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A Comprehensive Overview of Genetic and Environmental Influences in Autism Spectrum Disorder Etiology: Processes, Interplay, and Prospects for Future Research

Sarhang Hasan Azeez

Biology Department, College of Education, Salahaddin University–Erbil, Iraq.

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Abstract

backgrounds: Autism Spectrum Disorder (ASD) is a complex and varied neurodevelopmental condition marked by challenges in social communication and the presence of restricted, repetitive behaviors. Its increasing global prevalence highlights a crucial public health need to understand its origins. Modern research has moved beyond the traditional "nature versus nurture" debate, demonstrating that ASD results from dynamic interactions between genetic susceptibility and environmental factors, which influence brain development during sensitive prenatal and early postnatal periods. This review consolidates current knowledge on genetic and environmental risks, examines biological mechanisms, and identifies directions for future research.

Methods: A thorough narrative review was performed by systematically searching PubMed, Scopus, and Google Scholar for peer-reviewed articles published between 2010 and 2025. Search terms included combinations such as "autism spectrum disorder," "etiology," "genetics," "environment," "gene-environment interaction," and "epigenetics." Articles were chosen based on relevance, study design, and scientific impact, with emphasis on meta-analyses, large cohort studies, and experimental models.

Results: The genetic basis of ASD is highly diverse, involving rare, impactful *de novo* mutations, inherited common variants that add to polygenic risk, and syndromic forms. Well-supported environmental risk factors include advanced parental age, maternal immune activation, prenatal exposure to teratogens like valproate, and certain pregnancy complications. Importantly, gene-environment interactions are significant, where genetic predisposition increases vulnerability to environmental factors. Epigenetic mechanisms, such as DNA methylation changes in immune and synaptic pathways, appear to be key in mediating these interactions.

conclusion: Evidence supports a "multi-hit" model, where combined genetic and environmental risks disrupt specific neurodevelopmental pathways. Key challenges include determining causality for environmental factors, defining precise timing of exposures, and integrating multi-omics data across varied populations. Future research should focus on large prospective birth cohorts with detailed phenotypic data, advanced experimental models to test interactions, and greater inclusion of diverse global populations. A deeper understanding is necessary to advance toward personalized risk assessment and prevention strategies.

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Correspondence:
Sarhang Hasan Azeez
E-mail: sarhang.azeez@su.edu.krd

Introduction

The prevalence of Autism Spectrum Disorder (ASD) has risen significantly over recent decades, a trend only partly explained by improved awareness and diagnostic changes [1]. This increase has driven greater attention to its complex, multifactorial origins. The outdated "genes versus environment" perspective has been replaced by an integrative model in which ASD emerges from interactions between genetic susceptibility and environmental exposures during critical phases of brain development [2,3]. This biopsychosocial-ecological model recognizes that while genetics establish a foundation of risk, environmental factors often act as triggers or modifiers.

ASD is clinically and etiologically diverse, ranging from individuals with significant intellectual disabilities to those with high cognitive abilities, along with differences in language, sensory processing, and co-occurring conditions. This diversity reflects the variety of underlying causes. Clarifying these causes is essential for developing individualized approaches to support, intervention, and prevention.

This review aims to summarize and evaluate current evidence on major genetic and environmental contributors to ASD. It begins by outlining the complex genetic structure, from rare high-impact variants to polygenic risk. It then reviews epidemiological findings on modifiable prenatal and perinatal environmental factors. A core section discusses gene-environment interaction (GxE) mechanisms, focusing on epigenetics as a central mediator. Finally, it addresses integrated neurobiological pathways, current research limitations, and future priorities, emphasizing the need for a unified approach that translates findings into clinical applications.

Genetic Foundations of ASD

ASD has one of the highest heritability estimates among neuropsychiatric disorders, with twin studies suggesting 74–93% heritability [4]. This strong genetic influence is, however, highly heterogeneous, involving a range of variants from rare, high-penetrance mutations to common variants with small effects.

Rare High-Effect Variants

De novo mutations, which appear spontaneously and are not present in parents, contribute notably to ASD cases in families with one affected child. Sequencing studies have identified over 100 robust ASD risk genes, many involved in specific biological functions [5].

- **Synaptic Genes:** Genes critical for synapse formation and function—such as neurexins (*NRXN1*), neuroligins (*NLGN3*, *NLGN4X*), and SHANK (*SHANK3*)—are frequently implicated. Disruptions here can affect the excitatory/inhibitory balance important for neural circuits [6].
- **Chromatin and Transcriptional Regulation:** Genes like *CHD8*, *ARID1B*, and *ADNP* regulate gene expression by modifying chromatin structure. Their reduced function can lead to broad changes in gene activity during brain development, impacting neurogenesis and differentiation [7].
- **Copy Number Variants (CNVs):** These chromosomal deletions or duplications, such as 16p11.2 and 15q11.2-13.1, often involve multiple genes and are linked to variable phenotypes, intellectual disability, and physical features [8].

Common Variants and Polygenic Risk

Most inherited risk comes from the combined effect of many common single nucleotide polymorphisms (SNPs), each with a small individual impact. Genome-wide association studies (GWAS) have identified several risk loci and shown that polygenic risk scores can differentiate cases from controls and relate to autistic traits in the general population [9]. These variants are enriched in regulatory regions active in fetal brain development and point to pathways involved in neuronal growth and communication [10].

Syndromic ASD

In about 10–20% of cases, ASD occurs as part of a known genetic syndrome, such as Fragile X (*FMR1*), Rett (*MECP2*), or Tuberous Sclerosis (*TSC1/TSC2*) [11]. Studying these conditions provides critical insights into specific biological pathways—like synaptic protein synthesis or mTOR signaling—that can lead to ASD symptoms.

Environmental Risk Factors

Epidemiological studies have identified several non-genetic factors linked to increased ASD risk, primarily acting before birth. While each factor may modestly increase relative risk, their population-wide impact makes them significant from a public health standpoint.

Prenatal and Perinatal Exposures

- **Advanced Parental Age:** Both older maternal (≥35 years) and paternal (≥40 years) age are associated with higher ASD risk. Paternal age is tied to increased *de novo* mutations in sperm, while maternal age may relate to changes in the uterine environment or pregnancy complications [12,13].
- **Maternal Health and Immune Activation:** Maternal metabolic conditions (e.g., obesity, diabetes) and immune activation are linked to ASD risk. Maternal Immune Activation (MIA), well-studied in animals, involves inflammatory responses that can cross the

placenta, affecting fetal brain development and later behavior [14,15].

• **Pharmacological Exposures:** Prenatal exposure to certain medications is a recognized risk. Valproic acid, used for epilepsy and mood disorders, is a well-documented risk factor, likely through epigenetic changes [16]. Evidence for SSRIs remains unclear due to potential confounding by maternal mental health [17].

• **Pregnancy and Birth Complications:** Conditions like preeclampsia, placental problems, low birth weight, and preterm birth are associated with elevated ASD risk [18,19]. These may directly affect the fetal brain through inflammation, hypoxia, or nutrient deficits, or reflect shared genetic susceptibility.

Broader Environmental and Postnatal Factors

• **Air Pollution:** Exposure to fine particles and traffic-related pollutants, especially late in pregnancy and early in life, is associated with increased ASD risk in multiple studies [20]. Possible mechanisms include inflammation, oxidative stress, and endocrine disruption.

• **The Gut-Brain Axis:** Altered gut microbiota and gastrointestinal issues are common in ASD [21]. Animal studies suggest that gut microbes can influence brain function and behavior through immune, neural, and metabolic pathways, potentially affecting symptom severity [22].

Interaction Mechanisms: GxE and Epigenetics

Gene-environment interactions (GxE) occur when the effect of an environmental exposure on ASD risk varies based on an individual's genetic background.

Examples of GxE in ASD

• **MET and Air Pollution:** A variant in the *MET* gene, involved in immune and brain functions, can strengthen the link between traffic pollution and ASD, indicating a combined effect [23].

• **CACNA1C and Prenatal Stress:** Variants in the CACNA1C calcium channel gene may influence how maternal stress during pregnancy affects child social and emotional development [24].

• **MTHFR and Maternal Nutrition:** Genetic differences in folate metabolism can interact with low maternal folate intake to increase ASD risk, showing how genetics can modify dietary impacts [25].

Epigenetics as a Mediator

Epigenetic modifications—such as DNA methylation—can create lasting changes in gene expression in response to environmental exposures, serving as a molecular link between environment and development.

• **Environmental Programming:** Prenatal exposures like MIA, valproate, or stress can lead to persistent methylation changes in genes related to immunity, stress response, and neuronal signaling [26,27], creating a "molecular record" that shapes neurodevelopment.

• **Epigenetic Signatures in ASD:** Studies of brain tissue and accessible cells (e.g., blood) have found methylation differences in ASD-related pathways, offering potential biomarkers of risk and dysregulated biology [28,29].

Discussion

A leading model for ASD etiology is convergent neurodevelopmental disruption, where diverse genetic and environmental factors affect common pathways: (1) gene regulation and chromatin function, (2) synaptic balance and plasticity, (3) neuroinflammation, and (4) brain connectivity [30,31]. The "multi-hit" threshold model suggests that ASD may result from various combinations of genetic and environmental factors, with some individuals having high genetic risk and others experiencing significant environmental exposure [32].

Current Challenges

• **Causality vs. Correlation:** Establishing causality for environmental factors is difficult due to confounding variables. Methods like Mendelian randomization offer promise but require large samples [33].

• **Timing and Specificity:** The developmental timing of exposures is critical—effects may differ by trimester. Dose-response relationships and which specific exposures are most harmful need further study [34].

• **Sex Differences:** The higher prevalence of ASD in males (~4:1) is not fully understood. Explanations include a female protective effect, sex-specific genetic influences, hormonal factors, or diagnostic biases [35]. Research should stratify by sex.

• **Unexplained Risks:** Some heritability is still unaccounted for, possibly due to rare variants or complex interactions. Similarly, known environmental factors explain only part of the risk, indicating other undiscovered influences [35].

Future Directions and Applications

1. Longitudinal Cohorts: Large, diverse cohorts with detailed exposure, biological, and outcome data are needed to track development from early pregnancy.

2. Multi-Omics Integration: Combining genomic, epigenetic, and other molecular data will help build causal models and identify biomarkers.

3. Advanced Experimental Models: Using human stem cell-derived neurons and organoids allows controlled study of GxE in human systems, aided by computational tools [38].

4. Global Diversity: Including underrepresented populations in research is essential for generalizable findings and equitable benefits [39].

5. Translation to Practice: Improved GxE understanding could lead to better prenatal counseling, public health measures to reduce exposures, and targeted interventions for specific subgroups [40].

Conclusion

ASD etiology exemplifies complex disease biology, arising from cumulative interactions between genetic vulnerabilities and environmental factors, primarily during prenatal brain development. The old debate of genes versus environment has been replaced by a dynamic, interactive model in which epigenetics plays a key mediating role.

Progress requires moving beyond associations to clarify the precise mechanisms through which genes and environment interact. Collaborative, multidisciplinary efforts integrating epidemiology, neuroscience, genetics, and data science are essential. Through longitudinal, multi-omics, and experimental approaches that account for GxE, we can advance toward personalized strategies for support and prevention, improving outcomes for individuals and families across the autism spectrum.

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The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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