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Review

Autism Spectrum Disorder: A Review of Genomic Risk Factors, Diagnostic and Pharmacotherapeutic Strategies

Zohor Azher[1*]

[1]Department of Medical Genetics, Faculty of Medicine, Umm Al-Qura University; zaazher@uqu.edu.sa
[*]Correspondence: zaazher@uqu.edu.sa

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Abstract: Autism Spectrum Disorder (ASD) is a multifactorial neurodevelopmental condition characterized by impairments in social communication and delayed language development, repetitive behaviors, and sensory processing abnormalities. The genetic background of ASD remains incompletely understood due to significant genetic heterogeneity and complexity. This review aims to present current insights into the genetic landscape of ASD, focusing on both common and rare genomic variations. We describe candidate genes associated with ASD, as they are involved in synaptic function and neuronal signaling, making these findings potential therapeutic targets. This review emphasizes the importance of integrating comprehensive clinical assessments with advanced genetic investigations to enhance accurate diagnosis, develop personalized management plans, and guide future therapeutic strategies for ASD.

Keywords: Autism spectrum disorder; Genomic variations; Structural variations, Single gene variants, Diagnosis, Treatment.

1. Introduction

Autism spectrum disorder (ASD) encompasses a heterogeneous group of early-onset neurodevelopmental disorders. These conditions are primarily characterized by deficits in social interaction and communication, alongside restricted, repetitive behavior patterns, activities, or interests. Growing evidence has implicated mutations and structural genomic variations in several candidate genes as significant contributors to ASD susceptibility.

Clinically, ASD is defined by persistent challenges in social communication and interaction, coupled with restrictive and repetitive behavioral patterns manifesting across various settings (1). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), introduced in 2013, consolidated the previously distinct categories of autistic disorder, Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), and childhood disintegrative disorder under the unified diagnosis of "autism spectrum disorder" to better reflect the clinical and genetic overlap among these disorders (2).

ASD can generally be classified into two broad clinical categories: isolated (non-syndromic) ASD and syndromic ASD. In its isolated form, ASD presents

without accompanying physical anomalies or additional clinical features. In contrast, syndromic ASD occurs in association with other neurodevelopmental or systemic manifestations, including global developmental delay, seizure disorders, congenital malformations, dysmorphic features, or metabolic disturbances such as obesity. Distinguishing between these two forms of ASD is clinically valuable, as it guides the diagnostic approach and the management strategies, informing the extent and nature of genetic testing and individualized care strategies.

This review focuses on non-syndromic ASD, given its high prevalence and genetic heterogeneity—both discussed in detail below—which make it a critical target for improved diagnostics and management. We aim to provide an updated overview of the clinical presentation, underlying genomic architecture, and diagnostic strategies employed in assessing and managing individuals with ASD.

2. Prevalence of ASD

The global prevalence of autism spectrum disorder (ASD) has risen substantially over the past several decades (3). According to the U.S. Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network, the estimated prevalence of ASD among 8-year-old children in the United States was approximately 1 in 36 in 2020, reflecting a steady increase from 1 in 44 in 2018 (4). This condition affects individuals across all racial, ethnic, and socioeconomic backgrounds, and shows a well-documented male predominance**,** with boys being about four times more likely to be diagnosed than girls (4).

In Saudi Arabia, recent estimates from the Ministry of Health indicate a prevalence of approximately 1 in 160 children diagnosed with ASD (5). Notably, the number of ASD diagnoses in Saudi children has increased over the past decade, a trend likely driven by enhanced public awareness, improved diagnostic capacity, and increased recognition among healthcare providers, educators, and parents (5). Despite these advances, accurate prevalence data across the Kingdom remains limited due to a lack of communication and data sharing between diagnostic centers and the national education system (5). For example, a 2013 study conducted in Taif reported an autism prevalence of 0.035% among 22,950 primary school children aged 7 to 12 years (6). In a more recent regional study, Sabbagh et al. documented a prevalence of 2.81 per 1,000 children in Makkah and Jeddah, a figure lower than global estimates (7).

Across other Arab countries, ASD prevalence rates appear higher than those reported in many developing nations. Taha and Hussein estimated the number of confirmed ASD cases among ethnic Arabs at approximately 42,500, though a significant number of cases remain undiagnosed (8). A systematic review evaluating the epidemiology of ASD within Gulf countries reported prevalence rates ranging from 1.4 to 29 per 10,000 individuals (9). These figures highlight the growing awareness and recognition of ASD within the Arab region, while simultaneously emphasizing the need for improved national registries, comprehensive epidemiological studies, and collaborative research initiatives to better understand the regional burden and etiological contributors to ASD.

3. Clinical Features of ASD

ASD is characterized by a constellation of clinical features that typically manifest within the first two years of life (10). According to the American Psychiatric Association (2013), the presentation of ASD is broadly categorized into core symptoms and associated (secondary) features (11). The core features include persistent deficits in social communication and interaction, as well as restricted, repetitive patterns of behavior, interests, or activities. Language impairment, reduced eye contact, and stereotyped movements are commonly observed within this domain.

Secondary symptoms encompass a range of behavioral and psychiatric comorbidities, including hyperactivity, aggression, self-injurious behaviors, anxiety, and major depressive episodes (12). While most individuals with ASD exhibit language delays and hyperactivity in early childhood, difficulties with social relationships, emotional dysregulation, and mood disturbances often become more pronounced during adolescence (13).

Additionally, a subset of individuals—up to 17%—may develop catatonia, a severe neuropsychiatric syndrome characterized by marked motor and behavioral abnormalities such as stupor, mutism, posturing, and agitation, during late adolescence or early adulthood (14,15). This highlights the importance of ongoing clinical surveillance for evolving

psychiatric and neurological complications in individuals with ASD across the lifespan.

Given the overlapping behavioral features**,** differential diagnosis is essential, particularly to distinguish ASD from other disorders such as social anxiety disorder, intellectual disability, and attention-deficit/hyperactivity disorder (ADHD). Early and accurate identification, facilitated by standardized diagnostic tools and multidisciplinary evaluation, plays a crucial role in guiding management and support strategies.

4. Risk Factors Associated with ASD

The etiology of autism spectrum disorder (ASD) is multifactorial, involving the interplay of genetic susceptibility and environmental influences. A growing body of evidence has identified several categories of risk factors associated with ASD, which can broadly be classified into environmental, pharmacotherapeutic, and genetic determinants.

4.1. **Environmental Factors**

Systematic reviews and meta-analyses have consistently implicated various prenatal, perinatal, and maternal health factors as contributors to ASD risk (16). Several maternal health factors have been associated with increased ASD risk in offspring. Maternal overweight and obesity during pregnancy have been linked to an increased risk, with odds ratios of approximately 1.28 (95% CI: 1.19–1.36) and 1.36 (95% CI: 1.03–1.78), respectively. Furthermore, each five kg/m² increase in maternal body mass index (BMI) is associated with a 16% increased risk (17). Maternal infections during pregnancy have also been implicated, with an elevated risk (OR ≈ 1.13, 95% CI: 1.03–1.23), and even higher when infections required hospitalization (OR ≈ 1.30, 95% CI: 1.14–1.50) (18). Additionally, preeclampsia and other hypertensive disorders have been associated with ASD, with a reported relative risk of 1.50 (95% CI: 1.04–2.18) (19).

While some studies have explored the associations between environmental exposures, such as air pollution, and maternal psychological stress during pregnancy, the variability in study methodologies and findings across populations has made it difficult to establish consistent conclusions (20,21). Nutritional deficiencies, particularly in essential elements such as vitamin D, vitamin B12, and zinc, have been proposed as contributing factors in ASD development, though current evidence remains inconclusive (16).

Conversely, no consistent association has been found between ASD risk and caesarean delivery or assisted conception techniques, despite earlier hypotheses suggesting possible links (22).

4.2. **Pharmacotherapeutic Factors**

Certain prenatal pharmacological exposures have also been implicated in ASD risk. The most well-established example is valproic acid, an antiepileptic medication whose prenatal exposure has been consistently associated with an increased incidence of ASD (23).

In contrast, concerns regarding the use of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), during pregnancy have not been confirmed by rigorous, well-controlled studies (24). Similarly, multiple attempts have been made to find links between ASD and vaccinations, particularly the MMR (measles, mumps, and rubella) vaccine, but extensive research has conclusively debunked this association (25).

4.3. **Genetic Factors**

Genetic predisposition plays a substantial role in ASD etiology. Twin and family-based studies indicate that heritable factors account for approximately 74–93% of ASD risk (26,27). While earlier models proposed broadly inherited susceptibility, advances in genomic technologies have shifted focus toward heterogeneous individual genetic variants contributing to ASD risk (27,28).

The genetic architecture of ASD is complex, encompassing common and rare variants that may be inherited or occur de novo and exert additive, dominant, or recessive effects (29). Common variants—defined as genetic changes in more than 1% of the general population—are believed to confer modest risk individually but act cumulatively to influence ASD liability (30). According to a large-scale genomic study by Gaugler et al., approximately 49% of ASD risk is attributable to common inherited variants, with 3% due to de novo variants, 3% to rare inherited variants, and the remaining is unexplained (Figure 1) (31).

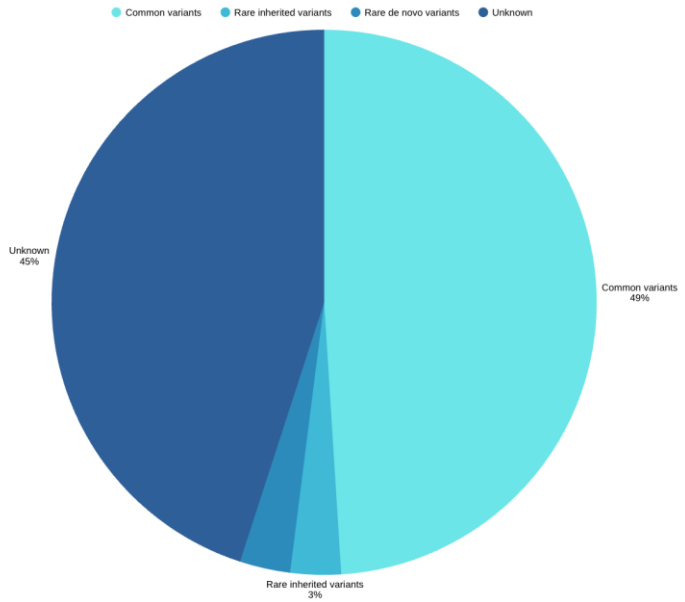

Figure 1. Pie chart illustrating the estimated contributions of different genetic variants to ASD risk. The most significant portion of genetic liability is attributed to common variants (49%), while rare inherited and de novo variants contribute 3% each. The remaining cases are unexplained; data adapted from Gaugler et al., 2014 (*Nature Genetics*).

Genetic variations contributing to ASD can occur at either the chromosomal level (Genomic structural variants, SVs) or the single-gene level (e.g., single-nucleotide variants, SNVs, and small insertions or deletions, Indels), further underscoring the genetic and multifactorial nature of ASD susceptibility.

4.3.1. **Chromosomal Variations in ASD**

Chromosomal abnormalities represent an important genetic risk factor in the etiology of ASD, with several recurrent cytogenetic alterations consistently implicated in affected individuals. Among these, sex chromosome aneuploidies, particularly 47,XXY (Klinefelter syndrome) and 47,XYY, have been associated with an increased risk of ASD and ASD-related traits (32).

Additionally, structural chromosomal rearrangements such as reciprocal translocations have been documented in ASD cases. A notable example is the t(4;14)(q31.3;q24.1) translocation, predominantly observed in patients diagnosed with Asperger's disorder. This translocation is often familial and may present with either pathogenic consequences or remain clinically silent (32).

Certain chromosomal regions are recognized for harboring recurrent copy number variations (CNVs) that are strongly associated with Autism Spectrum Disorder (ASD). Deletions and duplications in the 16p11.2 region are among the most frequently reported, contributing to ASD risk and overlapping neurodevelopmental phenotypes (33). Similarly, duplications involving the imprinted Prader-Willi/Angelman region at 15q11–q13, as well as 10q and 22q, represent another well-established genomic structural variant in ASD (34).

It is increasingly recognized that the phenotypic heterogeneity of ASD associated with chromosomal variations is influenced not only by the primary structural changes but also by genetic modifiers, including SNVs and epigenetic alterations, which collectively modulate clinical expression and severity.

4.3.2. **Single Gene Variations in ASD**

Although ASD is predominantly a polygenic and multifactorial condition, numerous studies have identified rare, high-impact variants in individual genes contributing to ASD risk. Several of these genes are involved in synaptic development, neurotransmission, and neuronal signaling, providing critical insights into the molecular basis and therapeutic targets of ASD.

4.3.2.1. **Neuroligin (*NLGN*) Genes**

Neuroligins (*NLGNs*) are postsynaptic cell adhesion molecules that play essential roles in synapse formation, maturation, and synaptic neurotransmission (35). Located at both excitatory and inhibitory synapses, *NLGN* gene mutations have been implicated in several neuropsychiatric disorders, including ASD (36). Notably, missense mutations in *NLGN3* (Xq13.1, MIM #300336) and *NLGN4* (Xp22.31, MIM #300427) have been associated with ASD (37). Experimental models, such as *NLGN3* R451C mutant mice, demonstrate autism-like behaviors and increased dendritic spine density, further underscoring the functional consequences of *NLGN* mutations in synaptic regulation (38).

4.3.2.2. **Neurexin (*NRXN*) Genes**

Neurexins (*NRXN*s) are a family of highly conserved presynaptic cell adhesion molecules that interact with neuroligins to regulate synapse formation, specialization, and plasticity (35). In mammals, three distinct genes—*NRXN1*, *NRXN2*, and *NRXN3*—exist,

each producing multiple isoforms. Rare deletions and point mutations in *NRXN1* have been consistently associated with ASD in both clinical and genomic studies (39), reinforcing the role of synaptic cell adhesion molecules in ASD pathogenesis.

4.3.2.3. ***SHANK3* Gene**

The *SHANK3* gene (22q13.33, MIM #606230) encodes a scaffolding protein that anchors receptors, ion channels, and signaling molecules within the postsynaptic density of excitatory synapses (40). Disruption of *SHANK3* impairs synaptic signaling and plasticity, contributing to ASD-like phenotypes. The Human Gene Mutation Database (HGMD) lists over 100 disease-associated *SHANK3* variants, with substantial experimental evidence derived from animal models. *Shank3* knockout mice exhibit social deficits, repetitive behaviors, and abnormal synaptic morphology, which can be partially rescued by interventions such as optogenetic stimulation of dorsal raphe Pet1 neurons. This demonstrates the gene's direct role in regulating social behaviors (41).

4.3.2.4. ***CACNA1*C Gene:**

The *CACNA1C* gene, located on chromosome 12p13.33, encodes the alpha-1C subunit of the L-type voltage-dependent calcium channel, a crucial regulator of synaptic transmission, neuronal excitability, and intracellular signaling in the central nervous system (42). Dysregulation of ion channel function has been implicated in various neurodevelopmental and neuropsychiatric disorders.

Mutations in *CACNA1C* and other L-type calcium channel genes have been associated with monogenic syndromes presenting with ASD-like features, most notably Timothy syndrome and Fragile X syndrome (43). Additionally, evidence from genome-wide association studies (GWAS) supports the involvement of *CACNA1C* in susceptibility to ASD. In a Chinese Han population, a significant association was reported between the single-nucleotide polymorphism (SNP) rs1006737 within *CACNA1C* and increased ASD risk (n=553 ASD cases) (44). These findings position *CACNA1C* as a promising candidate gene in ASD genetics, particularly in relation to ion channel dysfunction contributing to atypical synaptic and neurodevelopmental processes.

4.3.2.5. ***SLC6A4* Gene:**

The *SLC6A4* gene, encoding the serotonin transporter (5-HTT/SERT), plays a pivotal role in modulating serotonergic signaling by mediating serotonin reuptake from synaptic clefts into presynaptic neurons. Dysregulation of serotonin homeostasis has long been implicated in neurodevelopmental and psychiatric disorders, including ASD. Among the most studied polymorphisms within *SLC6A4* is the 5-HTTLPR, a variable number tandem repeat (VNTR) in the promoter region with two primary alleles: long (L) and short (S), which differentially affect gene expression and serotonin uptake efficiency (45,46). Genetic studies have yielded mixed findings regarding the association between 5-HTTLPR variants and ASD:

- **Association with the S allele:** Observed in a large family-based study including 1,528 ASD cases from 390 families (47).
- **Association with the L allele:** Reported in a family-based design encompassing 34 families (48).
- **No significant association:** Several studies and meta-analyses have found no clear relationship between 5-HTTLPR variants and ASD risk (49).

Rare missense variants within *SLC6A4*, including Gly56Ala, Ile425Leu, Phe465Leu, and Leu550Val, have been identified in families with ASD, obsessive-compulsive disorder (OCD), and social anxiety disorder (50,51). Linkage studies have repeatedly demonstrated suggestive signals at chromosome 17q11, the *SLC6A4* locus, particularly in male-only ASD families and those exhibiting rigid-compulsive behaviors (52,53).

Biochemical studies have reported elevated whole blood serotonin (hyperserotonemia) in a subset of individuals with ASD, and certain *SLC6A4* variants have been associated with increased transporter function and altered serotonin reuptake dynamics (54,55). Moreover, SSRIs targeting SERT have demonstrated partial efficacy in alleviating specific ASD symptoms, further supporting a serotonergic component in ASD pathophysiology (56).

Despite inconsistencies in genetic association studies and meta-analyses, converging evidence from genetic, biochemical, behavioral, and pharmacological studies positions *SLC6A4* as a key candidate gene in ASD,

requiring continued investigation, particularly in the context of rare variants, serotonergic system dysregulation, and sensory processing abnormalities (57).

5. Diagnosis of Autism Spectrum Disorder (ASD)

ASD diagnosis is primarily based on clinical assessment, which involves observing behaviors related to communication, social interaction, and repetitive or restricted interests and activities. There is no definitive laboratory or imaging test for ASD, making clinical assessment essential for early recognition and intervention (58,59).

5.1. **Clinical Diagnosis of ASD**

The clinical diagnosis of ASD relies on detailed observation of an individual's behavior and developmental history, focusing on domains such as communication skills, social interactions, interests, and repetitive behaviors (60). Evaluation is ideally conducted by experienced professionals in neurodevelopmental disorders, including developmental pediatricians, pediatric neurologists, and child and adolescent psychiatrists (61).

The most widely used diagnostic frameworks are the DSM-5 criteria, adapted by the American Psychiatric Association, and the ICD-10 classification (62). The DSM-5 evaluates persistent deficits in social communication and interaction, accompanied by restricted, repetitive patterns of behavior, manifesting in early childhood, causing clinically significant functional impairment and is not better explained by intellectual disability alone.Several standardized diagnostic instruments are also employed:

- **Autism Diagnostic Interview-Revised (ADI-R):** A structured, caregiver-based interview that assesses communication, social interaction, and repetitive behaviors, applicable from 18 months onward (63).
- **Autism Diagnostic Observation Schedule Second Edition (ADOS-2):** A semi-structured, standardized assessment of communication, social interaction, and play across various developmental and language levels (64).
- **Childhood Autism Rating Scale (CARS):** A tool used to differentiate ASD severity in children over 2 years by assessing behavior across 15 domains.
- **Gilliam Autism Rating Scale, Second Edition (GARS-2):** A questionnaire-based tool designed for teachers, clinicians, and parents to identify ASD symptoms in neurodevelopmental disorders aged 3–22 years (64).

Early diagnosis can be promoted by raising ASD awareness among families and communities, facilitating collaboration between primary care providers and specialists, improving screening tools, and increasing accessibility to neurodevelopmental services.

ASD diagnosis still has challenges for certain groups of individuals, which can lead to misrecognition, delayed identification, and delayed intervention subsequently. Diagnosing ASD in females is particularly complex due to distinct differences in symptom presentation compared to males. Standard autism diagnostic criteria and tools have centered primarily on male populations, contributing to a limited understanding of how autism manifests in girls. Additionally, many females are skilled at masking their symptoms, often appearing socially engaged and adapting their behavior to fit in with peers, which can result in misinterpreting their difficulties by clinicians. Individuals with higher cognitive abilities may be able to further compensate for social and communication challenges, making their symptoms less apparent during assessments. Concerning underrepresented individuals, children from Black and low-income families are frequently diagnosed later than their white and higher-income peers. This disparity arises from multiple factors, including reduced access to diagnostic services, cultural stigma surrounding developmental disorders, and implicit bias within healthcare systems.

5.2. **Genetic Testing in ASD**

With advancing genomic technologies, genetic testing has become an integral part of the diagnostic evaluation for individuals with neurodevelopmental disorders, including ASD. The American College of Medical Genetics and Genomics (ACMG) recommends chromosomal microarray analysis (CMA) as the first-

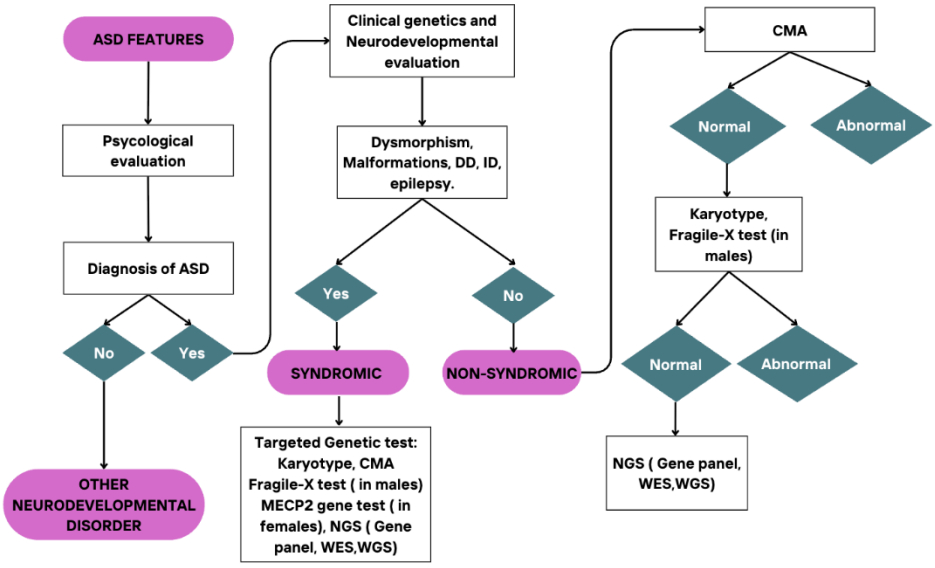

Figure 2: Flowchart outlining the diagnostic pathway for individuals with ASD. DD: developmental delay; ID: intellectual disability; CMA: chromosomal microarray; NGS: next-generation sequencing; WES: whole-exome sequencing; WGS: whole-genome sequencing.

tier test, followed by karyotyping and Fragile X testing as second-line investigations (Figure 2) (65).

Although CMA has demonstrated superior diagnostic yield, identifying pathogenic CNVs in a subset of ASD cases, limitations in accessibility and variant interpretation remain, making G-banded karyotyping a practical alternative in specific clinical settings (66). Fragile X syndrome and chromosomal abnormalities have been detected in approximately 2.2% and 6.8% of ASD cases, respectively, using these methods (66).

The advent of next-generation sequencing (NGS), including whole-exome sequencing (WES), whole-genome sequencing (WGS), and targeted gene panels, has further expanded the genetic landscape of ASD, enabling the identification of rare de novo variants and candidate risk loci (67). NGS-based studies have confirmed novel CNV loci and rare single-nucleotide variants associated with ASD and related neurodevelopmental disorders (68).

Additional relevant investigations include mitochondrial DNA analysis, MECP2 sequencing in females with regression, and Angelman syndrome testing (69).

Genetic testing not only aids in establishing an etiological diagnosis but also facilitates family planning, risk counseling, medical surveillance for comorbidities, and early referral to appropriate support services. As research advances, genetic insights are anticipated to inform targeted, gene-based therapies for selected subtypes of ASD in the coming decade.

6. Management of ASD

Management of ASD requires a comprehensive, multidisciplinary approach designed for the individual's developmental skills, behavioral challenges, and comorbid conditions. Early detection and intervention remain the cornerstone of effective care, aiming to improve quality of life and long-term functional outcomes.

6.1. **Early Monitoring and Intervention**

Early identification of ASD during infancy or early childhood, followed by timely and continuous intervention, is crucial in improving developmental, communicative, and behavioral outcomes (70). Structured caregiver involvement is crucial in monitoring developmental milestones, facilitating early access to healthcare, and providing psychosocial support (71).

Early interventions have demonstrated substantial benefits in improving language acquisition, social interaction skills, and adaptive behavior. These interventions also enhance greater independence in affected individuals. Targeted support during early childhood, particularly for genetically predisposed

cases identified through genetic screening, can help optimize developmental skills and improve quality of life (72).

6.2. Treatment strategies:

Treatment for ASD includes a range of approaches aimed at improving skills and reducing symptoms. Behavioral interventions, such as Applied Behavior Analysis (ABA), focus on reinforcing positive behaviors and reducing challenging ones. Developmental therapies emphasize building communication and social skills. Educational interventions provide structured, individualized learning in school settings. Additionally, speech and language therapy, occupational therapy, and physical therapy help address specific developmental needs (73).

6.3. **Preventive and pharmacological strategies:**

Preventive strategies have gained attention in recent years. Notably, prenatal folic acid supplementation has been associated with a reduced risk of ASD and other neurodevelopmental disorders, with evidence suggesting a gene–environment interaction effect (74).

Pharmacological treatments in ASD primarily address associated symptoms such as anxiety, depression, irritability, and obsessive-compulsive behaviors rather than core ASD features. SSRIs and other antidepressants are frequently prescribed in clinical practice (75,76). However, their efficacy in managing mood and anxiety disorders in children with ASD remains under-researched, with current prescribing practices largely extrapolated from data in neurotypical populations (77).

It is important to note that children with ASD may exhibit heightened sensitivity to SSRI side effects, including behavioral activation, agitation, and sleep disturbances (76). Expert consensus recommends initiating SSRIs at low doses, with gradual titration and close monitoring for adverse effects, ensuring an optimal risk–benefit evaluation on a case-by-case basis (78).

7. Conclusion

ASD is a complex and heterogeneous neurodevelopmental disorder with diverse genetic and environmental etiologies. The integration of clinical assessments with advanced genetic testing has significantly improved the ability to diagnose and characterize ASD. Early intervention remains crucial in enhancing developmental skills and improving the quality of life for individuals affected by the condition. Emerging evidence highlights the role of common and rare genetic variants and environmental exposures in ASD etiology. As genomic technologies continue to evolve, they hold promise for identifying new therapeutic targets and personalised management approaches based on individual genotype. Continued collaboration between clinicians and researchers is critical to transform emerging genetic insights into effective, lifelong interventions for individuals with ASD.

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