The Genetic and Epigenetic Factors Affecting Autism Spectrum Disorder

Annika Pathak

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Abstract

This article investigates the genetic aspects of Autism Spectrum Disorder (ASD), which is a condition that impacts many individuals and families. The genetic underpinnings of ASD are examined in this article, emphasizing its heritability and the role of genetic predisposition in familial cases. Research indicates that ASD has a strong genetic component, with studies demonstrating an increased likelihood of diagnosis in individuals with affected relatives. Beyond genetic inheritance, this article also explores environmental influences on ASD risk. Epigenetics, in particular, provides insight into how external factors, such as prenatal exposure to toxins, maternal health, and early childhood experiences, can modify gene expression. These modifications may contribute to the development of ASD, even in individuals with a genetic predisposition. Environmental factors may interact with genetic vulnerabilities to influence symptom severity and presentation. Studying these interactions helps researchers understand the broader range of ASD risk factors.

Furthermore, the article will discuss key indicators of ASD, including social communication challenges, repetitive behaviors, and sensory sensitivities. Understanding these symptoms, along with their genetic and environmental origins, is essential for early diagnosis and intervention. The interaction between genetics and environmental factors highlights the complexity of ASD and underscores the need for further research to improve diagnostic methods and treatment strategies. By analyzing the current literature on ASD's genetic and environmental determinants, this article provides a comprehensive review of the factors contributing to the disorder. Expanding knowledge in this area can enhance awareness and support future research efforts to better understand, diagnose, and manage Autism Spectrum Disorder.

Introduction

Autism Spectrum Disorder, also known as ASD, is a neurodevelopmental disorder that affects about one in fifty-nine children in the United States (Hyman et al., 2019). The prevalence of ASD has increased twentyfold over the last thirty years (Mottron & Bzdok, 2020). This is likely due to broader diagnostic criteria and the recognition of autism as a multi-causal spectrum disorder (Fombonne, 2009; King & Bearman, 2009; Rice, 2013; Wing & Potter, 2002). The etiology of ASD is complex, involving a combination of genetic heritability, epigenetic modifications, and environmental influences (Masini et al., 2020).

Genetics is the study of heredity and the transmission of genes from parents to offspring. Epigenetics expands upon this foundation by examining the various factors that influence gene expression (*Epigenetics, Health, and Disease*, 2025). Specific DNA mutations have been identified as contributing factors to ASD. These mutations can disrupt typical brain development, resulting in a range of neurological and behavioral symptoms. (Talkowski et al., 2014). Additionally, many children with ASD experience co-occurring medical conditions, such as

anxiety or epilepsy, further complicating the process of diagnosis and treatment for families (Hyman et al., 2019). Epigenetics also plays a crucial role in the genetics of ASD, as it is the influence of environmental factors on gene expression. Maternal health during pregnancy, as well as exposure to certain environmental chemicals, has been shown to affect fetal development and potentially influence the risk of ASD (Jackson & Robinson, 2001).

This review aims to explore and identify specific alterations that contribute to ASD. It explores the role of environmental factors and epigenetics in regulating the expression of genes associated with ASD. Additionally, the review analyzes key diagnostic indicators and the varying presentations of individuals across the autism spectrum. By investigating the heritability of ASD and the influence of epigenetic mechanisms, this review seeks to provide a deeper understanding of the complexities of ASD.

The Genetic Basis of ASD Inheritance

Genetics plays a crucial role in determining ASD inheritance. Between 50% and 90% of the risk may be attributed to genetics (Muhle et al., 2004). This suggests that if one child in a family is diagnosed with ASD, there is a significantly higher likelihood that another sibling may also be affected. Siblings of children with autism spectrum disorder (ASD) have a 20% chance of also being diagnosed with ASD, which is significantly higher than the general population (Hyman et al., 2019). A heterogeneous collection of genes has been implicated in the heritability of ASD, along with other neurodevelopmental disorders, which may lead to varied clinical presentations of ASD (Talkowski et al., 2014). This highlights the need for a personalized approach when diagnosing and treating ASD, as each child's unique genetic profile can influence both their experience of the disorder and their response to interventions (Mottron & Bzdok, 2020).

Revisiting the heritability of ASD, twin studies provide valuable insights, showing that identical twins are more likely to be diagnosed with ASD compared to non-identical twins, revealing the significant role of genetics in the disorder's transmission (Muhle et al., 2004). This pattern suggests that ASD often runs in families, with closer genetic ties increasing the chances of another diagnosis (Hyman et al., 2019). While some cases of ASD may arise spontaneously, the genetic pattern is too consistent to disregard. The heritability of ASD is partially linked to gene mutations located on specific chromosomes, and these mutations may also be associated with other genetic disorders. For instance, Duchenne Muscular Dystrophy (DMD), a disorder caused by a gene mutation occurring during meiosis, has been found to co-occur in a significant number of boys who are also on the autism spectrum (Muhle et al., 2004). Although the frequency of mutations in individual genes is not determined by sex, ASD is observed to occur four times more frequently in males than in females. This suggests that the genetic abnormality may reside on the X chromosome, as males have only one X chromosome and cannot compensate for an altered gene with a second X chromosome (Werling, 2016).

However, recent research has identified additional chromosomal abnormalities beyond the X chromosome. Genome-wide association studies have revealed single nucleotide polymorphisms (SNPs) and variations in the *CDH10* and *CDH9* genes, located on a somatic chromosome. *CDH10* and *CDH9* are genes that encode cadherin proteins for cell adhesion, and are common genetic variations in ASD (Wang et al., 2009). Further linking autism to other genetic disorders, another potential genetic alteration that may influence the development of ASD involves the number of acetylcholine receptors. Studies have shown a reduction in these

receptors in the cerebellum of individuals with autism (Muhle et al., 2004). Notably, the locus for the gene encoding these receptors is also associated with epilepsy and schizophrenia, suggesting that ASD may share genetic pathways with these disorders. Therefore, research on genes influencing ASD has highlighted multiple potential causes, many of which are traced to both somatic and sex chromosomes.

There is compelling evidence that somatic chromosomes provide significant contributions to ASD as well as sex chromosomes. For instance, abnormalities such as duplications on chromosome 15, a somatic chromosome, have been associated with phenotypes including language delay, intellectual disability, and epilepsy—traits that overlap with the autism phenotype. Moreover, abnormalities at this locus have been identified in up to 3% of individuals with ASD in the studied population (Muhle et al, 2004). The link between chromosome 15 abnormalities and ASD, yet the fact that not all individuals with autism exhibit this abnormality, suggests that no single gene or chromosome can account for the development of ASD. This is affirmed by prominent ASD researcher Micheal Talkowski, who states that the most common abnormality in chromosome 16 accounts for just 1% of all ASD cases (Talkowski et al., 2014). For over 75% of cases involving ASD, the larger genetic cause remains elusive, despite having multiple small linkages (Fatemi, 2015). Therefore, abnormalities in chromosomes 15 and 16, gene mutations arising from meiosis, acetylcholine receptor variations, and other factors likely contribute to the complex etiology of ASD.

Epigenetic Factors Influencing ASD Inheritance

Epigenetics is an emerging field of research that significantly contributes to our understanding of Autism Spectrum Disorder. This field examines how environmental factors can lead to changes in gene expression, effectively turning genes “on” and “off” (*Epigenetics, Health, and Disease*, 2025). Research suggests that 40-50% of the variance in ASD may be linked to environmental factors, including drug exposure, toxins, and nutrition (Gaugler et al., 2014; Deng et al., 2015; Edelson & Saudino, 2009). Exposure to certain environmental factors (Table 1) can result in the formation of copy number variations (CNV), which affect gene expression and contribute to the prevalence of the disorder. CNVs are the differing number of copies of a specific DNA segment. Individuals with ASD are typically found to have three to five times as many CNVs as those without the condition (Pinto et al., 2010; Marshall et al., 2008).

Key epigenetic factors influencing ASD include DNA methylation, histone modifications, and microRNAs (miRNAs) (Masini et al., 2020). DNA methylation, the most common of these, involves the addition of a methyl group to DNA, effectively silencing genes and reducing protein production within a cell (*Genetics Basics*, 2024*)*. Studies on lymphoblastoid cells and whole-blood DNA from monozygotic twins who differ in ASD diagnosis have identified numerous differentially methylated regions (DMRs) between the twins and control samples (Nguyen et al., 2010). Zhu et al (2019) found 400 DMRs in the placentas of children diagnosed with ASD compared to those of typically developing children, most of which were located in the promoter regions of genes related to brain development (Zhu et al., 2019). Furthermore, they discovered that the methylation levels of two specific DMRs, located in the *CYP2E1* and *IRS2* genes, were linked to both the child’s genetic makeup and the mother’s use of prenatal vitamins (Zhu et al., 2019). This underscores how external factors, such as prenatal vitamin use, can interact with gene regulation and potentially contribute to the development of ASD.

Additionally, Kimura et al. identified a possible biomarker for adult ASD, discovering that a specific CpG methylation site, a site where a guanine follows a cytosine that can be methylated, was more methylated in the whole-blood DNA of ASD patients compared to controls (Kimura et al., 2019). This site is located on the *PPP2R2C* gene, which was found to be down-regulated in people with ASD (Kimura et al., 2019). This discovery provides evidence that gene expression in ASD is influenced by environmental factors, as the reduced activity of this site in those with ASD indicates that external factors have influenced its gene expression. Parental age is a well-established environmental risk factor (Wu et al., 2016). A meta-analysis of 27 studies examining the relationship between advanced parental age and ASD found that for every 10-year increase in either parent's age, the risk of ASD in their child increases by 20% (Wu et al., 2016). Further research suggests that age-related changes in DNA methylation in sperm may be linked to a heightened risk of ASD in offspring (Atsem et al., 2016). These findings underscore the role of environmental factors in influencing the expression of genes associated with ASD. Additionally, elevated testosterone levels are often observed in individuals with ASD, indicating that prenatal exposure to sex steroids may contribute to the development of the disorder (Werling, 2016).

Maternal health is a significant contributing factor to the development of ASD. Pregnant individuals who smoke, use substances, or take certain medications may increase the risk of developing ASD in their child (Masini et al., 2020). Additionally, inadequate nutrition can lead to irregular gene expression in the fetus, potentially contributing to the development of ASD (Masini et al., 2020). The health and habits of the mother are environmental factors that do not directly stem from the child, but influence the expression of the genes that the child already has, which may lead to ASD.

Exposure to environmental chemicals may also influence ASD risk. Research suggests that exposure to certain pollutants has the potential to alter the expression of genes involved in brain development (Jeddi et al., 2016). Such alterations in gene expression can disrupt normal brain function and may contribute to the behavioral symptoms commonly associated with ASD. Notable environmental chemicals that have been identified as potential risk factors for ASD include polychlorinated biphenyls (PCBs), lead, bisphenol A (BPA), mercury, and various pesticides (Keil & Lein, 2016). Alterations in DNA methylation resulting from PCB exposure have been shown to impact sexual development and modify gene expression patterns in the brain, with these effects varying by sex (Keil & Lein, 2016). This is particularly significant as hormones, which are regulated by these genetic changes, play a critical role in brain development. The disruption of the endocrine hormone has been proposed as a contributing factor to ASD, particularly given the disorder's higher prevalence in males compared to females (Keil & Lein, 2016). Recognizing the role of epigenetics in ASD is crucial because it emphasizes the need for a closer look at how environmental factors can influence gene expression, especially during the critical developmental stages of childhood.

Table 1: List of epigenetic factors and their effects

Key epigenetic Factors	Effects observed	Citations
Exposure to toxins, drugs, and components of nutrition	Copy Number Variations (CNVs) in affected genes	Pinto et al., 2010; Marshall et al., 2008
DNA Methylation, Histone Modifications, microRNAs	Gene silencing and reduction in protein synthesis	Masini et al., 2020
Differentially methylated regions (DMRs)	Affecting the promoter regions of the gene responsible for brain development	Nguyen et al., 2010
Use of prenatal vitamins during pregnancy	DMRs in *CYP2E1* and *IRS2* genes	Zhu et al., 2019
CPG methylation site	Down-regulation of *PPP2R2C* gene expression	Kimura et al., 2019
Parental Age	Age-related changes in sperm quality	Wu et al., 2016; Atsem et al., 2016
Malnutrition and smoking	Affecting gene expression	Masini et al., 2020
Environmental chemicals (PCBs, lead, BPA, mercury, and pesticides)	Affects the endocrine system	Keil & Lein, 2016

The Key Indicators of Autism Spectrum Disorder

Early identification of ASD is crucial in ensuring that children receive the necessary interventions and support. Although genetics and epigenetics are integral in the development of ASD, behavior remains the most observable indicator. Parents are often the first to notice early signs, such as difficulties with social interactions and the presence of repetitive behaviors. In 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the primary guide for diagnosing mental health conditions, consolidated all subtypes of ASD into a single category and highlighted the need to recognize other developmental and behavioral issues or symptoms that might be present along with ASD (Hyman et al., 2019). The DSM-5 criteria divided ASD symptoms into three domains: problems with social interactions, communication difficulties, and repetitive behaviors (Hyman et al., 2019).

The DSM-5 outlines two core domains of behavior associated with ASD: social communication and interaction and repetitive behaviors (Hyman et al., 2019). These criteria provide valuable guidelines and specific patterns that help in the identification of ASD. Although

the symptoms of ASD originate in the brain, they manifest as various behaviors that can change depending on factors like age, language skills, and cognitive abilities (Hyman et al., 2019). Common examples include difficulties in understanding others' intentions, limited eye contact, and unusual use of gestures. These symptoms can lead to challenges in social communication, pretend play, and interactions with peers (Hyman et al., 2019). The identification of these observable behaviors reveals a consistent pattern among individuals with ASD, facilitating early recognition and diagnosis in those exhibiting these characteristic symptoms.

Co-occurring medical conditions may serve as additional indicators of ASD and should be considered during the diagnostic process (Hyman et al., 2019). Several screening tools, such as the Modified Checklist for Autism in Toddlers (M-CHAT), are available to assist in identifying these potential indicators, thereby facilitating early intervention (Hyman et al., 2019). Monitoring developmental milestones is critical, as even subtle deviations in communication and social interaction can signal the presence of ASD. The involvement of family members is also crucial, as their observations can provide invaluable insights into the child's behaviors and developmental patterns during the diagnostic process (Hyman et al., 2019). Furthermore, sensitivities to sensory input, such as heightened reactions to loud noises or specific textures, are important diagnostic clues. These sensory differences often coexist with the social and behavioral symptoms of ASD, further highlighting their significance in the diagnostic evaluation (Balasco et al., 2020).

Discussion

The literature reviewed reveals that ASD arises from the interplay between genetic predispositions and environmental influences, indicating that it is not solely the result of inherited genetic factors but also how ecological parameters affect gene activity. Research further suggests that DNA modifications, such as methylation, play a significant role in gene function, particularly in genes critical for brain and nervous system development. This could explain the broad variability in ASD symptoms, as these genetic alterations affect the functioning of key developmental genes. In summary, DNA changes, such as methylation in specific genes, are pivotal in both the onset and the manifestation of ASD. These alterations may provide valuable insights into the diverse presentations of ASD, enhancing our ability to better understand and assess where individuals fall on the spectrum.

The future of ASD research in genetics and epigenetics holds great promise for improving diagnosis and treatment. The latest development indicates the design of a drug controlling the DNA methylation process as a prevention strategy (Gholamalizadeh et al., 2024). As genetic research continues to identify specific genes and genetic variations linked to ASD, there is potential for more precise, personalized interventions. Additional genetic markers could be uncovered, allowing for more targeted behavioral therapies that enhance ASD treatment. Research into how epigenetic modifications, like DNA methylation, could eventually lead to preventive strategies or therapies that could potentially regulate the effect of these epigenetic changes.

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