

Research Progress on Genetic and Environmental Risk Factors, Clinical Manifestations, and Intervention Strategies of Autism Spectrum Disorder

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Abstract: Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized primarily by deficits in social communication and repetitive, stereotyped behaviors. Its global prevalence has continued to rise, making it a significant public health concern. This paper provides a systematic review of recent research on the genetic and environmental risk factors, clinical manifestations, and intervention strategies related to ASD. Genetic studies indicate that the heritability of ASD is approximately 50%, and genome-wide association studies (GWAS) as well as copy number variation (CNV) analyses have revealed the potential involvement of cadherin genes (such as CDH10 and CDH9) and genes related to synaptic function. However, the genetic mechanisms underlying 75% of cases remain unclear. In terms of environmental factors, advanced paternal age, maternal infections during pregnancy, chemical exposures, and perinatal complications have all been shown to significantly increase the risk of ASD, with gene-environment interactions becoming a focal point of current research. Clinically, the core symptoms of ASD include social communication deficits and repetitive behaviors, while comorbid sensory abnormalities and psychiatric disorders (such as anxiety and ADHD) further complicate treatment. Behavioral therapies remain the primary intervention approach; applied behavior analysis (ABA), the Early Start Denver Model (ESDM), and function-based comprehensive interventions have proven effective in improving patient functioning. Pharmacological treatments (such as risperidone and aripiprazole) are mainly used to alleviate secondary symptoms, but there is still a lack of targeted therapies for core social deficits. Future research should integrate precision medicine and interdisciplinary collaboration to explore innovative treatments, including neuroimmune modulation and gene editing, aiming to improve patients' quality of life and reduce the societal burden.

Keywords: Autism spectrum disorder, Genetic factors, Environmental factors, Behavioral intervention, Pharmacological treatment

1. Introduction

Autism (also known as autism spectrum disorder [ASD]) is a group of complex neurodevelopmental disorders, defined by social communication deficits and restricted, repetitive behaviors. The clinical manifestations primarily include social interaction difficulties, communication impairments, and

narrow interests with stereotypical, repetitive behaviors, with social interaction difficulties being the core symptom [1].

The global prevalence of ASD has been on the rise, particularly since the early 1990s, when the incidence of ASD began to increase sharply. A report by the U.S. Centers for Disease Control and Prevention (CDC) states that ASD has become a global issue. According to the autism screening data released by the CDC at the end of March 2023, one in every 36 children aged 8 years has been confirmed to have ASD. Similarly, the “Development Status Report on Autism (ASD) Education and Rehabilitation Industry in China” showed that the number of ASD patients in China has exceeded 14 million, with more than 3 million children with autism aged 0-14.

ASD is a highly heterogeneous condition, requiring a comprehensive exploration through various fields such as psychology, genetics, and cognitive neuroscience to understand its underlying pathophysiological mechanisms. Research into ASD helps further our understanding of the deeper connections between the brain and social behavior, exploring the nature of human social abilities and emotional processing, which holds valuable clinical and scientific significance. In recent years, research into the pathological mechanisms of ASD has gradually shifted from focusing solely on genetic factors to studying gene-environment interactions. However, the biological basis of the core symptoms remains unclear. Although no known cure currently exists, early identification and intervention have enabled many children with ASD to receive support and education that improve their quality of life, thereby alleviating the unnecessary economic burden of treatment for ASD patients and their families. This paper aims to systematically review the genetic and environmental risk factors, clinical manifestations, and intervention strategies for ASD, with the goal of providing direction for future research.

2. Genetic Factors

The heritability of ASD is approximately 50%, and even higher in monozygotic twins [2].

The etiology of ASD is complex, involving both genetic and environmental factors, with genetics playing a key role in the pathogenesis of the disorder. While early theories suggested that ASD was caused by maternal child-rearing practices (such as the “refrigerator mother” theory), modern research indicates that genetic factors are the primary cause of ASD. Folstein and Rutter’s twin study on ASD was the first to confirm the significant genetic contribution to ASD, and subsequent meta-analyses have supported a heritability rate of up to 50%, with minimal impact from shared environmental factors [3].

Genome-wide association studies (GWAS) scan large populations to identify single nucleotide polymorphisms (SNPs) associated with ASD risk. In one GWAS, six genetic variants associated with ASD were identified, including variants located in the CDH10 and CDH9 genes, which encode cadherins that are crucial for cell-cell adhesion. These cadherin-related variants are common genetic alterations in ASD. However, despite analyzing genetic data from over 1,000 ASD families, GWAS has not effectively identified all potential associated loci, suggesting that the genetic effects of common variants on ASD pathogenesis may be relatively limited. The pathogenesis of ASD is also closely related to copy number variations (CNV). CNV involves large DNA segments being duplicated or deleted in the genome, potentially affecting the function of multiple genes and being linked to neurodevelopmental processes, synaptic function, and cell signaling. Since 2005, the development of whole exome sequencing (WES) and microarray technologies has enabled scientists to identify different types of CNVs. These variations mainly include DNA fragment differences greater than 1 kb and single nucleotide variations (SNVs), highlighting the heterogeneity of the genetic basis of ASD. Studies suggest that CNVs contribute approximately 15% to ASD, while SNVs contribute 7%. Although some variants have complete penetrance, most genetic variations are

variable or incompletely penetrant. Currently, the understanding of the etiology of ASD remains limited, with the genetic causes of most ASD cases (>75%) still unclear [4].

3. Environmental Factors

Although genetic factors account for approximately 50% of the risk for ASD, the role of environmental factors during the prenatal and perinatal periods should not be overlooked. Advanced parental age, cesarean delivery, prematurity, and low birth weight are all risk factors for ASD. Exposure to specific chemicals (such as drugs and pesticides) and viral infections during pregnancy is also associated with ASD. These findings highlight the crucial role of maternal health and environmental protection in preventing ASD [5].

3.1. Prenatal Factors

3.1.1. Parental Age

Parental age, particularly advanced paternal age (APA), is a clear environmental risk factor for ASD and is associated with various psychiatric disorders. Meta-analyses have shown that for every 10-year increase in parental age, the risk of ASD in children increases by 20%. Changes in sperm DNA methylation, reduced cortical thickness in ASD offspring, and mouse model experiments all support the association between APA and ASD, revealing that APA-related genetic and epigenetic changes may be inherited across generations, further confirming the impact mechanism [4].

3.1.2. Maternal Diseases During Pregnancy

Studies have shown that maternal diseases are associated with an increased risk of ASD. Meta-analyses indicate that children born to diabetic mothers have a 62% higher risk of ASD compared to those born to non-diabetic mothers. Another study found that pre-pregnancy diabetes increases the risk of ASD by 74%, while gestational diabetes raises the risk by 43%. These findings emphasize the importance of maternal health in neurodevelopmental outcomes in offspring. Additionally, maternal viral and bacterial infections can increase the risk of ASD in infants, but it is the immune response they trigger, rather than the viruses or bacteria themselves, that plays a key role. Two meta-analyses found that maternal autoimmune diseases increased the risk of ASD in offspring. Studies also show that mothers of children with ASD exhibit elevated levels of inflammatory markers and antibodies during pregnancy. Animal studies suggest that maternal immune activation may lead to abnormal brain development in offspring, with behavior phenotypes similar to clinical features of ASD, providing experimental support for the hypothesis that maternal immune dysfunction affects neurodevelopment [4].

3.1.3. Chemical Exposure

Exposure to toxic exogenous substances is also a potential environmental risk factor for ASD. Brominated flame retardants, for example, can cause mitochondrial toxicity and are related to mitochondrial dysfunction in ASD patients. Exposure to heavy metals, high concentrations of inorganic mercury, and organophosphate pesticides also increases the risk of ASD. Both persistent and non-persistent organic pollutants, such as phthalates, bisphenol A, dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs), are associated with ASD. Studies suggest that prenatal exposure to PCBs and PBDEs may disrupt calcium ion-dependent synaptic plasticity pathways, inducing abnormalities in neuronal network connectivity, while synaptic dysfunction has been confirmed as one of the core neuropathological features of ASD [4].

3.2. Perinatal Factors

Perinatal risk factors are also important in the pathogenesis of ASD. Two meta-analyses, which included 60 obstetric factors, revealed a significant correlation between ASD risk and obstetric conditions such as umbilical cord complications, birth injury, and multiple births. Other studies have pointed out that specific factors, such as cesarean section and induction of labor, are also associated with an increased risk of ASD, emphasizing the importance of perinatal management. 4

Fetal exposure to sex hormones is a potential risk factor for ASD. The fetal testosterone theory can explain the higher prevalence of ASD in males, although it remains controversial, as elevated testosterone levels in females with ASD resemble those of males and controls. Baron-Cohen and others hypothesized that testosterone exposure during the prenatal masculinization window affects brain development. Researchers have detected higher levels of sex hormones and cortisol in amniotic fluid samples from male ASD offspring [4].

3.3. Postnatal Factors

Maternal health significantly impacts the risk of ASD, with prenatal nutrition being especially critical, as deficiencies in specific nutrients can be detrimental to fetal development. Research suggests that short interpregnancy intervals (SIPI; defined as pregnancies occurring less than 12 months after a previous delivery) may increase the risk of ASD. The mechanism may be related to insufficient recovery of key physiological indicators such as maternal iron stores and thyroid hormone levels, leading to abnormal placental oxidative stress microenvironments [4].

Current studies also suggest that maternal micronutrient deficiencies during pregnancy may be associated with an increased risk of ASD in offspring. The Swedish National Birth Cohort study indicated that lower levels of vitamin D during pregnancy were related to higher rates of ASD in offspring. Notably, ASD children are often associated with metabolic abnormalities in trace elements like zinc and copper. Animal experiments further suggest that zinc deficiency during pregnancy may exacerbate social behavior deficits in offspring by affecting the function of synaptic-related proteins. While some studies have observed that zinc supplementation improves behavioral abnormalities in ASD animal models, human clinical evidence remains insufficient, and the timing of micronutrient interventions must be considered for specificity [4].

In addition to genetic and environmental factors, the clinical manifestations and intervention strategies for ASD also warrant attention.

4. Clinical Symptoms

ASD is a complex neurodevelopmental disorder, with clinical symptoms including social interaction difficulties, communication difficulties, and repetitive and stereotyped behavior patterns. According to the latest research and diagnostic criteria, the clinical presentation of ASD is highly heterogeneous, meaning that the manifestations may vary significantly between individuals [6-8].

4.1. Core Symptoms

Social interaction difficulties are one of the core features of ASD. These difficulties may manifest as challenges in understanding or responding to interpersonal relationships. For example, patients may have difficulty interpreting non-verbal social cues, such as facial expressions and body language, or they may struggle to establish and maintain relationships [8-9]. Additionally, communication difficulties, both verbal and non-verbal, are also typical characteristics of ASD. This can include delayed or absent language development and challenges in communication, such as understanding and using language [6, 8].

Repetitive and stereotyped behavior patterns are another core feature of ASD. This may include repetitive actions, such as rocking or spinning objects, or insisting on specific routines and patterns in daily activities. Patients may be highly sensitive to changes in the environment and may exhibit strong resistance to even small changes in their daily routines [8-9].

4.2. Non-Core Symptoms

In addition to these core symptoms, individuals with ASD may also exhibit sensory processing abnormalities, which may include heightened sensitivity or insufficient response to certain sounds, lights, or tactile stimuli [10-11]. These sensory abnormalities can lead to difficulties in daily life, such as feeling distressed in noisy environments or experiencing discomfort when touching certain materials.

Psychological and behavioral issues are also common in individuals with ASD. Research has shown a higher comorbidity rate of psychiatric disorders in individuals with ASD, such as anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD) [12]. These comorbidities can exacerbate the social and communication difficulties of patients, increasing the complexity of treatment and management.

ASD is a complex neurodevelopmental disorder with diverse clinical presentations and high individual variability. Understanding the core symptoms of ASD and its comorbid issues is crucial for developing effective treatment plans. Ongoing research into the pathophysiology of ASD is expected to lead to the development of more effective therapeutic methods in the future.

5. Behavioral Intervention

ASD intervention faces challenges due to unknown etiology, high disability rates, and the need for lifelong intervention. There is a lack of systematic reviews in domestic research. Key intervention methods include: Applied Behavior Analysis (ABA), based on classical conditioning, which establishes behavioral-environmental connections through DTT and PRT; the Social-Emotional Communication Intervention Model (SCERTS), which strengthens interpersonal communication (Social Communication, SC), self-regulation of emotional responses (Emotional Regulation, ER), and transactional support (Transactional Support, TS) in natural contexts; Exercise Intervention (EI), which promotes social self-care through physical activities; Play Therapy (PT), which uses play as a medium to promote expression and development, including sandplay, child-centered, and structured play therapy; Music Therapy (MT), which uses individualized music programs to improve emotions and social interaction; Sensory Integration Training (SIT), which improves multiple abilities through activities; and Video Modeling Instruction (VMI), which enhances various skills through video imitation [13].

Interventions for repetitive and stereotyped behaviors in children with ASD are mainly divided into three categories: antecedent-based, consequence-based, and integrated interventions. Antecedent-based interventions reduce behavior occurrences by modifying or removing the triggering variables or introducing appropriate stimuli. Common strategies include stimulus control, environmental reinforcement, antecedent movements, and unconditioned reinforcement. Consequence-based interventions support alternative behaviors by removing or altering the results that reinforce repetitive behaviors. Common strategies include differential reinforcement, response cost, extinction, and over-correction. Most studies use consequence-based interventions, but it is essential to analyze the behavior function and select appropriate alternative behaviors and reinforcers. Integrated strategies yield better results, such as combining environmental reinforcement, punishment, and response cost. Integrated interventions include music, art, and sensory integration training [14].

Behavioral intervention is at the core of ASD treatment, with ABA being the mainstream method. It breaks down complex behaviors and teaches new skills through positive reinforcement. While it can improve various abilities in children with ASD, it has been controversial for its focus on eliminating behaviors rather than cultivating skills. Speech therapy can enhance communication abilities in children with ASD, while occupational therapy (OT) is beneficial for children with sensory processing difficulties, helping develop fine motor skills, coordination, and sensory integration abilities, and increasing participation in daily activities. Additionally, social skills training, parent education, and training are important auxiliary methods that improve children's social behaviors, enhance parent-child interaction, reduce parental stress, and optimize child behavior [15].

In 1987, Lovaas introduced Discrete Trial Training (DTT), or Lovaas Applied Behavior Analysis, which became a cornerstone of ASD treatment for children. After decades of research, various adaptations of the method have been developed to effectively address core ASD disorders like social and speech challenges. Evidence-based behavioral interventions are divided into Comprehensive Treatment Models (CTM) and Focused Interventions. CTMs, such as Early Intensive Behavioral Intervention (EIBI) and the Early Start Denver Model (ESDM), use intensive, multidisciplinary strategies to improve language and cognitive skills in young children within natural environments. Focused interventions target specific skills or areas, such as social training and cognitive-behavioral interventions, to effectively address urgent behavioral issues. Peer-mediated instruction and intervention (PMII) and the Picture Exchange Communication System (PECS) are also important examples. Behavioral interventions are most effective when started early, but they are also applicable to older children, adolescents, and adults, with goals shifting to social and vocational skills. Research on behavioral interventions for adults with ASD needs to be expanded [16].

Interventions for self-injurious behaviors in children with ASD based on functional assessment have been proven effective. Intervention strategies vary depending on whether the function is to escape, gain attention or material rewards, or receive automatic reinforcement. Escape function interventions use antecedent and consequence event strategies, such as adjusting task difficulty, providing breaks, gradually increasing task participation, and emphasizing comprehensive, systematic approaches. Methods differ for children with varying intellectual abilities and ages. For children with severe intellectual disabilities, communication for escape is taught using pictures or gestures, while for children with mild intellectual disabilities, verbal help-seeking is encouraged. Attention or material reward function interventions allow children to access attention or rewards, using functional communication training and delayed gratification strategies. Automatic reinforcement function interventions often use antecedent events and positive behavior training, such as controlling specific stimuli, providing alternative stimuli, and fostering play skills. The intervention strategies for children with different intellectual abilities also differ. For children with mild intellectual disabilities, self-monitoring is encouraged, while for those with severe intellectual disabilities, direct involvement with medication may be required [17].

6. Pharmacological Treatment

The primary drugs for treating repetitive and stereotyped behaviors in children with ASD spectrum disorders include atypical antipsychotics (such as risperidone), serotonin reuptake inhibitors, and opioid receptor antagonists. McDougle pointed out that risperidone significantly reduces repetitive behaviors, but it is accompanied by side effects such as drowsiness and weight gain. The effectiveness of serotonin reuptake inhibitors and opioid receptor antagonists remains controversial. Although pharmacological treatments show significant short-term effects, their side effects are notable, and their long-term efficacy requires further research and validation. Therefore, medications are not recommended for use in routine educational interventions [14].

6.1. Current Status of Pharmacology

Currently, the pharmacology of ASD is still in the early stages of development, with a lack of validated interventions targeting core symptoms and unified assessment tools. Despite hundreds of trials and dozens of drug tests, only risperidone and aripiprazole have been approved by the FDA for treating irritability and aggression associated with ASD. Commonly used drugs include stimulants to control hyperactivity, impulsivity, and attention deficits, SSRIs for alleviating anxiety and depression, and anxiolytics for severe anxiety cases. Non-psychiatric drugs also play important roles, such as naltrexone for controlling self-injurious behaviors and aggression, melatonin for improving sleep disorders, clonidine and guanfacine for controlling hyperactivity and impulsivity, and memantine for managing repetitive behaviors and aggression. These drugs primarily target specific challenges associated with ASD [15].

6.2. Research Progress on Pharmacological Treatment

Research on pharmacological treatments for ASD involves various drugs. Among neurotransmitter-based drugs, SSRIs are ineffective for treating ASD and have side effects, but low doses of fluoxetine can improve repetitive behaviors. In glutamatergic drugs, mGluR5 antagonists have shown questionable effects in the treatment of fragile X syndrome (FXS), memantine has some improvements for adult ASD patients but insufficient evidence, and D-cycloserine's effect on treating ASD in children remains controversial. Among atypical antipsychotics, risperidone can control hyperactivity and irritability in children with ASD but has significant side effects, while aripiprazole can improve stereotyped behaviors and irritability in children with ASD and has better safety. Leptin, melatonin, oxytocin, and bumetanide also show potential for treating ASD, but more research is needed to verify their effectiveness [18].

Xu et al. used *Toxoplasma gondii* soluble tachyzoite antigen-induced maternal immune activation (MIA) to create a mouse model with both immune dysfunction and ASD-like behaviors. The offspring exhibited peripheral and central nervous system immune abnormalities, and their CD4⁺ T cell lineage resembled that of ASD patients, along with core ASD symptoms. The study found that by adoptively transferring highly active regulatory T cells (Treg), which migrated into the brain under the influence of CCL22 and regulated neural function through cytokines such as PD-1 and IL-10, ASD-like behaviors in mice could be improved. This lays the foundation for the engineered modification of Treg cells to treat ASD. Additionally, Roche's V1a receptor antagonist balovaptan received FDA breakthrough therapy designation but was discontinued in phase III clinical trials due to poor results in phase II. Novartis and Sangamo are developing zinc finger protein gene editing therapy, and Yamo Pharmaceuticals' L1-79 has also received FDA fast track designation. These new therapies and drugs may have future potential in treating ASD [18].

6.3. Challenges in Future Drug Development

Neuroimaging evidence suggests that children with ASD experience excessive cortical growth and abnormal white matter development during the critical developmental period of 2-3 years, and these structural changes are correlated with the severity of social deficits. Current pharmacological treatments primarily focus on alleviating secondary symptoms, with the FDA having approved only two dopamine modulators (risperidone and aripiprazole) for controlling aggressive behaviors, but they do not improve the core social deficits. Globally, many investigational drugs focus on neurotransmitter regulation (e.g., vasopressin and oxytocin receptor targets). Roche's balovaptan was discontinued due to not meeting endpoints in phase III clinical trials, while Yamo Pharmaceuticals' L1-79 showed some efficacy in phase II trials. At present, China's pharmaceutical development focuses mainly on generic drugs, and the 'new use of old drugs' strategy for bumetanide has shown

potential in preliminary clinical trials, but the evidence is limited. It is worth noting that non-psychoactive components like cannabidiol (CBD) have improved repetitive behaviors in ASD animal models, but human studies have only been approved for comorbid epilepsy treatment, and interventions for core symptoms remain to be breakthroughs [19].

In recent decades, the use of psychotropic drugs has significantly increased, with about two-thirds of adolescents with ASD receiving medication. Approximately 70% of ASD patients have comorbid mental health conditions such as ADHD, irritability, aggression, and emotional anxiety issues. Mandell et al. reported that 56% of patients used at least one psychotropic medication, and 20% used three or more. ASD patients often undergo polypharmacy, including off-label uses. The polypharmacy rate ranges from 12% to 35%. The reasons for the increase in prescription rates are unclear, but may be related to improved diagnoses and increased awareness among clinicians, as well as demographic factors such as insurance status, race, ethnicity, and geography. Challenging behaviors and mental health diagnoses are factors influencing polypharmacy. Polypharmacy is common because one treatment may be ineffective for another comorbidity. For example, metformin downregulates the mTOR pathway and works well when combined with stimulants for ADHD and SSRIs for anxiety [16].

7. Conclusion

The complex etiology and high heterogeneity of ASD necessitate multidisciplinary collaborative research. While genetic and environmental risks are becoming clearer, breakthroughs are still needed in the biological mechanisms of core symptoms. Current interventions focus on behavioral therapies, with pharmacological treatments limited to symptom management. In the future, the focus must shift to precision medicine and innovative therapies to improve the quality of life for patients and reduce the societal burden.

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