minetti C, Rivière JB, Srour M, Efthymiou S, Maroofian R, Houlden H, Vernes SC, Zara F, Striano P, Nagy V. Genotype-phenotype correlation in contactin-associated protein-like 2 (CNTNAP-2) developmental disorder. *Hum Genet* 2023; **142**: 909-925 [PMID: 37183190 DOI: 10.1007/s00439-023-02552-2]

78 **Peñagarikano O**, Geschwind DH. What does *CNTNAP2* reveal about autism spectrum disorder? *Trends Mol Med* 2012; **18**: 156-163 [PMID: 22365836 DOI: 10.1016/j.molmed.2012.01.003]

79 **Gandhi T**, Canepa CR, Adeyelu TT, Adeniyi PA, Lee CC. Neuroanatomical Alterations in the *CNTNAP2* Mouse Model of Autism Spectrum Disorder. *Brain Sci* 2023; **13** [PMID: 37371370 DOI: 10.3390/brainsci13060891]

80 **Chiocchetti AG**, Kopp M, Waltes R, Haslinger D, Duketis E, Jarczok TA, Poustka F, Voran A, Graab U, Meyer J, Klauck SM, Fulda S, Freitag CM. Variants of the *CNTNAP2* 5' promoter as risk factors for autism spectrum disorders: a genetic and functional approach. *Mol Psychiatry* 2015; **20**: 839-849 [PMID: 25224256 DOI: 10.1038/mp.2014.103]

81 **Leblond CS**, Nava C, Polge A, Gauthier J, Huguet G, Lumbroso S, Giuliano F, Stordeur C, Depienne C, Mouzat K, Pinto D, Howe J, Lemière N, Durand CM, Guibert J, Ey E, Toro R, Peyre H, Mathieu A, Amsellem F, Rastam M, Gillberg IC, Rappold GA, Holt R, Monaco AP, Maestrini E, Galan P, Heron D, Jacquette A, Afenjar A, Rastetter A, Brice A, Devillard F, Assouline B, Laffargue F, Lespinasse J, Chiesa J, Rivier F, Bonneau D, Regnault B, Zelenika D, Delepine M, Lathrop M, Sanlaville D, Schluth-Bolard C, Edery P, Perrin L, Tabet AC, Schmeisser MJ, Boeckers TM, Coleman M, Sato D, Szatmari P, Scherer SW, Rouleau GA, Betancur C, Leboyer M, Gillberg C, Delorme R, Bourgeron T. Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: a gradient of severity in cognitive impairments. *PLoS Genet* 2014; **10**: e1004580 [PMID: 25188300 DOI: 10.1371/journal.pgen.1004580]

82 **Shi R**, Redman P, Ghose D, Hwang H, Liu Y, Ren X, Ding LJ, Liu M, Jones KJ, Xu W. Shank Proteins Differentially Regulate Synaptic Transmission. *eNeuro* 2017; **4** [PMID: 29250591 DOI: 10.1523/ENEURO.0163-15.2017]

83 **Sato D**, Lionel AC, Leblond CS, Prasad A, Pinto D, Walker S, O'Connor I, Russell C, Drmic IE, Hamdan FF, Michaud JL, Endris V, Roeth R, Delorme R, Huguet G, Leboyer M, Rastam M, Gillberg C, Lathrop M, Stavropoulos DJ, Anagnostou E, Weksberg R, Fombonne E, Zwaigenbaum L, Fernandez BA, Roberts W, Rappold GA, Marshall CR, Bourgeron T, Szatmari P, Scherer SW. SHANK1 Deletions in Males with Autism Spectrum Disorder. *Am J Hum Genet* 2012; **90**: 879-887 [PMID: 22503632 DOI: 10.1016/j.ajhg.2012.03.017]

84 **Zaslavsky K**, Zhang WB, McCready FP, Rodrigues DC, Deneault E, Loo C, Zhao M, Ross PJ, El Hajjar J, Romm A, Thompson T, Piekna A, Wei W, Wang Z, Khattak S, Mufteev M, Pasceri P, Scherer SW, Salter MW, Ellis J. SHANK2 mutations associated with autism spectrum disorder cause hyperconnectivity of human neurons. *Nat Neurosci* 2019; **22**: 556-564 [PMID: 30911184 DOI: 10.1038/s41593-019-0365-8]

85 **Dhaliwal J**, Qiao Y, Calli K, Martell S, Race S, Chijiwa C, Glodjo A, Jones S, Rajcan-Separovic E, Scherer SW, Lewis S. Contribution of Multiple Inherited Variants to Autism Spectrum Disorder (ASD) in a Family with 3 Affected Siblings. *Genes (Basel)* 2021; **12** [PMID: 34356069 DOI: 10.3390/genes12071053]

86 **Durand CM**, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsäter H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, de Mas P, Bieth E, Rogé B, Héron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. Mutations in the gene encoding the synaptic scaffolding protein *SHANK3* are associated with autism spectrum disorders. *Nat Genet* 2007; **39**: 25-27 [PMID: 17173049 DOI: 10.1038/ng1933]

87 **Egger JIM**, Verhoeven WMA, Groenendijk-Reijenga R, Kant SG. Phelan-McDermid syndrome due to *SHANK3* mutation in an intellectually

disabled adult male: successful treatment with lithium. *BMJ Case Rep* 2017; **2017** [PMID: 28963116 DOI: 10.1136/bcr-2017-220778]
88 **Manning C**, Hurd PL, Read S, Crespi B. *SHANK3* Genotype Mediates Speech and Language Phenotypes in a Nonclinical Population. *Autism Res Treat* 2021; **2021**: 6634584 [PMID: 34188957 DOI: 10.1155/2021/6634584]
89 **Zhou Y**, Kaiser T, Monteiro P, Zhang X, Van der Goes MS, Wang D, Barak B, Zeng M, Li C, Lu C, Wells M, Amaya A, Nguyen S, Lewis M, Sanjana N, Zhou Y, Zhang M, Zhang F, Fu Z, Feng G. Mice with Shank3 Mutations Associated with ASD and Schizophrenia Display Both Shared and Distinct Defects. *Neuron* 2016; **89**: 147-162 [PMID: 26687841 DOI: 10.1016/j.neuron.2015.11.023]
90 **Liu C**, Wang Y, Deng J, Lin J, Hu C, Li Q, Xu X. Social Deficits and Repetitive Behaviors Are Improved by Early Postnatal Low-Dose VPA Intervention in a Novel shank3-Deficient Zebrafish Model. *Front Neurosci* 2021; **15**: 682054 [PMID: 34566559 DOI: 10.3389/fnins.2021.682054]
91 **Uchino S**, Waga C. Novel Therapeutic Approach for Autism Spectrum Disorder: Focus on *SHANK3*. *Curr Neuropharmacol* 2015; **13**: 786-792 [PMID: 26511836 DOI: 10.2174/1570159x13666151029105547]
92 **Roach KL**, Hershberger PE, Rutherford JN, Molokie RE, Wang ZJ, Wilkie DJ. The AVPR1A Gene and Its Single Nucleotide Polymorphism rs10877969: A Literature Review of Associations with Health Conditions and Pain. *Pain Manag Nurs* 2018; **19**: 430-444 [PMID: 29503216 DOI: 10.1016/j.pmn.2018.01.003]
93 **Meyer-Lindenberg A**, Kolachana B, Gold B, Olsh A, Nicodemus KK, Mattay V, Dean M, Weinberger DR. Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. *Mol Psychiatry* 2009; **14**: 968-975 [PMID: 18490926 DOI: 10.1038/mp.2008.54]
94 **László K**, Vörös D, Correia P, Fazekas CL, Török B, Plangár I, Zelena D. Vasopressin as Possible Treatment Option in Autism Spectrum Disorder. *Biomedicines* 2023; **11** [PMID: 37892977 DOI: 10.3390/biomedicines11102603]
95 **Charles R**, Sakurai T, Takahashi N, Elder GA, Gama Sosa MA, Young LJ, Buxbaum JD. Introduction of the human AVPR1A gene substantially alters brain receptor expression patterns and enhances aspects of social behavior in transgenic mice. *Dis Model Mech* 2014; **7**: 1013-1022 [PMID: 24924430 DOI: 10.1242/dmm.017053]
96 **Wilczyński KM**, Stasik A, Cichoń L, Augúsciak-Duma A, Janas-Kozik M. Polymorphisms in Oxytocin and Vasopressin Receptor Genes as a Factor Shaping the Clinical Picture and the Risk of ASD in Males. *Brain Sci* 2023; **13** [PMID: 37190654 DOI: 10.3390/brainsci13040689]
97 **LoParo D**, Waldman ID. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Mol Psychiatry* 2015; **20**: 640-646 [PMID: 25092245 DOI: 10.1038/mp.2014.77]
98 **Meyer M**, Jurek B, Alfonso-Prieto M, Ribeiro R, Milenkovic VM, Winter J, Hoffmann P, Wetzel CH, Giorgetti A, Carloni P, Neumann ID. Structure-function relationships of the disease-linked A218T oxytocin receptor variant. *Mol Psychiatry* 2022; **27**: 907-917 [PMID: 34980886 DOI: 10.1038/s41380-021-01241-8]
99 **Liu X**, Kawashima M, Miyagawa T, Otowa T, Latt KZ, Thiri M, Nishida H, Sugiyama T, Tsurusaki Y, Matsumoto N, Mabuchi A, Tokunaga K, Sasaki T. Novel rare variations of the oxytocin receptor (OXTR) gene in autism spectrum disorder individuals. *Hum Genome Var* 2015; **2**: 15024 [PMID: 27081536 DOI: 10.1038/hgv.2015.24]
100 **Mariggiò MA**, Palumbi R, Vinella A, Laterza R, Petruzzelli MG, Peschechera A, Gabellone A, Gentile O, Vincenti A, Margari L. DRD1 and DRD2 Receptor Polymorphisms: Genetic Neuromodulation of the Dopaminergic System as a Risk Factor for ASD, ADHD and ASD/ADHD Overlap. *Front Neurosci* 2021; **15**: 705890 [PMID: 34658761 DOI: 10.3389/fnins.2021.705890]
101 **Pavăl D**, Micluția IV. The Dopamine Hypothesis of Autism Spectrum Disorder Revisited: Current Status and Future Prospects. *Dev Neurosci* 2021; **43**: 73-83 [PMID: 34010842 DOI: 10.1159/000515751]
102 **Hettinger JA**, Liu X, Hudson ML, Lee A, Cohen IL, Michaelis RC, Schwartz CE, Lewis SM, Holden JJ. DRD2 and PPP1R1B (DARPP-32) polymorphisms independently confer increased risk for autism spectrum disorders and additively predict affected status in male-only affected sib-pair families. *Behav Brain Funct* 2012; **8**: 19 [PMID: 22559203 DOI: 10.1186/1744-9081-8-19]
103 **DiCarlo GE**, Wallace MT. Modeling dopamine dysfunction in autism spectrum disorder: From invertebrates to vertebrates. *Neurosci Biobehav Rev* 2022; **133**: 104494 [PMID: 34906613 DOI: 10.1016/j.neubiorev.2021.12.017]
104 **Nakajima S**, Gerretsen P, Takeuchi H, Caravaggio F, Chow T, Le Foll B, Mulsant B, Pollock B, Graff-Guerrero A. The potential role of dopamine D_3 receptor neurotransmission in cognition. *Eur Neuropsychopharmacol* 2013; **23**: 799-813 [PMID: 23791072 DOI: 10.1016/j.euroneuro.2013.05.006]
105 **Savitz J**, Hodgkinson CA, Martin-Soelch C, Shen PH, Szczepanik J, Nugent A, Herscovitch P, Grace AA, Goldman D, Drevets WC. The functional DRD3 Ser9Gly polymorphism (rs6280) is pleiotropic, affecting reward as well as movement. *PLoS One* 2013; **8**: e54108 [PMID: 23365649 DOI: 10.1371/journal.pone.0054108]
106 **Langen M**, Kas MJ, Staal WG, van Engeland H, Durston S. The neurobiology of repetitive behavior: of mice…. *Neurosci Biobehav Rev* 2011; **35**: 345-355 [PMID: 20156480 DOI: 10.1016/j.neubiorev.2010.02.004]
107 **de Krom M**, Staal WG, Ophoff RA, Hendriks J, Buitelaar J, Franke B, de Jonge MV, Bolton P, Collier D, Curran S, van Engeland H, van Ree JM. A common variant in DRD3 receptor is associated with autism spectrum disorder. *Biol Psychiatry* 2009; **65**: 625-630 [PMID: 19058789 DOI: 10.1016/j.biopsych.2008.09.035]
108 **Gonzales ML**, LaSalle JM. The role of MeCP2 in brain development and neurodevelopmental disorders. *Curr Psychiatry Rep* 2010; **12**: 127-134 [PMID: 20425298 DOI: 10.1007/s11920-010-0097-7]
109 **Gulmez Karaca K**, Brito DVC, Oliveira AMM. MeCP2: A Critical Regulator of Chromatin in Neurodevelopment and Adult Brain Function. *Int J Mol Sci* 2019; **20** [PMID: 31527487 DOI: 10.3390/ijms20184577]
110 **Peters SU**, Hundley RJ, Wilson AK, Warren Z, Vehorn A, Carvalho CM, Lupski JR, Ramocki MB. The behavioral phenotype in MECP2 duplication syndrome: a comparison with idiopathic autism. *Autism Res* 2013; **6**: 42-50 [PMID: 23169761 DOI: 10.1002/aur.1262]
111 **Wen Z**, Cheng TL, Li GZ, Sun SB, Yu SY, Zhang Y, Du YS, Qiu Z. Identification of autism-related MECP2 mutations by whole-exome sequencing and functional validation. *Mol Autism* 2017; **8**: 43 [PMID: 28785396 DOI: 10.1186/s13229-017-0157-5]
112 **Ezeonwuka CD**, Rastegar M. MeCP2-Related Diseases and Animal Models. *Diseases* 2014; **2**: 45-70 [PMID: 28191346 DOI: 10.3390/diseases2010045]
113 **Khoja S**, Haile MT, Chen LY. Advances in neurexin studies and the emerging role of neurexin-2 in autism spectrum disorder. *Front Mol Neurosci* 2023; **16**: 1125087 [PMID: 36923655 DOI: 10.3389/fnmol.2023.1125087]
114 **Cooper JN**, Mittal J, Sangadi A, Klassen DL, King AM, Zalta M, Mittal R, Eshraghi AA. Landscape of NRXN1 Gene Variants in Phenotypic Manifestations of Autism Spectrum Disorder: A Systematic Review. *J Clin Med* 2024; **13** [PMID: 38610832 DOI: 10.3390/jcm13072067]
115 **Gauthier J**, Siddiqui TJ, Huashan P, Yokomaku D, Hamdan FF, Champagne N, Lapointe M, Spiegelman D, Noreau A, Lafrenière RG,

Fathalli F, Joober R, Krebs MO, DeLisi LE, Mottron L, Fombonne E, Michaud JL, Drapeau P, Carbonetto S, Craig AM, Rouleau GA. Truncating mutations in NRXN2 and NRXN1 in autism spectrum disorders and schizophrenia. *Hum Genet* 2011; **130**: 563-573 [PMID: 21424692 DOI: 10.1007/s00439-011-0975-z]

116 **Shan D**, Song Y, Zhang Y, Ho CW, Xia W, Li Z, Ge F, Ou Q, Dai Z, Dai Z. Neurexin dysfunction in neurodevelopmental and neuropsychiatric disorders: a PRIMSA-based systematic review through iPSC and animal models. *Front Behav Neurosci* 2024; **18**: 1297374 [PMID: 38380150 DOI: 10.3389/fnbeh.2024.1297374]

117 **Cast TP**, Boesch DJ, Smyth K, Shaw AE, Ghebrial M, Chanda S. An Autism-Associated Mutation Impairs Neuroligin-4 Glycosylation and Enhances Excitatory Synaptic Transmission in Human Neurons. *J Neurosci* 2021; **41**: 392-407 [PMID: 33268543 DOI: 10.1523/JNEUROSCI.0404-20.2020]

118 **Nguyen TA**, Lehr AW, Roche KW. Neuroligins and Neurodevelopmental Disorders: X-Linked Genetics. *Front Synaptic Neurosci* 2020; **12**: 33 [PMID: 32848696 DOI: 10.3389/fnsyn.2020.00033]

119 **Trobiani L**, Meringolo M, Diamanti T, Bourne Y, Marchot P, Martella G, Dini L, Pisani A, De Jaco A, Bonsi P. The neuroligins and the synaptic pathway in Autism Spectrum Disorder. *Neurosci Biobehav Rev* 2020; **119**: 37-51 [PMID: 32991906 DOI: 10.1016/j.neubiorev.2020.09.017]

120 **Montanaro FAM**, Mandarino A, Alesi V, Schwartz C, Sepulveda DJC, Skinner C, Friez M, Piccolo G, Novelli A, Zanni G, Dentici ML, Vicari S, Alfieri P. *PTCHD1* gene mutation/deletion: the cognitive-behavioral phenotyping of four case reports. *Front Psychiatry* 2023; **14**: 1327802 [PMID: 38288059 DOI: 10.3389/fpsyt.2023.1327802]

121 **Halewa J**, Marouillat S, Dixneuf M, Thépault RA, Ung DC, Chatron N, Gérard B, Ghoumid J, Lesca G, Till M, Smol T, Couque N, Ruaud L, Chune V, Grotto S, Verloes A, Vuillaume ML, Toutain A, Raynaud M, Laumonnier F. Novel missense mutations in *PTCHD1* alter its plasma membrane subcellular localization and cause intellectual disability and autism spectrum disorder. *Hum Mutat* 2021; **42**: 848-861 [PMID: 33856728 DOI: 10.1002/humu.24208]

122 **Filges I**, Röthlisberger B, Blattner A, Boesch N, Demougin P, Wenzel F, Huber AR, Heinimann K, Weber P, Miny P. Deletion in Xp22.11: *PTCHD1* is a candidate gene for X-linked intellectual disability with or without autism. *Clin Genet* 2011; **79**: 79-85 [PMID: 21091464 DOI: 10.1111/j.1399-0004.2010.01590.x]

123 **Serretti A**, Calati R, Mandelli L, De Ronchi D. Serotonin transporter gene variants and behavior: a comprehensive review. *Curr Drug Targets* 2006; **7**: 1659-1669 [PMID: 17168841 DOI: 10.2174/138945006779025419]

124 **Muller CL**, Anacker AMJ, Veenstra-VanderWeele J. The serotonin system in autism spectrum disorder: From biomarker to animal models. *Neuroscience* 2016; **321**: 24-41 [PMID: 26577932 DOI: 10.1016/j.neuroscience.2015.11.010]

125 **Miozzo R**, Eaton WW, Joseph Bienvenu O 3rd, Samuels J, Nestadt G. The serotonin transporter gene polymorphism (SLC6A4) and risk for psychiatric morbidity and comorbidity in the Baltimore ECA follow-up study. *Compr Psychiatry* 2020; **102**: 152199 [PMID: 32911381 DOI: 10.1016/j.comppsych.2020.152199]

126 **Coutinho AM**, Oliveira G, Morgadinho T, Fesel C, Macedo TR, Bento C, Marques C, Ataíde A, Miguel T, Borges L, Vicente AM. Variants of the serotonin transporter gene (SLC6A4) significantly contribute to hyperserotonemia in autism. *Mol Psychiatry* 2004; **9**: 264-271 [PMID: 15094787 DOI: 10.1038/sj.mp.4001409]

127 **Rasmussen AH**, Rasmussen HB, Silahtaroglu A. The DLGAP family: neuronal expression, function and role in brain disorders. *Mol Brain* 2017; **10**: 43 [PMID: 28870203 DOI: 10.1186/s13041-017-0324-9]

128 **Rodríguez-Palmero A**, Boerrigter MM, Gómez-Andrés D, Aldinger KA, Marcos-Alcalde Í, Popp B, Everman DB, Lovgren AK, Arpin S, Bahrambeigi V, Beunders G, Bisgaard AM, Bjerregaard VA, Bruel AL, Challman TD, Cogné B, Coubes C, de Man SA, Denommé-Pichon AS, Dye TJ, Elmslie F, Feuk L, García-Miñaúr S, Gertler T, Giorgio E, Gruchy N, Haack TB, Haldeman-Englert CR, Haukanes BI, Hoyer J, Hurst ACE, Isidor B, Soller MJ, Kushary S, Kvarnung M, Landau YE, Leppig KA, Lindstrand A, Kleinendorst L, MacKenzie A, Mandrile G, Mendelsohn BA, Moghadasi S, Morton JE, Moutton S, Müller AJ, O'Leary M, Pacio-Míguez M, Palomares-Bralo M, Parikh S, Pfundt R, Pode-Shakked B, Rauch A, Repnikova E, Revah-Politi A, Ross MJ, Ruivenkamp CAL, Sarrazin E, Savatt JM, Schlüter A, Schönewolf-Greulich B, Shad Z, Shaw-Smith C, Shieh JT, Shohat M, Spranger S, Thiese H, Mau-Them FT, van Bon B, van de Burgt I, van de Laar IMBH, van Drie E, van Haelst MM, van Ravenswaaij-Arts CM, Verdura E, Vitobello A, Waldmüller S, Whiting S, Zweier C, Prada CE, de Vries BBA, Dobyns WB, Reiter SF, Gómez-Puertas P, Pujol A, Tümer Z. DLG4-related synaptopathy: a new rare brain disorder. *Genet Med* 2021; **23**: 888-899 [PMID: 33597769 DOI: 10.1038/s41436-020-01075-9]

129 **Ebert DH**, Greenberg ME. Activity-dependent neuronal signalling and autism spectrum disorder. *Nature* 2013; **493**: 327-337 [PMID: 23325215 DOI: 10.1038/nature11860]

130 **Banerjee S**, Riordan M, Bhat MA. Genetic aspects of autism spectrum disorders: insights from animal models. *Front Cell Neurosci* 2014; **8**: 58 [PMID: 24605088 DOI: 10.3389/fncel.2014.00058]

131 **Kang JQ**, Macdonald RL. Molecular Pathogenic Basis for GABRG2 Mutations Associated With a Spectrum of Epilepsy Syndromes, From Generalized Absence Epilepsy to Dravet Syndrome. *JAMA Neurol* 2016; **73**: 1009-1016 [PMID: 27367160 DOI: 10.1001/jamaneurol.2016.0449]

132 **Zhao H**, Mao X, Zhu C, Zou X, Peng F, Yang W, Li B, Li G, Ge T, Cui R. GABAergic System Dysfunction in Autism Spectrum Disorders. *Front Cell Dev Biol* 2021; **9**: 781327 [PMID: 35198562 DOI: 10.3389/fcell.2021.781327]

133 **Mele M**, Costa RO, Duarte CB. Alterations in GABA(A)-Receptor Trafficking and Synaptic Dysfunction in Brain Disorders. *Front Cell Neurosci* 2019; **13**: 77 [PMID: 30899215 DOI: 10.3389/fncel.2019.00077]

134 **Kurtz-Nelson EC**, Beighley JS, Hudac CM, Gerdts J, Wallace AS, Hoekzema K, Eichler EE, Bernier RA. Co-occurring medical conditions among individuals with ASD-associated disruptive mutations. *Child Health Care* 2020; **49**: 361-384 [PMID: 33727758 DOI: 10.1080/02739615.2020.1741361]

135 **Freitas GA**, Niswender CM. *GRM7* gene mutations and consequences for neurodevelopment. *Pharmacol Biochem Behav* 2023; **225**: 173546 [PMID: 37003303 DOI: 10.1016/j.pbb.2023.173546]

136 **Nisar S**, Bhat AA, Masoodi T, Hashem S, Akhtar S, Ali TA, Amjad S, Chawla S, Bagga P, Frenneaux MP, Reddy R, Fakhro K, Haris M. Genetics of glutamate and its receptors in autism spectrum disorder. *Mol Psychiatry* 2022; **27**: 2380-2392 [PMID: 35296811 DOI: 10.1038/s41380-022-01506-w]

137 **Wang X**, Gao C, Zhang Y, Hu S, Qiao Y, Zhao Z, Gou L, Song J, Wang Q. Overexpression of mGluR7 in the Prefrontal Cortex Attenuates Autistic Behaviors in Mice. *Front Cell Neurosci* 2021; **15**: 689611 [PMID: 34335187 DOI: 10.3389/fncel.2021.689611]

138 **Noroozi R**, Taheri M, Movafagh A, Mirfakhraie R, Solgi G, Sayad A, Mazdeh M, Darvish H. Glutamate receptor, metabotropic 7 (*GRM7*) gene variations and susceptibility to autism: A case-control study. *Autism Res* 2016; **9**: 1161-1168 [PMID: 27312574 DOI: 10.1002/aur.1640]

139 **Fisher NM**, Seto M, Lindsley CW, Niswender CM. Metabotropic Glutamate Receptor 7: A New Therapeutic Target in Neurodevelopmental Disorders. *Front Mol Neurosci* 2018; **11**: 387 [PMID: 30405350 DOI: 10.3389/fnmol.2018.00387]

140 **Bryn V**, Halvorsen B, Ueland T, Isaksen J, Kolkova K, Ravn K, Skjeldal OH. Brain derived neurotrophic factor (*BDNF*) and autism spectrum disorders (ASD) in childhood. *Eur J Paediatr Neurol* 2015; **19**: 411-414 [PMID: 25847750 DOI: 10.1016/j.ejpn.2015.03.005]

141 **Bathina S**, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci* 2015; **11**: 1164-1178 [PMID: 26788077 DOI: 10.5114/aoms.2015.56342]

142 **Han YMY**, Yau SY, Chan MMY, Wong CK, Chan AS. Altered Cytokine and *BDNF* Levels in Individuals with Autism Spectrum Disorders. *Brain Sci* 2022; **12** [PMID: 35447993 DOI: 10.3390/brainsci12040460]

143 **Kasarpalkar NJ**, Kothari ST, Dave UP. Brain-Derived Neurotrophic Factor in children with Autism Spectrum Disorder. *Ann Neurosci* 2014; **21**: 129-133 [PMID: 25452672 DOI: 10.5214/ans.0972.7531.210403]

144 **Nishimura K**, Nakamura K, Anitha A, Yamada K, Tsujii M, Iwayama Y, Hattori E, Toyota T, Takei N, Miyachi T, Iwata Y, Suzuki K, Matsuzaki H, Kawai M, Sekine Y, Tsuchiya K, Sugihara G, Suda S, Ouchi Y, Sugiyama T, Yoshikawa T, Mori N. Genetic analyses of the brain-derived neurotrophic factor (*BDNF*) gene in autism. *Biochem Biophys Res Commun* 2007; **356**: 200-206 [PMID: 17349978 DOI: 10.1016/j.bbrc.2007.02.135]

145 **Ilchibaeva T**, Tsybko A, Lipnitskaya M, Eremin D, Milutinovich K, Naumenko V, Popova N. Brain-Derived Neurotrophic Factor (*BDNF*) in Mechanisms of Autistic-like Behavior in BTBR Mice: Crosstalk with the Dopaminergic Brain System. *Biomedicines* 2023; **11** [PMID: 37239153 DOI: 10.3390/biomedicines11051482]

146 **Sleiman SF**, Henry J, Al-Haddad R, El Hayek L, Abou Haidar E, Stringer T, Ulja D, Karuppagounder SS, Holson EB, Ratan RR, Ninan I, Chao MV. Exercise promotes the expression of brain derived neurotrophic factor (*BDNF*) through the action of the ketone body β-hydroxybutyrate. *Elife* 2016; **5** [PMID: 27253067 DOI: 10.7554/eLife.15092]

147 **Marosi K**, Mattson MP. *BDNF* mediates adaptive brain and body responses to energetic challenges. *Trends Endocrinol Metab* 2014; **25**: 89-98 [PMID: 24361004 DOI: 10.1016/j.tem.2013.10.006]

148 **Sytnyk V**, Leshchyns'ka I, Schachner M. Neural Cell Adhesion Molecules of the Immunoglobulin Superfamily Regulate Synapse Formation, Maintenance, and Function. *Trends Neurosci* 2017; **40**: 295-308 [PMID: 28359630 DOI: 10.1016/j.tins.2017.03.003]

149 **Marui T**, Funatogawa I, Koishi S, Yamamoto K, Matsumoto H, Hashimoto O, Nanba E, Nishida H, Sugiyama T, Kasai K, Watanabe K, Kano Y, Sasaki T, Kato N. Association of the neuronal cell adhesion molecule (*NRCAM*) gene variants with autism. *Int J Neuropsychopharmacol* 2009; **12**: 1-10 [PMID: 18664314 DOI: 10.1017/S1461145708009127]

150 **Lo LH**, Lai KO. Dysregulation of protein synthesis and dendritic spine morphogenesis in ASD: studies in human pluripotent stem cells. *Mol Autism* 2020; **11**: 40 [PMID: 32460854 DOI: 10.1186/s13229-020-00349-y]

151 **Betancur C**, Sakurai T, Buxbaum JD. The emerging role of synaptic cell-adhesion pathways in the pathogenesis of autism spectrum disorders. *Trends Neurosci* 2009; **32**: 402-412 [PMID: 19541375 DOI: 10.1016/j.tins.2009.04.003]

152 **Mohan V**, Gomez JR, Maness PF. Expression and Function of Neuron-Glia-Related Cell Adhesion Molecule (**NrCAM**) in the Amygdalar Pathway. *Front Cell Dev Biol* 2019; **7**: 9 [PMID: 30766872 DOI: 10.3389/fcell.2019.00009]

153 **Guhathakurta S**, Singh AS, Sinha S, Chatterjee A, Ahmed S, Ghosh S, Usha R. Analysis of serotonin receptor 2A gene (*HTR2A*): association study with autism spectrum disorder in the Indian population and investigation of the gene expression in peripheral blood leukocytes. *Neurochem Int* 2009; **55**: 754-759 [PMID: 19647026 DOI: 10.1016/j.neuint.2009.07.008]

154 **Zhang G**, Stackman RW Jr. The role of serotonin 5-HT2A receptors in memory and cognition. *Front Pharmacol* 2015; **6**: 225 [PMID: 26500553 DOI: 10.3389/fphar.2015.00225]

155 **Cieslinska A**, Fiedorowicz E, Jarmolowska B, Kordulewska N, Kostyra E, Moszynska M, Savelkoul HF. Polymorphisms rs6313 and rs6314 in Serotonin Receptor Gene (*HTR2A*) and Serotonin Concentration in Autistic Children. *Neuropsychiatry* 2019; **9** [DOI: 10.4172/neuropsychiatry.1000547]

156 **Luppi AI**, Girn M, Rosas FE, Timmermann C, Roseman L, Erritzoe D, Nutt DJ, Stamatakis EA, Spreng RN, Xing L, Huttner WB, Carhart-Harris RL. A role for the serotonin 2A receptor in the expansion and functioning of human transmodal cortex. *Brain* 2024; **147**: 56-80 [PMID: 37703310 DOI: 10.1093/brain/awad311]

157 **Poniatowski ŁA**, Wojdasiewicz P, Krawczyk M, Szukiewicz D, Gasik R, Kubaszewski Ł, Kurkowska-Jastrzębska I. Analysis of the Role of CX3CL1 (Fractalkine) and Its Receptor *CX3CR1* in Traumatic Brain and Spinal Cord Injury: Insight into Recent Advances in Actions of Neurochemokine Agents. *Mol Neurobiol* 2017; **54**: 2167-2188 [PMID: 26927660 DOI: 10.1007/s12035-016-9787-4]

158 **Pawelec P**, Ziemka-Nalecz M, Sypecka J, Zalewska T. The Impact of the CX3CL1/*CX3CR1* Axis in Neurological Disorders. *Cells* 2020; **9** [PMID: 33065974 DOI: 10.3390/cells9102277]

159 **Luo Y**, Wang Z. The Impact of Microglia on Neurodevelopment and Brain Function in Autism. *Biomedicines* 2024; **12** [PMID: 38255315 DOI: 10.3390/biomedicines12010210]

160 **Cho SH**, Sun B, Zhou Y, Kauppinen TM, Halabisky B, Wes P, Ransohoff RM, Gan L. *CX3CR1* protein signaling modulates microglial activation and protects against plaque-independent cognitive deficits in a mouse model of Alzheimer disease. *J Biol Chem* 2011; **286**: 32713-32722 [PMID: 21771791 DOI: 10.1074/jbc.M111.254268]

161 **Fan G**, Ma J, Ma R, Suo M, Chen Y, Zhang S, Zeng Y, Chen Y. Microglia Modulate Neurodevelopment in Autism Spectrum Disorder and Schizophrenia. *Int J Mol Sci* 2023; **24** [PMID: 38139124 DOI: 10.3390/ijms242417297]

162 **Ishizuka K**, Fujita Y, Kawabata T, Kimura H, Iwayama Y, Inada T, Okahisa Y, Egawa J, Usami M, Kushima I, Uno Y, Okada T, Ikeda M, Aleksic B, Mori D, Someya T, Yoshikawa T, Iwata N, Nakamura H, Yamashita T, Ozaki N. Rare genetic variants in *CX3CR1* and their contribution to the increased risk of schizophrenia and autism spectrum disorders. *Transl Psychiatry* 2017; **7**: e1184 [PMID: 28763059 DOI: 10.1038/tp.2017.173]

163 **Di Lascio S**, Fornasari D, Benfante R. The Human-Restricted Isoform of the α7 nAChR, CHRFAM7A: A Double-Edged Sword in Neurological and Inflammatory Disorders. *Int J Mol Sci* 2022; **23** [PMID: 35408823 DOI: 10.3390/ijms23073463]

164 **Vallés AS**, Barrantes FJ. Dysregulation of Neuronal Nicotinic Acetylcholine Receptor-Cholesterol Crosstalk in Autism Spectrum Disorder. *Front Mol Neurosci* 2021; **14**: 744597 [PMID: 34803605 DOI: 10.3389/fnmol.2021.744597]

165 **Bacchelli E**, Battaglia A, Cameli C, Lomartire S, Tancredi R, Thomson S, Sutcliffe JS, Maestrini E. Analysis of *CHRNA7* rare variants in autism spectrum disorder susceptibility. *Am J Med Genet A* 2015; **167A**: 715-723 [PMID: 25655306 DOI: 10.1002/ajmg.a.36847]

166 **Gillentine MA**, Yin J, Bajic A, Zhang P, Cummock S, Kim JJ, Schaaf CP. Functional Consequences of *CHRNA7* Copy-Number Alterations in Induced Pluripotent Stem Cells and Neural Progenitor Cells. *Am J Hum Genet* 2017; **101**: 874-887 [PMID: 29129316 DOI: 10.1016/j.ajhg.2017.09.024]

167 **Castro AC**, Monteiro P. Auditory Dysfunction in Animal Models of Autism Spectrum Disorder. *Front Mol Neurosci* 2022; **15**: 845155 [PMID: 35493332 DOI: 10.3389/fnmol.2022.845155]

168 **Myers SJ**, Yuan H, Kang JQ, Tan FCK, Traynelis SF, Low CM. Distinct roles of *GRIN2A* and *GRIN2B* variants in neurological conditions. *F1000Res* 2019; **8** [PMID: 31807283 DOI: 10.12688/f1000research.18949.1]

169 **Shepard N**, Baez-Nieto D, Iqbal S, Kurganov E, Budnik N, Campbell AJ, Pan JQ, Sheng M, Farsi Z. Differential functional consequences of *GRIN2A* mutations associated with schizophrenia and neurodevelopmental disorders. *Sci Rep* 2024; **14**: 2798 [PMID: 38307912 DOI: 10.1038/s41598-024-53102-3]

170 **Benítez-burraco A**, Hoshi K, Murphy E. Language deficits in *GRIN2A* mutations and Landau-Kleffner syndrome as neural dysrhythmias. *J Neurolinguistics* 2023; **67**: 101139 [DOI: 10.1016/j.jneuroling.2023.101139]

171 **Bertocchi I**, Eltokhi A, Rozov A, Chi VN, Jensen V, Bus T, Pawlak V, Serafino M, Sonntag H, Yang B, Burnashev N, Li SB, Obenhaus HA, Both M, Niewoehner B, Single FN, Briese M, Boerner T, Gass P, Rawlins JNP, Köhr G, Bannerman DM, Sprengel R. Voltage-independent GluN2A-type NMDA receptor Ca(2+) signaling promotes audiogenic seizures, attentional and cognitive deficits in mice. *Commun Biol* 2021; **4**: 59 [PMID: 33420383 DOI: 10.1038/s42003-020-01538-4]

172 **Ma SL**, Tang NL, Zhang YP, Ji LD, Tam CW, Lui VW, Chiu HF, Lam LC. Association of prostaglandin-endoperoxide synthase 2 (*PTGS2*) polymorphisms and Alzheimer's disease in Chinese. *Neurobiol Aging* 2008; **29**: 856-860 [PMID: 17234302 DOI: 10.1016/j.neurobiolaging.2006.12.011]

173 **Al-Beltagi M**, Saeed NK, Bediwy AS, Alhawamdeh R, Qaraghuli S. Effects of COVID-19 on children with autism. *World J Virol* 2022; **11**: 411-425 [PMID: 36483100 DOI: 10.5501/wjv.v11.i6.411]

174 **Kalinski P**. Regulation of immune responses by prostaglandin E2. *J Immunol* 2012; **188**: 21-28 [PMID: 22187483 DOI: 10.4049/jimmunol.1101029]

175 **Joly-Amado A**, Kulkarni N, Nash KR. Reelin Signaling in Neurodevelopmental Disorders and Neurodegenerative Diseases. *Brain Sci* 2023; **13** [PMID: 37891846 DOI: 10.3390/brainsci13101479]

176 **Lammert DB**, Howell BW. *RELN* Mutations in Autism Spectrum Disorder. *Front Cell Neurosci* 2016; **10**: 84 [PMID: 27064498 DOI: 10.3389/fncel.2016.00084]

177 **Folsom TD**, Fatemi SH. The involvement of Reelin in neurodevelopmental disorders. *Neuropharmacology* 2013; **68**: 122-135 [PMID: 22981949 DOI: 10.1016/j.neuropharm.2012.08.015]

178 **O'Brien EK**, Zhang X, Nishimura C, Tomblin JB, Murray JC. Association of specific language impairment (SLI) to the region of 7q31. *Am J Hum Genet* 2003; **72**: 1536-1543 [PMID: 12721956 DOI: 10.1086/375403]

179 **Newbury DF**, Bonora E, Lamb JA, Fisher SE, Lai CS, Baird G, Jannoun L, Slonims V, Stott CM, Merricks MJ, Bolton PF, Bailey AJ, Monaco AP; International Molecular Genetic Study of Autism Consortium. *FOXP2* is not a major susceptibility gene for autism or specific language impairment. *Am J Hum Genet* 2002; **70**: 1318-1327 [PMID: 11894222 DOI: 10.1086/339931]

180 **Kast RJ**, Lanjewar AL, Smith CD, Levitt P. *FOXP2* exhibits projection neuron class specific expression, but is not required for multiple aspects of cortical histogenesis. *Elife* 2019; **8** [PMID: 31099752 DOI: 10.7554/eLife.42012]

181 **Antonucci F**, Corradini I, Fossati G, Tomasoni R, Menna E, Matteoli M. SNAP-25, a Known Presynaptic Protein with Emerging Postsynaptic Functions. *Front Synaptic Neurosci* 2016; **8**: 7 [PMID: 27047369 DOI: 10.3389/fnsyn.2016.00007]

182 **Bolognesi E**, Guerini FR, Carta A, Chiappedi M, Sotgiu S, Mensi MM, Agliardi C, Zanzottera M, Clerici M. The Role of SNAP-25 in Autism Spectrum Disorders Onset Patterns. *Int J Mol Sci* 2023; **24** [PMID: 37762342 DOI: 10.3390/ijms241814042]

183 **Guerini FR**, Bolognesi E, Chiappedi M, Manca S, Ghezzo A, Agliardi C, Sotgiu S, Usai S, Matteoli M, Clerici M. SNAP-25 single nucleotide polymorphisms are associated with hyperactivity in autism spectrum disorders. *Pharmacol Res* 2011; **64**: 283-288 [PMID: 21497654 DOI: 10.1016/j.phrs.2011.03.015]

184 **Lenart J**, Bratek E, Lazarewicz JW, Zieminska E. Changes in the Expression of SNAP-25 Protein in the Brain of Juvenile Rats in Two Models of Autism. *J Mol Neurosci* 2020; **70**: 1313-1320 [PMID: 32367505 DOI: 10.1007/s12031-020-01543-6]

185 **Szymanowicz O**, Drużdż A, Słowikowski B, Pawlak S, Potocka E, Goutor U, Konieczny M, Ciastoń M, Lewandowska A, Jagodziński PP, Kozubski W, Dorszewska J. A Review of the CACNA Gene Family: Its Role in Neurological Disorders. *Diseases* 2024; **12** [PMID: 38785745 DOI: 10.3390/diseases12050090]

186 **Lory P**, Nicole S, Monteil A. Neuronal Cav3 channelopathies: recent progress and perspectives. *Pflugers Arch* 2020; **472**: 831-844 [PMID: 32638069 DOI: 10.1007/s00424-020-02429-7]

187 **Strom SP**, Stone JL, Ten Bosch JR, Merriman B, Cantor RM, Geschwind DH, Nelson SF. High-density SNP association study of the 17q21 chromosomal region linked to autism identifies *CACNA1G* as a novel candidate gene. *Mol Psychiatry* 2010; **15**: 996-1005 [PMID: 19455149 DOI: 10.1038/mp.2009.41]

188 **Liao X**, Li Y. Genetic associations between voltage-gated calcium channels and autism spectrum disorder: a systematic review. *Mol Brain* 2020; **13**: 96 [PMID: 32571372 DOI: 10.1186/s13041-020-00634-0]

189 **Jacob TC**. Neurobiology and Therapeutic Potential of α5-GABA Type A Receptors. *Front Mol Neurosci* 2019; **12**: 179 [PMID: 31396049 DOI: 10.3389/fnmol.2019.00179]

190 **Zurek AA**, Kemp SW, Aga Z, Walker S, Milenkovic M, Ramsey AJ, Sibille E, Scherer SW, Orser BA. α5GABAA receptor deficiency causes autism-like behaviors. *Ann Clin Transl Neurol* 2016; **3**: 392-398 [PMID: 27231709 DOI: 10.1002/acn3.303]

191 **DeLorey TM**. GABRB3 gene deficient mice: a potential model of autism spectrum disorder. *Int Rev Neurobiol* 2005; **71**: 359-382 [PMID: 16512358 DOI: 10.1016/s0074-7742(05)71015-1]

192 **Sabo SL**, Lahr JM, Offer M, Weekes A, Sceniak MP. *GRIN2B*-related neurodevelopmental disorder: current understanding of pathophysiological mechanisms. *Front Synaptic Neurosci* 2022; **14**: 1090865 [PMID: 36704660 DOI: 10.3389/fnsyn.2022.1090865]

193 **Hu C**, Chen W, Myers SJ, Yuan H, Traynelis SF. Human *GRIN2B* variants in neurodevelopmental disorders. *J Pharmacol Sci* 2016; **132**: 115-121 [PMID: 27818011 DOI: 10.1016/j.jphs.2016.10.002]

194 **Pan Y**, Chen J, Guo H, Ou J, Peng Y, Liu Q, Shen Y, Shi L, Liu Y, Xiong Z, Zhu T, Luo S, Hu Z, Zhao J, Xia K. Association of genetic variants of *GRIN2B* with autism. *Sci Rep* 2015; **5**: 8296 [PMID: 25656819 DOI: 10.1038/srep08296]

195 **Zoodsma JD**, Keegan EJ, Moody GR, Bhandiwad AA, Napoli AJ, Burgess HA, Wollmuth LP, Sirotkin HI. Disruption of *grin2B*, an ASD-associated gene, produces social deficits in zebrafish. *Mol Autism* 2022; **13**: 38 [PMID: 36138431 DOI: 10.1186/s13229-022-00516-3]

196 **Guzmán YF**, Ramsey K, Stolz JR, Craig DW, Huentelman MJ, Narayanan V, Swanson GT. A gain-of-function mutation in the *GRIK2* gene causes neurodevelopmental deficits. *Neurol Genet* 2017; **3**: e129 [PMID: 28180184 DOI: 10.1212/NXG.0000000000000129]

197 **Stolz JR**, Foote KM, Veenstra-Knol HE, Pfundt R, Ten Broeke SW, de Leeuw N, Roht L, Pajusalu S, Part R, Rebane I, Õunap K, Stark Z, Kirk EP, Lawson JA, Lunke S, Christodoulou J, Louie RJ, Rogers RC, Davis JM, Innes AM, Wei XC, Keren B, Mignot C, Lebel RR, Sperber SM, Sakonju A, Dosa N, Barge-Schaapveld DQCM, Peeters-Scholte CMPCD, Ruivenkamp CAL, van Bon BW, Kennedy J, Low KJ, Ellard S, Pang L, Junewick JJ, Mark PR, Carvill GL, Swanson GT. Clustered mutations in the *GRIK2* kainate receptor subunit gene underlie diverse neurodevelopmental disorders. *Am J Hum Genet* 2021; **108**: 1692-1709 [PMID: 34375587 DOI: 10.1016/j.ajhg.2021.07.007]

198 **Xie X**, Hou F, Li L, Chen Y, Liu L, Luo X, Gu H, Li X, Zhang J, Gong J, Song R. Polymorphisms of Ionotropic Glutamate Receptor-Related Genes and the Risk of Autism Spectrum Disorder in a Chinese Population. *Psychiatry Investig* 2019; **16**: 379-385 [PMID: 31132842 DOI: 10.30773/pi.2019.02.26.3]

199 **Nomura T**, Taniguchi S, Wang YZ, Yeh NH, Wilen AP, Castillon CCM, Foote KM, Xu J, Armstrong JN, Savas JN, Swanson GT, Contractor A. A Pathogenic Missense Mutation in Kainate Receptors Elevates Dendritic Excitability and Synaptic Integration through Dysregulation of SK Channels. *J Neurosci* 2023; **43**: 7913-7928 [PMID: 37802657 DOI: 10.1523/JNEUROSCI.1259-23.2023]

200 **Mellios N**, Papageorgiou G, Gorgievski V, Maxson G, Hernandez M, Otero M, Varangis M, Dell'Orco M, Perrone-Bizzozero N, Tzavara E. Regulation of neuronal circ*Homer1* biogenesis by PKA/CREB/ERK-mediated pathways and effects of glutamate and dopamine receptor blockade. *Res Sq* 2024 [PMID: 38260249 DOI: 10.21203/rs.3.rs-3547375/v1]

201 **Banerjee A**, Luong JA, Ho A, Saib AO, Ploski JE. Overexpression of *Homer1*a in the basal and lateral amygdala impairs fear conditioning and induces an autism-like social impairment. *Mol Autism* 2016; **7**: 16 [PMID: 26929812 DOI: 10.1186/s13229-016-0077-9]

202 **Meliskova V**, Havranek T, Bacova Z, Bakos J. The role of selected postsynaptic scaffolding proteins at glutamatergic synapses in autism-related animal models. *J Integr Neurosci* 2021; **20**: 1047-1057 [PMID: 34997728 DOI: 10.31083/j.jin2004106]

203 **Miles JH**. Autism spectrum disorders--a genetics review. *Genet Med* 2011; **13**: 278-294 [PMID: 21358411 DOI: 10.1097/GIM.0b013e3181ff67ba]

204 **Gillberg C**. Chromosomal disorders and autism. *J Autism Dev Disord* 1998; **28**: 415-425 [PMID: 9813777 DOI: 10.1023/a:1026004505764]

205 **Belkady B**, Elkhattabi L, Elkarhat Z, Zarouf L, Razoki L, Aboulfaraj J, Nassereddine S, Cadi R, Rouba H, Barakat A. Chromosomal Abnormalities in Patients with Intellectual Disability: A 21-Year Retrospective Study. *Hum Hered* 2018; **83**: 274-282 [PMID: 31064002 DOI: 10.1159/000499710]

206 **Chaste P**, Betancur C, Gérard-Blanluet M, Bargiacchi A, Kuzbari S, Drunat S, Leboyer M, Bourgeron T, Delorme R. High-functioning autism spectrum disorder and fragile X syndrome: report of two affected sisters. *Mol Autism* 2012; **3**: 5 [PMID: 22738402 DOI: 10.1186/2040-2392-3-5]

207 **McCary LM**, Roberts JE. Early identification of autism in fragile X syndrome: a review. *J Intellect Disabil Res* 2013; **57**: 803-814 [PMID: 22974167 DOI: 10.1111/j.1365-2788.2012.01609.x]

208 **Kalsner L**, Chamberlain SJ. Prader-Willi, Angelman, and 15q11-q13 Duplication Syndromes. *Pediatr Clin North Am* 2015; **62**: 587-606 [PMID: 26022164 DOI: 10.1016/j.pcl.2015.03.004]

209 **DiStefano C**, Gulsrud A, Huberty S, Kasari C, Cook E, Reiter LT, Thibert R, Jeste SS. Identification of a distinct developmental and behavioral profile in children with Dup15q syndrome. *J Neurodev Disord* 2016; **8**: 19 [PMID: 27158270 DOI: 10.1186/s11689-016-9152-y]

210 **Szczawińska-Popłonyk A**, Schwartzmann E, Chmara Z, Głukowska A, Krysa T, Majchrzycki M, Olejnicki M, Ostrowska P, Babik J. Chromosome 22q11.2 Deletion Syndrome: A Comprehensive Review of Molecular Genetics in the Context of Multidisciplinary Clinical Approach. *Int J Mol Sci* 2023; **24** [PMID: 37176024 DOI: 10.3390/ijms24098317]

211 **Ousley O**, Evans AN, Fernandez-Carriba S, Smearman EL, Rockers K, Morrier MJ, Evans DW, Coleman K, Cubells J. Examining the Overlap between Autism Spectrum Disorder and 22q11.2 Deletion Syndrome. *Int J Mol Sci* 2017; **18** [PMID: 28524075 DOI: 10.3390/ijms18051071]

212 **Wolstencroft J**, Mandy W, Skuse D. Mental health and neurodevelopment in children and adolescents with Turner syndrome. *Womens Health (Lond)* 2022; **18**: 17455057221133635 [PMID: 36472167 DOI: 10.1177/17455057221133635]

213 **Björlin Avdic H**, Butwicka A, Nordenström A, Almqvist C, Nordenskjöld A, Engberg H, Frisén L. Neurodevelopmental and psychiatric disorders in females with Turner syndrome: a population-based study. *J Neurodev Disord* 2021; **13**: 51 [PMID: 34706642 DOI: 10.1186/s11689-021-09399-6]

214 **Boada R**, Janusz J, Hutaff-Lee C, Tartaglia N. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. *Dev Disabil Res Rev* 2009; **15**: 284-294 [PMID: 20014369 DOI: 10.1002/ddrr.83]

215 **Tartaglia NR**, Wilson R, Miller JS, Rafalko J, Cordeiro L, Davis S, Hessl D, Ross J. Autism Spectrum Disorder in Males with Sex Chromosome Aneuploidy: XXY/Klinefelter Syndrome, XYY, and XXYY. *J Dev Behav Pediatr* 2017; **38**: 197-207 [PMID: 28333849 DOI: 10.1097/DBP.0000000000000429]

216 **Abukhaled Y**, Hatab K, Awadhalla M, Hamdan H. Understanding the genetic mechanisms and cognitive impairments in Down syndrome: towards a holistic approach. *J Neurol* 2024; **271**: 87-104 [PMID: 37561187 DOI: 10.1007/s00415-023-11890-0]

217 **Spinazzi NA**, Santoro JD, Pawlowski K, Anzueto G, Howe YJ, Patel LR, Baumer NT. Co-occurring conditions in children with Down syndrome and autism: a retrospective study. *J Neurodev Disord* 2023; **15**: 9 [PMID: 36864370 DOI: 10.1186/s11689-023-09478-w]

218 **Yoon J**, Mao Y. Dissecting Molecular Genetic Mechanisms of 1q21.1 CNV in Neuropsychiatric Disorders. *Int J Mol Sci* 2021; **22** [PMID: 34071723 DOI: 10.3390/ijms22115811]

219 **Wapner RJ**, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, Savage M, Platt LD, Saltzman D, Grobman WA, Klugman S, Scholl T, Simpson JL, McCall K, Aggarwal VS, Bunke B, Nahum O, Patel A, Lamb AN, Thom EA, Beaudet AL, Ledbetter DH, Shaffer LG, Jackson L. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012; **367**: 2175-2184 [PMID: 23215555 DOI: 10.1056/NEJMoa1203382]

220 **Reiff M**, Giarelli E, Bernhardt BA, Easley E, Spinner NB, Sankar PL, Mulchandani S. Parents' perceptions of the usefulness of chromosomal microarray analysis for children with autism spectrum disorders. *J Autism Dev Disord* 2015; **45**: 3262-3275 [PMID: 26066358 DOI: 10.1007/s10803-015-2489-3]

221 **Batzir NA**, Shohat M, Maya I. Chromosomal Microarray Analysis (CMA) a Clinical Diagnostic Tool in the Prenatal and Postnatal Settings. *Pediatr Endocrinol Rev* 2015; **13**: 448-454 [PMID: 26540760]

222 **Jiang YH**, Wang Y, Xiu X, Choy KW, Pursley AN, Cheung SW. Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. *Crit Rev Clin Lab Sci* 2014; **51**: 249-262 [PMID: 24878448 DOI: 10.3109/10408363.2014.910747]

223 **Masini E**, Loi E, Vega-Benedetti AF, Carta M, Doneddu G, Fadda R, Zavattari P. An Overview of the Main Genetic, Epigenetic and Environmental Factors Involved in Autism Spectrum Disorder Focusing on Synaptic Activity. *Int J Mol Sci* 2020; **21** [PMID: 33167418 DOI: 10.3390/ijms21218290]

224 **Mahendiran T**, Dupuis A, Crosbie J, Georgiades S, Kelley E, Liu X, Nicolson R, Schachar R, Anagnostou E, Brian J. Sex Differences in

Social Adaptive Function in Autism Spectrum Disorder and Attention-Deficit Hyperactivity Disorder. *Front Psychiatry* 2019; **10**: 607 [PMID: 31572228 DOI: 10.3389/fpsyt.2019.00607]

225 **Horwitz E**, Vos M, De Bildt A, Greaves-Lord K, Rommelse N, Schoevers R, Hartman C. Sex differences in the course of autistic and co-occurring psychopathological symptoms in adolescents with and without autism spectrum disorder. *Autism* 2023; **27**: 1716-1729 [PMID: 36680498 DOI: 10.1177/13623613221146477]

226 **Jeste SS**, Geschwind DH. Disentangling the heterogeneity of autism spectrum disorder through genetic findings. *Nat Rev Neurol* 2014; **10**: 74-81 [PMID: 24468882 DOI: 10.1038/nrneurol.2013.278]

227 **Lockwood Estrin G**, Milner V, Spain D, Happé F, Colvert E. Barriers to Autism Spectrum Disorder Diagnosis for Young Women and Girls: a Systematic Review. *Rev J Autism Dev Disord* 2021; **8**: 454-470 [PMID: 34868805 DOI: 10.1007/s40489-020-00225-8]

228 **Dougherty JD**, Marrus N, Maloney SE, Yip B, Sandin S, Turner TN, Selmanovic D, Kroll KL, Gutmann DH, Constantino JN, Weiss LA. Can the "female protective effect" liability threshold model explain sex differences in autism spectrum disorder? *Neuron* 2022; **110**: 3243-3262 [PMID: 35868305 DOI: 10.1016/j.neuron.2022.06.020]

229 **Attermann J**, Obel C, Bilenberg N, Nordenbæk CM, Skytthe A, Olsen J. Traits of ADHD and autism in girls with a twin brother: a Mendelian randomization study. *Eur Child Adolesc Psychiatry* 2012; **21**: 503-509 [PMID: 22643885 DOI: 10.1007/s00787-012-0287-4]

230 **Rujeedawa T**, Zaman SH. The Diagnosis and Management of Autism Spectrum Disorder (ASD) in Adult Females in the Presence or Absence of an Intellectual Disability. *Int J Environ Res Public Health* 2022; **19** [PMID: 35162336 DOI: 10.3390/ijerph19031315]

231 **Van't Westeinde A**, Cauvet É, Toro R, Kuja-Halkola R, Neufeld J, Mevel K, Bölte S. Sex differences in brain structure: a twin study on restricted and repetitive behaviors in twin pairs with and without autism. *Mol Autism* 2020; **11**: 1 [PMID: 31893022 DOI: 10.1186/s13229-019-0309-x]

232 **Cruz S**, Zubizarreta SC, Costa AD, Araújo R, Martinho J, Tubío-Fungueiriño M, Sampaio A, Cruz R, Carracedo A, Fernández-Prieto M. Is There a Bias Towards Males in the Diagnosis of Autism? A Systematic Review and Meta-Analysis. *Neuropsychol Rev* 2024 [PMID: 38285291 DOI: 10.1007/s11065-023-09630-2]

233 **Mitra I**, Tsang K, Ladd-Acosta C, Croen LA, Aldinger KA, Hendren RL, Traglia M, Lavillaureix A, Zaitlen N, Oldham MC, Levitt P, Nelson S, Amaral DG, Hertz-Picciotto I, Fallin MD, Weiss LA. Pleiotropic Mechanisms Indicated for Sex Differences in Autism. *PLoS Genet* 2016; **12**: e1006425 [PMID: 27846226 DOI: 10.1371/journal.pgen.1006425]

234 **Pejhan S**, Rastegar M. Role of DNA Methyl-CpG-Binding Protein MeCP2 in Rett Syndrome Pathobiology and Mechanism of Disease. *Biomolecules* 2021; **11** [PMID: 33429932 DOI: 10.3390/biom11010075]

235 **Nguyen TA**, Wu K, Pandey S, Lehr AW, Li Y, Bemben MA, Badger JD 2nd, Lauzon JL, Wang T, Zaghloul KA, Thurm A, Jain M, Lu W, Roche KW. A Cluster of Autism-Associated Variants on X-Linked *NLGN4X* Functionally Resemble *NLGN4Y*. *Neuron* 2020; **106**: 759-768.e7 [PMID: 32243781 DOI: 10.1016/j.neuron.2020.03.008]

236 **Li M**, Usui N, Shimada S. Prenatal Sex Hormone Exposure Is Associated with the Development of Autism Spectrum Disorder. *Int J Mol Sci* 2023; **24** [PMID: 36768521 DOI: 10.3390/ijms24032203]

237 **Vashisth S**, Chahrour MH. Genomic strategies to untangle the etiology of autism: A primer. *Autism Res* 2023; **16**: 31-39 [PMID: 36415077 DOI: 10.1002/aur.2844]

238 **Durmaz AA**, Karaca E, Demkow U, Toruner G, Schoumans J, Cogulu O. Evolution of genetic techniques: past, present, and beyond. *Biomed Res Int* 2015; **2015**: 461524 [PMID: 25874212 DOI: 10.1155/2015/461524]

239 **Xie X**, Zhou R, Fang Z, Zhang Y, Wang Q, Liu X. Seeing beyond words: Visualizing autism spectrum disorder biomarker insights. *Heliyon* 2024; **10**: e30420 [PMID: 38694128 DOI: 10.1016/j.heliyon.2024.e30420]

240 **C Yuen RK**, Merico D, Bookman M, L Howe J, Thiruvahindrapuram B, Patel RV, Whitney J, Deflaux N, Bingham J, Wang Z, Pellecchia G, Buchanan JA, Walker S, Marshall CR, Uddin M, Zarrei M, Deneault E, D'Abate L, Chan AJ, Koyanagi S, Paton T, Pereira SL, Hoang N, Engchuan W, Higginbotham EJ, Ho K, Lamoureux S, Li W, MacDonald JR, Nalpathamkalam T, Sung WW, Tsoi FJ, Wei J, Xu L, Tasse AM, Kirby E, Van Etten W, Twigger S, Roberts W, Drmic I, Jilderda S, Modi BM, Kellam B, Szego M, Cytrynbaum C, Weksberg R, Zwaigenbaum L, Woodbury-Smith M, Brian J, Senman L, Iaboni A, Doyle-Thomas K, Thompson A, Chrysler C, Leef J, Savion-Lemieux T, Smith IM, Liu X, Nicolson R, Seifer V, Fedele A, Cook EH, Dager S, Estes A, Gallagher L, Malow BA, Parr JR, Spence SJ, Vorstman J, Frey BJ, Robinson JT, Strug LJ, Fernandez BA, Elsabbagh M, Carter MT, Hallmayer J, Knoppers BM, Anagnostou E, Szatmari P, Ring RH, Glazer D, Pletcher MT, Scherer SW. Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder. *Nat Neurosci* 2017; **20**: 602-611 [PMID: 28263302 DOI: 10.1038/nn.4524]

241 **Yuen T**, Carter MT, Szatmari P, Ungar WJ. Cost-effectiveness of Genome and Exome Sequencing in Children Diagnosed with Autism Spectrum Disorder. *Appl Health Econ Health Policy* 2018; **16**: 481-493 [PMID: 29651777 DOI: 10.1007/s40258-018-0390-x]

242 **Al-Mubarak B**, Abouelhoda M, Omar A, AlDhalaan H, Aldosari M, Nester M, Alshamrani HA, El-Kalioby M, Goljan E, Albar R, Subhani S, Tahir A, Asfahani S, Eskandrani A, Almusaiab A, Magrashi A, Shinwari J, Monies D, Al Tassan N. Whole exome sequencing reveals inherited and de novo variants in autism spectrum disorder: a trio study from Saudi families. *Sci Rep* 2017; **7**: 5679 [PMID: 28720891 DOI: 10.1038/s41598-017-06033-1]

243 **Searles Quick VB**, Wang B, State MW. Leveraging large genomic datasets to illuminate the pathobiology of autism spectrum disorders. *Neuropsychopharmacology* 2021; **46**: 55-69 [PMID: 32668441 DOI: 10.1038/s41386-020-0768-y]

244 **Kimura H**, Nakatochi M, Aleksic B, Guevara J, Toyama M, Hayashi Y, Kato H, Kushima I, Morikawa M, Ishizuka K, Okada T, Tsurusaki Y, Fujita A, Miyake N, Ogi T, Takata A, Matsumoto N, Buxbaum J, Ozaki N, Sebat J. Exome sequencing analysis of Japanese autism spectrum disorder case-control sample supports an increased burden of synaptic function-related genes. *Transl Psychiatry* 2022; **12**: 265 [PMID: 35811316 DOI: 10.1038/s41398-022-02033-6]

245 **Enriquez KD**, Gupta AR, Hoffman EJ. Signaling Pathways and Sex Differential Processes in Autism Spectrum Disorder. *Front Psychiatry* 2021; **12**: 716673 [PMID: 34690830 DOI: 10.3389/fpsyt.2021.716673]

246 **Shi X**, Lu C, Corman A, Nikish A, Zhou Y, Platt RJ, Iossifov I, Zhang F, Pan JQ, Sanjana NE. Heterozygous deletion of the autism-associated gene *CHD8* impairs synaptic function through widespread changes in gene expression and chromatin compaction. *Am J Hum Genet* 2023; **110**: 1750-1768 [PMID: 37802044 DOI: 10.1016/j.ajhg.2023.09.004]

247 **Dixon-Salazar TJ**, Silhavy JL, Udpa N, Schroth J, Bielas S, Schaffer AE, Olvera J, Bafna V, Zaki MS, Abdel-Salam GH, Mansour LA, Selim L, Abdel-Hadi S, Marzouki N, Ben-Omran T, Al-Saana NA, Sonmez FM, Celep F, Azam M, Hill KJ, Collazo A, Fenstermaker AG, Novarino G, Akizu N, Garimella KV, Sougnez C, Russ C, Gabriel SB, Gleeson JG. Exome sequencing can improve diagnosis and alter patient management. *Sci Transl Med* 2012; **4**: 138ra78 [PMID: 22700954 DOI: 10.1126/scitranslmed.3003544]

248 **Wang K**, Duan W, Duan Y, Yu Y, Chen X, Xu Y, Chen H, Huang H, Xiong B. A Bibliometric Insight of Genetic Factors in ASD: Emerging Trends and New Developments. *Brain Sci* 2020; **11** [PMID: 33396229 DOI: 10.3390/brainsci11010033]

249 **Brlek P**, Bulić L, Bračić M, Projić P, Škaro V, Shah N, Shah P, Primorac D. Implementing Whole Genome Sequencing (WGS) in Clinical Practice: Advantages, Challenges, and Future Perspectives. *Cells* 2024; **13** [PMID: 38534348 DOI: 10.3390/cells13060504]

250 **Bocher O**, Willer CJ, Zeggini E. Unravelling the genetic architecture of human complex traits through whole genome sequencing. *Nat Commun* 2023; **14**: 3520 [PMID: 37316478 DOI: 10.1038/s41467-023-39259-x]

251 **Zhou J**, Park CY, Theesfeld CL, Wong AK, Yuan Y, Scheckel C, Fak JJ, Funk J, Yao K, Tajima Y, Packer A, Darnell RB, Troyanskaya OG. Whole-genome deep-learning analysis identifies contribution of noncoding mutations to autism risk. *Nat Genet* 2019; **51**: 973-980 [PMID: 31133750 DOI: 10.1038/s41588-019-0420-0]

252 **Satam H**, Joshi K, Mangrolia U, Waghoo S, Zaidi G, Rawool S, Thakare RP, Banday S, Mishra AK, Das G, Malonia SK. Next-Generation Sequencing Technology: Current Trends and Advancements. *Biology (Basel)* 2023; **12** [PMID: 37508427 DOI: 10.3390/biology12070997]

253 **Medico-Salsench E**, Karkala F, Lanko K, Barakat TS. The non-coding genome in genetic brain disorders: new targets for therapy? *Essays Biochem* 2021; **65**: 671-683 [PMID: 34414418 DOI: 10.1042/EBC20200121]

254 **Yoo H**. Genetics of Autism Spectrum Disorder: Current Status and Possible Clinical Applications. *Exp Neurobiol* 2015; **24**: 257-272 [PMID: 26713075 DOI: 10.5607/en.2015.24.4.257]

255 **Ruzzo EK**, Pérez-Cano L, Jung JY, Wang LK, Kashef-Haghighi D, Hartl C, Singh C, Xu J, Hoekstra JN, Leventhal O, Leppä VM, Gandal MJ, Paskov K, Stockham N, Polioudakis D, Lowe JK, Prober DA, Geschwind DH, Wall DP. Inherited and De Novo Genetic Risk for Autism Impacts Shared Networks. *Cell* 2019; **178**: 850-866.e26 [PMID: 31398340 DOI: 10.1016/j.cell.2019.07.015]

256 **Szego MJ**, Zawati MH. Whole Genome Sequencing as a Genetic Test for Autism Spectrum Disorder: From Bench to Bedside and then Back Again. *J Can Acad Child Adolesc Psychiatry* 2016; **25**: 116-121 [PMID: 27274747]

257 **Mollon J**, Almasy L, Jacquemont S, Glahn DC. The contribution of copy number variants to psychiatric symptoms and cognitive ability. *Mol Psychiatry* 2023; **28**: 1480-1493 [PMID: 36737482 DOI: 10.1038/s41380-023-01978-4]

258 **Manoli DS**, State MW. Autism Spectrum Disorder Genetics and the Search for Pathological Mechanisms. *Am J Psychiatry* 2021; **178**: 30-38 [PMID: 33384012 DOI: 10.1176/appi.ajp.2020.20111608]

259 **Fetit R**, Price DJ, Lawrie SM, Johnstone M. Understanding the clinical manifestations of 16p11.2 deletion syndrome: a series of developmental case reports in children. *Psychiatr Genet* 2020; **30**: 136-140 [PMID: 32732550 DOI: 10.1097/YPG.0000000000000259]

260 **State MW**, Levitt P. The conundrums of understanding genetic risks for autism spectrum disorders. *Nat Neurosci* 2011; **14**: 1499-1506 [PMID: 22037497 DOI: 10.1038/nn.2924]

261 **Sønderby IE**, Ching CRK, Thomopoulos SI, van der Meer D, Sun D, Villalon-Reina JE, Agartz I, Amunts K, Arango C, Armstrong NJ, Ayesa-Arriola R, Bakker G, Bassett AS, Boomsma DI, Bülow R, Butcher NJ, Calhoun VD, Caspers S, Chow EWC, Cichon S, Ciufolini S, Craig MC, Crespo-Facorro B, Cunningham AC, Dale AM, Dazzan P, de Zubicaray GI, Djurovic S, Doherty JL, Donohoe G, Draganski B, Durdle CA, Ehrlich S, Emanuel BS, Espeseth T, Fisher SE, Ge T, Glahn DC, Grabe HJ, Gur RE, Gutman BA, Haavik J, Håberg AK, Hansen LA, Hashimoto R, Hibar DP, Holmes AJ, Hottenga JJ, Hulshoff Pol HE, Jalbrzikowski M, Knowles EEM, Kushan L, Linden DEJ, Liu J, Lundervold AJ, Martin-Brevet S, Martínez K, Mather KA, Mathias SR, McDonald-McGinn DM, McRae AF, Medland SE, Moberget T, Modenato C, Monereo Sánchez J, Moreau CA, Mühleisen TW, Paus T, Pausova Z, Prieto C, Ragothaman A, Reinbold CS, Reis Marques T, Repetto GM, Reymond A, Roalf DR, Rodriguez-Herreros B, Rucker JJ, Sachdev PS, Schmitt JE, Schofield PR, Silva AI, Stefansson H, Stein DJ, Tamnes CK, Tordesillas-Gutiérrez D, Ulfarsson MO, Vajdi A, van 't Ent D, van den Bree MBM, Vassos E, Vázquez-Bourgon J, Vila-Rodriguez F, Walters GB, Wen W, Westlye LT, Wittfeld K, Zackai EH, Stefánsson K, Jacquemont S, Thompson PM, Bearden CE, Andreassen OA; ENIGMA-CNV Working Group; ENIGMA 22q11. 2 Deletion Syndrome Working Group. Effects of copy number variations on brain structure and risk for psychiatric illness: Large-scale studies from the ENIGMA working groups on CNVs. *Hum Brain Mapp* 2022; **43**: 300-328 [PMID: 33615640 DOI: 10.1002/hbm.25354]

262 **Gatto CL**, Broadie K. Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder models. *Front Synaptic Neurosci* 2010; **2**: 4 [PMID: 21423490 DOI: 10.3389/fnsyn.2010.00004]

263 **Xu B**, Ho Y, Fasolino M, Medina J, O'Brien WT, Lamonica JM, Nugent E, Brodkin ES, Fuccillo MV, Bucan M, Zhou Z. Allelic contribution of Nrxn1α to autism-relevant behavioral phenotypes in mice. *PLoS Genet* 2023; **19**: e1010659 [PMID: 36848371 DOI: 10.1371/journal.pgen.1010659]

264 **Vicari S**, Napoli E, Cordeddu V, Menghini D, Alesi V, Loddo S, Novelli A, Tartaglia M. Copy number variants in autism spectrum disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **92**: 421-427 [PMID: 30797015 DOI: 10.1016/j.pnpbp.2019.02.012]

265 **Canitano R**, Bozzi Y. Autism Spectrum Disorder with Epilepsy: A Research Protocol for a Clinical and Genetic Study. *Genes (Basel)* 2023; **15** [PMID: 38254951 DOI: 10.3390/genes15010061]

266 **Merikangas AK**, Segurado R, Heron EA, Anney RJ, Paterson AD, Cook EH, Pinto D, Scherer SW, Szatmari P, Gill M, Corvin AP, Gallagher L. The phenotypic manifestations of rare genic CNVs in autism spectrum disorder. *Mol Psychiatry* 2015; **20**: 1366-1372 [PMID: 25421404 DOI: 10.1038/mp.2014.150]

267 **Keresztúri É**. Diversity and Classification of Genetic Variations in Autism Spectrum Disorder. *Int J Mol Sci* 2023; **24** [PMID: 38069091 DOI: 10.3390/ijms242316768]

268 **Keil-Stietz K**, Lein PJ. Gene×environment interactions in autism spectrum disorders. *Curr Top Dev Biol* 2023; **152**: 221-284 [PMID: 36707213 DOI: 10.1016/bs.ctdb.2022.11.001]

269 **Karimi P**, Kamali E, Mousavi SM, Karahmadi M. Environmental factors influencing the risk of autism. *J Res Med Sci* 2017; **22**: 27 [PMID: 28413424 DOI: 10.4103/1735-1995.200272]

270 **Pugsley K**, Scherer SW, Bellgrove MA, Hawi Z. Environmental exposures associated with elevated risk for autism spectrum disorder may augment the burden of deleterious de novo mutations among probands. *Mol Psychiatry* 2022; **27**: 710-730 [PMID: 34002022 DOI: 10.1038/s41380-021-01142-w]

271 **Atladóttir HO**, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord* 2010; **40**: 1423-1430 [PMID: 20414802 DOI: 10.1007/s10803-010-1006-y]

272 **Christensen J**, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013; **309**: 1696-1703 [PMID: 23613074 DOI: 10.1001/jama.2013.2270]

273 **Roberts EM**, English PB, Grether JK, Windham GC, Somberg L, Wolff C. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environ Health Perspect* 2007; **115**: 1482-1489 [PMID: 17938740

DOI: 10.1289/ehp.10168]
274 **Schmidt RJ**, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, Schmidt LC, Tassone F, Hertz-Picciotto I. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *Am J Clin Nutr* 2012; **96**: 80-89 [PMID: 22648721 DOI: 10.3945/ajcn.110.004416]
275 **Gardener H**, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics* 2011; **128**: 344-355 [PMID: 21746727 DOI: 10.1542/peds.2010-1036]
276 **Reichenberg A**, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, Rabinowitz J, Shulman C, Malaspina D, Lubin G, Knobler HY, Davidson M, Susser E. Advancing paternal age and autism. *Arch Gen Psychiatry* 2006; **63**: 1026-1032 [PMID: 16953005 DOI: 10.1001/archpsyc.63.9.1026]
277 **Kinney DK**, Barch DH, Chayka B, Napoleon S, Munir KM. Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder? *Med Hypotheses* 2010; **74**: 102-106 [PMID: 19699591 DOI: 10.1016/j.mehy.2009.07.052]
278 **Dutheil F**, Comptour A, Morlon R, Mermillod M, Pereira B, Baker JS, Charkhabi M, Clinchamps M, Bourdel N. Autism spectrum disorder and air pollution: A systematic review and meta-analysis. *Environ Pollut* 2021; **278**: 116856 [PMID: 33714060 DOI: 10.1016/j.envpol.2021.116856]
279 **Orsmond GI**, Seltzer MM. Adolescent siblings of individuals with an autism spectrum disorder: testing a diathesis-stress model of sibling well-being. *J Autism Dev Disord* 2009; **39**: 1053-1065 [PMID: 19291379 DOI: 10.1007/s10803-009-0722-7]
280 **Pennington BF**, McGrath LM, Rosenberg J, Barnard H, Smith SD, Willcutt EG, Friend A, Defries JC, Olson RK. Gene X environment interactions in reading disability and attention-deficit/hyperactivity disorder. *Dev Psychol* 2009; **45**: 77-89 [PMID: 19209992 DOI: 10.1037/a0014549]
281 **Belsky J**, Hartman S. Gene-environment interaction in evolutionary perspective: differential susceptibility to environmental influences. *World Psychiatry* 2014; **13**: 87-89 [PMID: 24497257 DOI: 10.1002/wps.20092]
282 **Frye RE**, Cakir J, Rose S, Palmer RF, Austin C, Curtin P, Arora M. Mitochondria May Mediate Prenatal Environmental Influences in Autism Spectrum Disorder. *J Pers Med* 2021; **11** [PMID: 33803789 DOI: 10.3390/jpm11030218]
283 **Grzadzinski R**, Amso D, Landa R, Watson L, Guralnick M, Zwaigenbaum L, Deák G, Estes A, Brian J, Bath K, Elison J, Abbeduto L, Wolff J, Piven J. Pre-symptomatic intervention for autism spectrum disorder (ASD): defining a research agenda. *J Neurodev Disord* 2021; **13**: 49 [PMID: 34654371 DOI: 10.1186/s11689-021-09393-y]
284 **Essex MJ**, Armstrong JM, Burk LR, Goldsmith HH, Boyce WT. Biological sensitivity to context moderates the effects of the early teacher-child relationship on the development of mental health by adolescence. *Dev Psychopathol* 2011; **23**: 149-161 [PMID: 21262045 DOI: 10.1017/S0954579410000702]
285 **Boyce WT**, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* 2005; **17**: 271-301 [PMID: 16761546 DOI: 10.1017/s0954579405050145]
286 **Jaffee SR**, Price TS. Genotype-environment correlations: implications for determining the relationship between environmental exposures and psychiatric illness. *Psychiatry* 2008; **7**: 496-499 [PMID: 20622930 DOI: 10.1016/j.mppsy.2008.10.002]
287 **Lemery-Chalfant K**, Kao K, Swann G, Goldsmith HH. Childhood temperament: passive gene-environment correlation, gene-environment interaction, and the hidden importance of the family environment. *Dev Psychopathol* 2013; **25**: 51-63 [PMID: 23398752 DOI: 10.1017/S0954579412000892]
288 **Klahr AM**, Thomas KM, Hopwood CJ, Klump KL, Burt SA. Evocative gene-environment correlation in the mother-child relationship: a twin study of interpersonal processes. *Dev Psychopathol* 2013; **25**: 105-118 [PMID: 23398756 DOI: 10.1017/S0954579412000934]
289 **Zhai J**, Li X, Zhou Y, Fan L, Xia W, Wang X, Li Y, Hou M, Wang J, Wu L. Correlation and predictive ability of sensory characteristics and social interaction in children with autism spectrum disorder. *Front Psychiatry* 2023; **14**: 1056051 [PMID: 37091701 DOI: 10.3389/fpsyt.2023.1056051]
290 **Kiselev IS**, Kulakova OG, Boyko AN, Favorova OO. DNA Methylation As an Epigenetic Mechanism in the Development of Multiple Sclerosis. *Acta Naturae* 2021; **13**: 45-57 [PMID: 34377555 DOI: 10.32607/actanaturae.11043]
291 **Kubota T**, Mochizuki K. Epigenetic Effect of Environmental Factors on Autism Spectrum Disorders. *Int J Environ Res Public Health* 2016; **13** [PMID: 27187441 DOI: 10.3390/ijerph13050504]
292 **Rahman MM**, Shu YH, Chow T, Lurmann FW, Yu X, Martinez MP, Carter SA, Eckel SP, Chen JC, Chen Z, Levitt P, Schwartz J, McConnell R, Xiang AH. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. *Environ Health Perspect* 2022; **130**: 17008 [PMID: 35040691 DOI: 10.1289/EHP9509]
293 **Boyce WT**, Sokolowski MB, Robinson GE. Genes and environments, development and time. *Proc Natl Acad Sci U S A* 2020; **117**: 23235-23241 [PMID: 32967067 DOI: 10.1073/pnas.2016710117]
294 **Singletary WM**. An integrative model of autism spectrum disorder: ASD as a neurobiological disorder of experienced environmental deprivation, early life stress and allostatic overload. *Neuropsychoanalysis* 2015; **17**: 81-119 [DOI: 10.1080/15294145.2015.1092334]
295 **Singletary WM**, Rice T. Autism Spectrum Disorders: There Remains a Place for Psychodynamic Psychiatry through Neuroplasticity, Emotion Regulation, Caring Connections, and Hope. *Psychodyn Psychiatry* 2023; **51**: 152-159 [PMID: 37260244 DOI: 10.1521/pdps.2023.51.2.152]
296 **Madore C**, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, Layé S. Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. *Neural Plast* 2016; **2016**: 3597209 [PMID: 27840741 DOI: 10.1155/2016/3597209]
297 **Lossi L**, Castagna C, Merighi A. An Overview of the Epigenetic Modifications in the Brain under Normal and Pathological Conditions. *Int J Mol Sci* 2024; **25** [PMID: 38612690 DOI: 10.3390/ijms25073881]
298 **Yoon SH**, Choi J, Lee WJ, Do JT. Genetic and Epigenetic Etiology Underlying Autism Spectrum Disorder. *J Clin Med* 2020; **9** [PMID: 32244359 DOI: 10.3390/jcm9040966]
299 **Keil KP**, Lein PJ. DNA methylation: a mechanism linking environmental chemical exposures to risk of autism spectrum disorders? *Environ Epigenet* 2016; **2** [PMID: 27158529 DOI: 10.1093/eep/dvv012]
300 **Liyanage VR**, Rastegar M. Rett syndrome and MeCP2. *Neuromolecular Med* 2014; **16**: 231-264 [PMID: 24615633 DOI: 10.1007/s12017-014-8295-9]
301 **Miller JL**, Grant PA. The role of DNA methylation and histone modifications in transcriptional regulation in humans. *Subcell Biochem* 2013; **61**: 289-317 [PMID: 23150256 DOI: 10.1007/978-94-007-4525-4_13]
302 **Tseng CJ**, McDougle CJ, Hooker JM, Zürcher NR. Epigenetics of Autism Spectrum Disorder: Histone Deacetylases. *Biol Psychiatry* 2022; **91**: 922-933 [PMID: 35120709 DOI: 10.1016/j.biopsych.2021.11.021]
303 **Zhang SF**, Gao J, Liu CM. The Role of Non-Coding RNAs in Neurodevelopmental Disorders. *Front Genet* 2019; **10**: 1033 [PMID: 31824553

DOI: 10.3389/fgene.2019.01033]

304 **Perini S**, Filosi M; Italian Autism Network, Domenici E. Candidate biomarkers from the integration of methylation and gene expression in discordant autistic sibling pairs. *Transl Psychiatry* 2023; **13**: 109 [PMID: 37012247 DOI: 10.1038/s41398-023-02407-4]

305 **Sun W**, Poschmann J, Cruz-Herrera Del Rosario R, Parikshak NN, Hajan HS, Kumar V, Ramasamy R, Belgard TG, Elanggovan B, Wong CCY, Mill J, Geschwind DH, Prabhakar S. Histone Acetylome-wide Association Study of Autism Spectrum Disorder. *Cell* 2016; **167**: 1385-1397.e11 [PMID: 27863250 DOI: 10.1016/j.cell.2016.10.031]

306 **Wang Z**, Lu T, Li X, Jiang M, Jia M, Liu J, Zhang D, Li J, Wang L. Altered Expression of Brain-specific Autism-Associated miRNAs in the Han Chinese Population. *Front Genet* 2022; **13**: 865881 [PMID: 35342389 DOI: 10.3389/fgene.2022.865881]

307 **Qin L**, Wang H, Ning W, Cui M, Wang Q. New advances in the diagnosis and treatment of autism spectrum disorders. *Eur J Med Res* 2024; **29**: 322 [PMID: 38858682 DOI: 10.1186/s40001-024-01916-2]

308 **Frye RE**, Rose S, Boles RG, Rossignol DA. A Personalized Approach to Evaluating and Treating Autism Spectrum Disorder. *J Pers Med* 2022; **12** [PMID: 35207636 DOI: 10.3390/jpm12020147]

309 **Pescosolido MF**, Yang U, Sabbagh M, Morrow EM. Lighting a path: genetic studies pinpoint neurodevelopmental mechanisms in autism and related disorders. *Dialogues Clin Neurosci* 2012; **14**: 239-252 [PMID: 23226950]

310 **Rowland ME**, Jajarmi JM, Osborne TSM, Ciernia AV. Insights Into the Emerging Role of Baf53b in Autism Spectrum Disorder. *Front Mol Neurosci* 2022; **15**: 805158 [PMID: 35185468 DOI: 10.3389/fnmol.2022.805158]

311 **Duffney LJ**, Zhong P, Wei J, Matas E, Cheng J, Qin L, Ma K, Dietz DM, Kajiwara Y, Buxbaum JD, Yan Z. Autism-like Deficits in *Shank3*-Deficient Mice Are Rescued by Targeting Actin Regulators. *Cell Rep* 2015; **11**: 1400-1413 [PMID: 26027926 DOI: 10.1016/j.celrep.2015.04.064]

312 **Biswas M**, Vanwong N, Sukasem C. Pharmacogenomics and non-genetic factors affecting drug response in autism spectrum disorder in Thai and other populations: current evidence and future implications. *Front Pharmacol* 2023; **14**: 1285967 [PMID: 38375208 DOI: 10.3389/fphar.2023.1285967]

313 **Stein K**, Maruf AA, Müller DJ, Bishop JR, Bousman CA. Serotonin Transporter Genetic Variation and Antidepressant Response and Tolerability: A Systematic Review and Meta-Analysis. *J Pers Med* 2021; **11** [PMID: 34945806 DOI: 10.3390/jpm11121334]

314 **Stoccoro A**, Conti E, Scaffei E, Calderoni S, Coppedè F, Migliore L, Battini R. DNA Methylation Biomarkers for Young Children with Idiopathic Autism Spectrum Disorder: A Systematic Review. *Int J Mol Sci* 2023; **24** [PMID: 37298088 DOI: 10.3390/ijms24119138]

315 **Goetz LH**, Schork NJ. Personalized medicine: motivation, challenges, and progress. *Fertil Steril* 2018; **109**: 952-963 [PMID: 29935653 DOI: 10.1016/j.fertnstert.2018.05.006]

316 **Lupia A**. Genes, cognition, and social behavior: next steps for foundations and researchers. *Politics Life Sci* 2011; **30**: 65-87 [PMID: 22702425 DOI: 10.2990/30_2_65]

317 **Choi L**, An JY. Genetic architecture of autism spectrum disorder: Lessons from large-scale genomic studies. *Neurosci Biobehav Rev* 2021; **128**: 244-257 [PMID: 34166716 DOI: 10.1016/j.neubiorev.2021.06.028]

318 **Abul-Husn NS**, Owusu Obeng A, Sanderson SC, Gottesman O, Scott SA. Implementation and utilization of genetic testing in personalized medicine. *Pharmgenomics Pers Med* 2014; **7**: 227-240 [PMID: 25206309 DOI: 10.2147/PGPM.S48887]

319 **Gershon ES**, Alliey-Rodriguez N. New ethical issues for genetic counseling in common mental disorders. *Am J Psychiatry* 2013; **170**: 968-976 [PMID: 23897273 DOI: 10.1176/appi.ajp.2013.12121558]

320 **Freitag CM**, Persico AM, Vorstman JAS. Developing Gene-Based Personalised Interventions in Autism Spectrum Disorders. *Genes (Basel)* 2022; **13** [PMID: 35741766 DOI: 10.3390/genes13061004]

321 **Ma T**, Wu H, Wang Y. Application of different treatment methods for autism. *TNS* 2023; **20**: 29-35 [DOI: 10.54254/2753-8818/20/20230705]

322 **Gitimoghaddam M**, Chichkine N, McArthur L, Sangha SS, Symington V. Applied Behavior Analysis in Children and Youth with Autism Spectrum Disorders: A Scoping Review. *Perspect Behav Sci* 2022; **45**: 521-557 [PMID: 36249174 DOI: 10.1007/s40614-022-00338-x]

323 **Bellini S**, Peters JK. Social skills training for youth with autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am* 2008; **17**: 857-873, x [PMID: 18775374 DOI: 10.1016/j.chc.2008.06.008]

324 **Aishworiya R**, Valica T, Hagerman R, Restrepo B. An Update on Psychopharmacological Treatment of Autism Spectrum Disorder. *Neurotherapeutics* 2022; **19**: 248-262 [PMID: 35029811 DOI: 10.1007/s13311-022-01183-1]

325 **Baspinar B**, Yardimci H. Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems? *Eurasian J Med* 2020; **52**: 292-297 [PMID: 33209084 DOI: 10.5152/eurasianjmed.2020.19230]

326 **Xiao YL**, Gong Y, Qi YJ, Shao ZM, Jiang YZ. Effects of dietary intervention on human diseases: molecular mechanisms and therapeutic potential. *Signal Transduct Target Ther* 2024; **9**: 59 [PMID: 38462638 DOI: 10.1038/s41392-024-01771-x]

327 **Huang M**, Qi Q, Xu T. Targeting *Shank3* deficiency and paresthesia in autism spectrum disorder: A brief review. *Front Mol Neurosci* 2023; **16**: 1128974 [PMID: 36846568 DOI: 10.3389/fnmol.2023.1128974]

328 **Radosavljevic M**, Svob Strac D, Jancic J, Samardzic J. The Role of Pharmacogenetics in Personalizing the Antidepressant and Anxiolytic Therapy. *Genes (Basel)* 2023; **14** [PMID: 37239455 DOI: 10.3390/genes14051095]

329 **Wang L**, Wang B, Wu C, Wang J, Sun M. Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. *Int J Mol Sci* 2023; **24** [PMID: 36768153 DOI: 10.3390/ijms24031819]

330 **Singh R**, Kisku A, Kungumaraj H, Nagaraj V, Pal A, Kumar S, Sulakhiya K. Autism Spectrum Disorders: A Recent Update on Targeting Inflammatory Pathways with Natural Anti-Inflammatory Agents. *Biomedicines* 2023; **11** [PMID: 36672623 DOI: 10.3390/biomedicines11010115]

331 **Ardhanareeswaran K**, Coppola G, Vaccarino F. The use of stem cells to study autism spectrum disorder. *Yale J Biol Med* 2015; **88**: 5-16 [PMID: 25745370]

332 **Chahrour M**, Kleiman RJ, Manzini MC. Translating genetic and preclinical findings into autism therapies. *Dialogues Clin Neurosci* 2017; **19**: 335-343 [PMID: 29398929 DOI: 10.31887/DCNS.2017.19.4/cmanzini]

333 **Nisar S**, Haris M. Neuroimaging genetics approaches to identify new biomarkers for the early diagnosis of autism spectrum disorder. *Mol Psychiatry* 2023; **28**: 4995-5008 [PMID: 37069342 DOI: 10.1038/s41380-023-02060-9]

334 **Emberti Gialloreti L**, Mazzone L, Benvenuto A, Fasano A, Alcon AG, Kraneveld A, Moavero R, Raz R, Riccio MP, Siracusano M, Zachor DA, Marini M, Curatolo P. Risk and Protective Environmental Factors Associated with Autism Spectrum Disorder: Evidence-Based Principles and Recommendations. *J Clin Med* 2019; **8** [PMID: 30744008 DOI: 10.3390/jcm8020217]

335 **Kanungo S**, Barr J, Crutchfield P, Fealko C, Soares N. Ethical Considerations on Pediatric Genetic Testing Results in Electronic Health

Records. *Appl Clin Inform* 2020; **11**: 755-763 [PMID: 33176390 DOI: 10.1055/s-0040-1718753]
336 **Sandhu A**, Kumar A, Rawat K, Gautam V, Sharma A, Saha L. Modernising autism spectrum disorder model engineering and treatment *via* CRISPR-Cas9: A gene reprogramming approach. *World J Clin Cases* 2023; **11**: 3114-3127 [PMID: 37274051 DOI: 10.12998/wjcc.v11.i14.3114]
337 **Duan L**, Ouyang K, Xu X, Xu L, Wen C, Zhou X, Qin Z, Xu Z, Sun W, Liang Y. Nanoparticle Delivery of CRISPR/Cas9 for Genome Editing. *Front Genet* 2021; **12**: 673286 [PMID: 34054927 DOI: 10.3389/fgene.2021.673286]
338 **Silverman JL**, Thurm A, Ethridge SB, Soller MM, Petkova SP, Abel T, Bauman MD, Brodkin ES, Harony-Nicolas H, Wöhr M, Halladay A. Reconsidering animal models used to study autism spectrum disorder: Current state and optimizing future. *Genes Brain Behav* 2022; **21**: e12803 [PMID: 35285132 DOI: 10.1111/gbb.12803]
339 **Li T**, Yang Y, Qi H, Cui W, Zhang L, Fu X, He X, Liu M, Li PF, Yu T. CRISPR/Cas9 therapeutics: progress and prospects. *Signal Transduct Target Ther* 2023; **8**: 36 [PMID: 36646687 DOI: 10.1038/s41392-023-01309-7]
340 **Pereira R**, Oliveira J, Sousa M. Bioinformatics and Computational Tools for Next-Generation Sequencing Analysis in Clinical Genetics. *J Clin Med* 2020; **9** [PMID: 31947757 DOI: 10.3390/jcm9010132]
341 **Abdelwahab MM**, Al-karawi KA, Semary HE. Integrating gene selection and deep learning for enhanced Autisms' disease prediction: a comparative study using microarray data. *MATH* 2024; **9**: 17827-17846 [DOI: 10.3934/math.2024867]
342 **Hu VW**. From genes to environment: using integrative genomics to build a "systems-level" understanding of autism spectrum disorders. *Child Dev* 2013; **84**: 89-103 [PMID: 22497667 DOI: 10.1111/j.1467-8624.2012.01759.x]
343 **Wang P**, Zhao D, Lachman HM, Zheng D. Enriched expression of genes associated with autism spectrum disorders in human inhibitory neurons. *Transl Psychiatry* 2018; **8**: 13 [PMID: 29317598 DOI: 10.1038/s41398-017-0058-6]
344 **Kim SH**, Chang MY. Application of Human Brain Organoids-Opportunities and Challenges in Modeling Human Brain Development and Neurodevelopmental Diseases. *Int J Mol Sci* 2023; **24** [PMID: 37569905 DOI: 10.3390/ijms241512528]
345 **Yen C**, Lin CL, Chiang MC. Exploring the Frontiers of Neuroimaging: A Review of Recent Advances in Understanding Brain Functioning and Disorders. *Life (Basel)* 2023; **13** [PMID: 37511847 DOI: 10.3390/life13071472]
346 **Chen J**, Liu J, Calhoun VD. The Translational Potential of Neuroimaging Genomic Analyses To Diagnosis And Treatment In The Mental Disorders. *Proc IEEE Inst Electr Electron Eng* 2019; **107**: 912-927 [PMID: 32051642 DOI: 10.1109/JPROC.2019.2913145]
347 **Li C**, Fleck JS, Martins-Costa C, Burkard TR, Themann J, Stuempflen M, Peer AM, Vertesy Á, Littleboy JB, Esk C, Elling U, Kasprian G, Corsini NS, Treutlein B, Knoblich JA. Single-cell brain organoid screening identifies developmental defects in autism. *Nature* 2023; **621**: 373-380 [PMID: 37704762 DOI: 10.1038/s41586-023-06473-y]
348 **Cheroni C**, Caporale N, Testa G. Autism spectrum disorder at the crossroad between genes and environment: contributions, convergences, and interactions in ASD developmental pathophysiology. *Mol Autism* 2020; **11**: 69 [PMID: 32912338 DOI: 10.1186/s13229-020-00370-1]
349 **Willsey AJ**, State MW. Autism spectrum disorders: from genes to neurobiology. *Curr Opin Neurobiol* 2015; **30**: 92-99 [PMID: 25464374 DOI: 10.1016/j.conb.2014.10.015]
350 **Yonan AL**, Palmer AA, Smith KC, Feldman I, Lee HK, Yonan JM, Fischer SG, Pavlidis P, Gilliam TC. Bioinformatic analysis of autism positional candidate genes using biological databases and computational gene network prediction. *Genes Brain Behav* 2003; **2**: 303-320 [PMID: 14606695 DOI: 10.1034/j.1601-183x.2003.00041.x]
351 **Peterson RE**, Kuchenbaecker K, Walters RK, Chen CY, Popejoy AB, Periyasamy S, Lam M, Iyegbe C, Strawbridge RJ, Brick L, Carey CE, Martin AR, Meyers JL, Su J, Chen J, Edwards AC, Kalungi A, Koen N, Majara L, Schwarz E, Smoller JW, Stahl EA, Sullivan PF, Vassos E, Mowry B, Prieto ML, Cuellar-Barboza A, Bigdeli TB, Edenberg HJ, Huang H, Duncan LE. Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. *Cell* 2019; **179**: 589-603 [PMID: 31607513 DOI: 10.1016/j.cell.2019.08.051]
352 **Marciano S**, Ionescu TM, Saw RS, Cheong RY, Kirik D, Maurer A, Pichler BJ, Herfert K. Combining CRISPR-Cas9 and brain imaging to study the link from genes to molecules to networks. *Proc Natl Acad Sci U S A* 2022; **119**: e2122552119 [PMID: 36161926 DOI: 10.1073/pnas.2122552119]
353 **Vorstman JA**, Spooren W, Persico AM, Collier DA, Aigner S, Jagasia R, Glennon JC, Buitelaar JK. Using genetic findings in autism for the development of new pharmaceutical compounds. *Psychopharmacology (Berl)* 2014; **231**: 1063-1078 [PMID: 24292384 DOI: 10.1007/s00213-013-3334-z]
354 **Bowman KS**, Suarez VD, Weiss MJ. Standards for Interprofessional Collaboration in the Treatment of Individuals With Autism. *Behav Anal Pract* 2021; **14**: 1191-1208 [PMID: 34868822 DOI: 10.1007/s40617-021-00560-0]
355 **Fulceri F**, Gila L, Caruso A, Micai M, Romano G, Scattoni ML. Building Bricks of Integrated Care Pathway for Autism Spectrum Disorder: A Systematic Review. *Int J Mol Sci* 2023; **24** [PMID: 37047213 DOI: 10.3390/ijms24076222]
356 **Al-Jawahiri R**, Milne E. Resources available for autism research in the big data era: a systematic review. *PeerJ* 2017; **5**: e2880 [PMID: 28097074 DOI: 10.7717/peerj.2880]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com