A Brief Overview of How Genetics, Epigenetics, and Environment Interact in Autism Spectrum Disorder

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Abstract

ASD seems to be strongly affected by various factors such as differences in genes. According to research, ASD is influenced by both biological and chemical processes. This summary assesses the strength of various studies and provides a short outline of the factors that may increase the risk of ASD. We review studies that explain why these factors may increase the risk of ASD. The authors end the review by discussing the potential effects of new findings on upcoming research in molecular areas.

Keywords: ***Autism spectrum disorder; genetics; molecular mechanisms; epigenetics; DNA methylation; rare variants; common variants.***

1. Introduction

Autism spectrum disorder is a condition that appears in early childhood and continues throughout a person's life. Children and adults with ASD experience difficulties with social skills and communication and also show rigidity and repetitive actions. It has been researched a lot since 1943 when Leo Kanner documented the first 11 cases which involved boys with social problems and different difficulties with language(1).

Epidemiology results suggest that, globally, autism affects approximately one percent of the population and four times as many men as women are diagnosed with autism. There is a wide range of how ASD can appear in people. Half of the individuals identified with ASD usually have intellectual difficulties and many of them also develop other mental health concerns. Often, these conditions are linked to depression, different anxiety disorders, ADHD, sleeping problems and stomach-related symptoms. Also, more than 35 percent of autistic people develop epilepsy; even some people with autism who have never had a seizure can show epileptic changes in their brainwaves. While these features are popularly associated with autism, autism experts still use consensus-based judgment as the main criteria, now including guidelines from the overarching category of ASD.

These studies have shown that autism is strongly influenced by inherited genes. What the studies found is this: For dizygotic twins (who share only about half their genes), the similarity is 30 percent; for monozygotic twins (identical worlds), it is 70-90 percent; and for non-twin siblings, it falls anywhere from 3 to 19 percent. The higher agreement in identical compared to fraternal twins for autism strongly points to a genetic reason behind the illness. Research that investigates the autism prevalence among relatives of affected individuals compared to the community helps prove the role of genetics. More evidence is provided by research on children with unique genetic conditions and autism(2).

Employing identical findings, it seems that growing together in the womb has a bigger effect on a sibling's development than genetics, but researchers do not understand the exact reasons. Besides ordinary genetic traits, researchers now think that ASD is related to changes that occur in molecules, both in genes and in ways genes are regulated. The risk of neurodevelopmental disorders can be evaluated using new and key ways tied to epigenetics in addition to genetic risk factors.

Examples of epigenetics include DNA methylation, changing histones and ATP-involved reorganization of DNA. As a result, the splicing process and transcription of messenger RNAs are controlled, affecting the process of starting transcription and the action of transcription binding factors. Alterations in DNA sequences of such genes as SNPs or CNVs might lead to changes in epigenetic regulation and contribute to ASD.

Experts in the field have detected more than 600 human genes related to development conditions such as intellectual disability and autism. Examples of these genes are DNA methyltransferase 3A (DNMT3A), HECT, UBA, WWE domain-containing E3 ubiquitin-protein ligase 1 (HUWE1) and chromodomain helicase DNA-binding protein 8 (CHD8). More evidence suggests that both neurodevelopmental and neuropsychiatric illnesses may involve some kind of genetic interference. Numerous genes identified in epigenetics help guide molecular pathways, whereas

others are involved in the functioning of neurons and their synapses.

Emphasis should be placed on the idea that there is not one main reason for all cases of ASD. Research should aim to reveal the molecular background and the role of various genes in ASD during key stages of development. It seems that both genetic and environmental factors (GxE) play a major role in humans and this effect is probably achieved by mechanisms such as epigenetics(3).

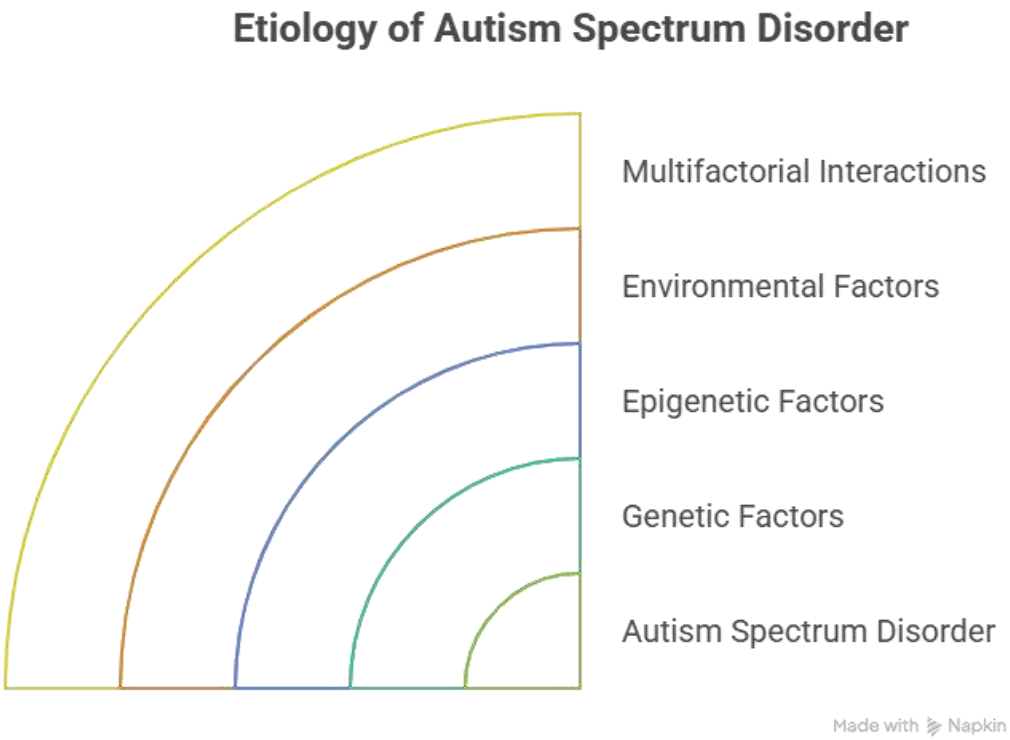

FIGURE 1 Etiology of Autism Spectrum Disorder

Here, I will look at what is known so far about genetic, epigenetic and environmental factors responsible for ASD and their relationship. We strive to gather latest information from these domains to suggest new approaches for detecting and managing the disease. Further discoveries on the biology of autism help make it possible to develop therapies that are better suited for autistic individuals.

2. The paper's body

Currently, experts in the field believe ASD is caused by the interaction of many different genes. Both old and recent studies involving twins have generally found the inheritance level to be higher than 30 percent. NGS technologies have allowed scientists to learn more about differences in genetics between individuals with ASD and those without. Identifying autism-relevant mutations in families is made easier by using the whole-genome sequencing (WGS) method(4).

One investigation of families with four members found that 31 percent of siblings shared similar mutations as the study's index ASD cases. The discovery proves that several distinct genetic causes, sometimes seen in a single family. Using genomic sequencing may reveal a lot about the genome, but classifying genetic variants is still very challenging. More than 200 genes involved in ASD have been shown by studies, but only 25-40 percent of ASD cases are explained by the mentioned risk variants.

Furthermore, most genetic mutations contribute to ASD in less than one percent of cases, meaning the way autism is passed on through genes is very complex and its symptoms can vary considerably. In recent years, researchers have looked into over a thousand possible autism genes. About 212 genes have been noted on the SFARI gene platform

for their role in interplay with environmental conditions in autism. Modern research uncovered ways in which issues in genes can influence the level of inflammatory cytokines in the body and lead to different behavioral effects in individuals with ASD(5).

Studies have discovered that genetic changes at six locations (1q21.1, 3q29, 7q11.23, 16p11.2, 15q11.2-13 and 22q11.2) are commonly associated with ASD in various research(6). Scientists have observed that these regions increase the likelihood of a person getting the condition.

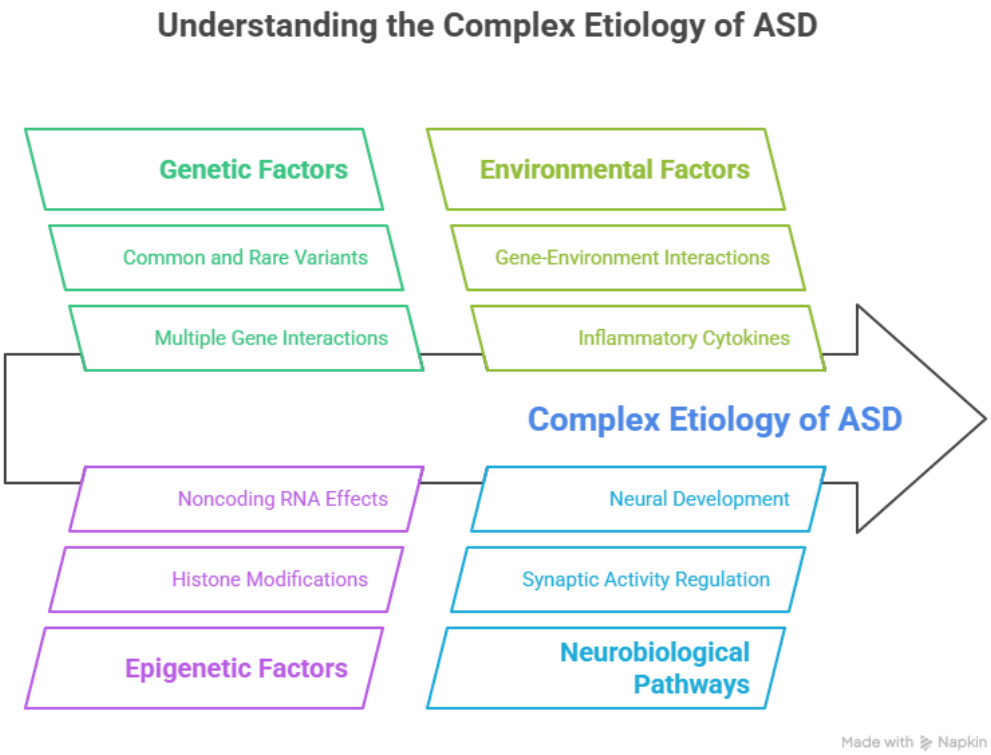

FIGURE 2 Understanding the Complex Etiology of ASD

Latest genetic studies have revealed many common and uncommon genes involved in autism in families. Most alterations that heritability studies identify in autism come from common genetic variations, as seen in the SNP-based heritability which is generally about 50 percent. Much like other widely-known neuropsychiatric diseases, common changes in genes that lead to autism tend to act in small ways, meaning accurate findings often require analyzing many people. The most recent GWAS study on ASD genomes found five significant loci related to ASD among the 18,381 patients studied(7). When we look at larger groups, we expect to find additional genetic loci as a result of the large SNP-based heritability shown in studies.

Various studies using WGS in ASD patients since 2011 have found rare changes in numerous autism-related genes. Consequently, scientists now believe that far more genetic factors might be involved in the development of autism. Many studies in scientific journals confirm that ASD is associated with greater numbers of de novo genetic mutations. Several research works emphasize the role of de novo mutations when there is a family history of common and rare genetic changes.

Numerous studies prove that many ASD-related changes in DNA contribute to the same neurobiological pathways behind the condition. They involve cell reproduction and transformation, growth of the nervous system, regulation of neurons, expressions of genes and reshaping of DNA within cells. It is clear that many genes connected to ASDs tend to be active in brain tissues during periods when the brain and nerves are forming. Groups of ASD-related genes help to explain the different brain and mental traits found in ASD.

Further study into ASD genes discovered during genetic mutation studies has revealed new aspects. It seems that certain genes within ASD could raise the possibility of schizophrenia, motor problems, epilepsy, sleeping issues, ADHD and intellectual disabilities. This means that people with the same disorders usually share ways in which their genes can be faulty(8).

Both molecular evidence and some studies suggest that genetic syndromes are able to affect epigenetic functions that play a role in ASD. According to research, 15 percent of syndromic ASD can be explained by epigenetic factors. Epigenetic differences at the functioning level have been related to a greater risk of ASD. Some of these changes are in HDACs, lysine demethylases, proteins containing bromo, chromo or Tudor domains, DNMTs, histone methyltransferases, acetyltransferases and chromatin-remodeling factors. It has been found that both ncRNAs and MBDs indirectly influence epigenetics by being involved in histone modification and controlling transcription.

This helps researchers gain a better overall understanding of what leads to ASD. This way of analyzing could make diagnosing ASD more accurate and choose treatments that affect the disturbed pathways of each specific type of ASD.

3.Environmental Factors and Epigenetic Markers in ASD

ASD refers to a complicated condition of development where individuals exhibit difficulties with interactions, speaking and routines. Although ASD is largely driven by genetics, we are finding that environmental factors also shape its epigenetic development. Epigenetics shows a way to understand how experiences during key stages of development might influence the brain enough to cause ASD.

Women are frequently exposed to certain environmental factors before their pregnancy

At this point, anything happening in the environment can strongly influence the growth and development of a baby's brain. Maternal contact with environmental insults such as chemical pollutants, illnesses, drugs and insufficient nutrition appears to increase chances of ASD. Exposure of pregnant women to PAHs, NO_2 and PM2.5 is linked to a raise in ASD in their children. Such pollutants may trigger oxidative stress and inflammation in the brain, possibly interfering with how the brain normally develops.

Infections and immune responses in a mother during pregnancy are recognized as important contributors to ASD. In some cases, when a mother's immune system is activated by infections like flu or autoimmune disorders, it can raise the cytokine interleukin-6 (IL-6). This cytokine may then move into the fetal brain and alter its development. Changes in the gene expression and connectivity pattern of the brain in ASD are related to the interaction between mothers and their unborn fetuses.

Using valproic acid (VPA), a well-known teratogen and anticonvulsant, in pregnancy continues to be linked with outcomes similar to ASD in both animal research and research on people. It has been observed that exposure to VPA can disturb normal HDAC function, changing gene expression via epigenetic means. The research indicates that drugs given during pregnancy might alter certain marks in genes tied to neurodevelopmental issues.

After Childbirth, the Environment Matters

Safety during pregnancy remains important, but what happens around the infant after birth can also have a big influence on their brain function. People have found that deficient nutrition, exposure to lead or mercury and stress during early childhood may increase the risk for ASD. Likewise, increased lead exposure early in life has been found to slow brain growth and cause problems related to ASD.

Early-life stress is also an important factor in postnatal development. Some reports show that harmful experiences in children can cause changes in the way their bodies regulate stress hormones such as cortisol which has consequences for both brain function and the behavioral changes seen in epigenetics. It seems that stress increases DNA methylation in genes that control the HPA axis, suggesting a possible link between stress in the environment and changes in brain development.

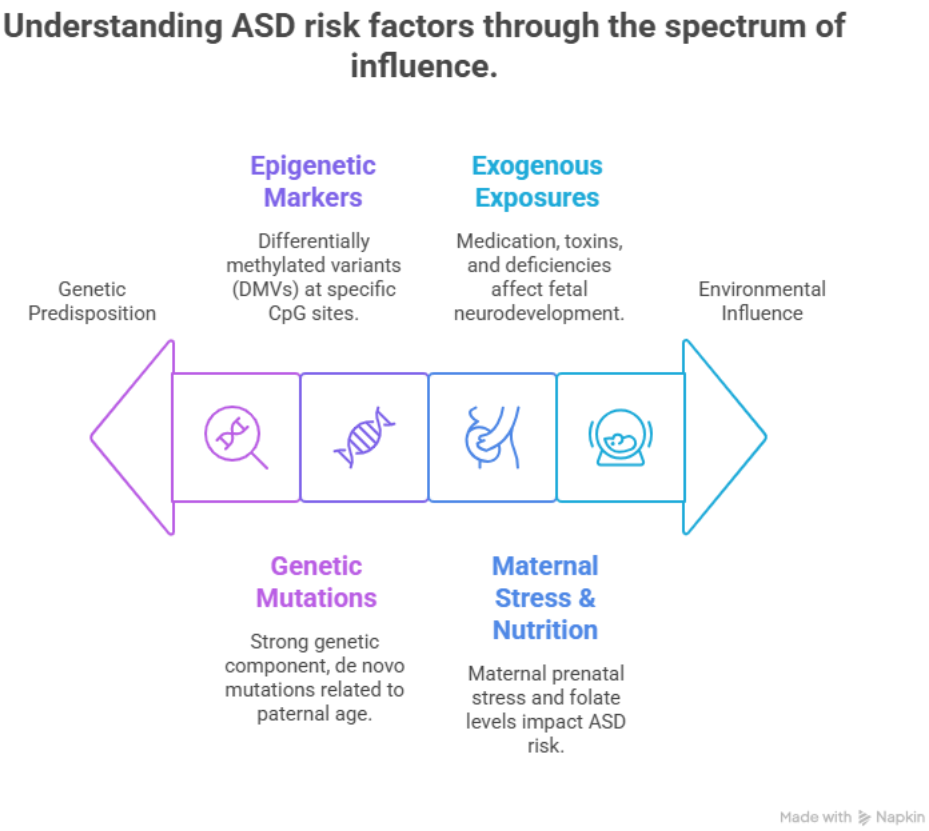

FIGURE 3 Understanding ASD risk factors through the spectrum of influence

Relationships between the environment and ASD are made possible by epigenetic mechanisms

They allow for a two-way interaction between the genome and the results of the environment. Out of the three key epigenetic techniques, DNA methylation, changing histones and non-coding RNAs play the biggest roles. In relation to ASD, researchers have spent the most time examining DNA methylation. A methyl group is often put on the cytosine in a CpG which then blocks the gene's expression if it happens in a gene's promoter region.

Scientific research has found that people with ASD have unusual patterns of DNA methylation in genes related to the brain, nerve cells and immune function. An example is that MECP2, a gene key to neurons and synapses, is often hypermethylated in people with ASD. Lack of methylation in the OXTR gene which encodes the oxytocin receptor, is correlated with difficulties in social cognition in ASD.

4.Conclusion and Future work

Since autism spectrum disorder involves many areas, it requires a unified way of trying to understand its biology. Understanding ASD requires molecular mechanisms when looking at patients with ASD, as genes or epigenetic factors alone are not always enough to fully illustrate what causes the condition. The variation in genetics and epigenetics suggests that multiple factors influence the different symptoms seen in ASD. Gathering information about genetics, epigenetics and the environment provides a better overview of the development of ASD.

Recognizing early on the person's genotype and epigenotype, along with their effects on the brain and ASD-related traits, greatly assists doctors in diagnosis and categorizing individuals with these disorders. A better understanding of molecular biology helps doctors diagnose diseases earlier and could improve the outcome for patients. Progress in research allows scientists to divide autistic patients into similar subgroups, resulting in better ways to treat the condition.

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Many factors contribute to the genetic makeup of ASD. In almost all cases, twin studies confirm that more than 70% of the influence over these factors comes from genes. Still, the types of genetic differences linked to ASD can range from those that have little effect on their own to those that may have a bigger effect. By studying genes across the genome and by sequencing the complete genome, as well as family information, experts have found clues linking hundreds of genes to ASD. The genes often interact in groups involved in brain development, synapses, cellular changes to DNA and regulation of transcription, connecting them under similar biological functions.

Epigenetics increases our understanding of the reasons behind ASD. Gene expression is regulated by DNA methylation patterns, modifications of histones and non-coding RNAs without affecting the DNA itself. Such changes in genes and the environment affect each other and influence the overall impact on a person. Analysis of differentially methylated regions in the brains of people with ASD in more than one tissue points to the suitability of epigenetic markers for diagnosis. In addition, epigenetic changes could explain the connection between exposure to risk factors and developing ASD, especially during the most important stages of brain growth.

ASD risk is often affected by the environment, mainly because of epigenetic factors. Development of the fetus can be influenced by a mother's age, hormonal or emotional changes, diet and some exposures to harmful substances. When exposures to toxins happen, they are most harmful during the time in the womb and the first months after birth. To prevent these problems, it is necessary to know what contributes to them and what factors we can adjust.

Fusing these three domains in research on ASD presents opportunities as well as difficulties. Ultra-fast and machine-based tools hold great potential for understanding the various influences among these factors. Looking at development from the prenatal stage up to childhood, research shows how both our genetic and non-genetic factors interact with a person's surroundings over their life.

The shared understanding can lead to new ways of diagnosing and treating diseases. When disrupted pathways are discovered, it allows scientists to target these paths in therapy and not only focus on treating behavioral issues. Because epigenetic changes may be reversed, they attract a lot of attention in the search for new therapies. Detecting and addressing risks related to genetics and epigenetics may assist in preventing the core challenges from taking shape.

Researchers should work on identifying the main areas that are important to learn more about ASD etiology. To understand genetic variation in ASD among various ethnicities, we should increase the number and range of the people studied. The combination of genomics, epigenomics, transcriptomics and proteomics data will help explain the biological causes of ASD. By studying their functions, the true reasons for each variant and modification can be separated from simply related effects. If several biomarkers are used together, it might become simpler to detect cancer early and provide personalized treatment.

Experts in the field should focus on how molecular science can be applied to medicine. Better ways to analyze genetic variants of uncertain meaning will help doctors reach the same conclusions. Recognizing the complexity of symptoms using ways to describe symptom patterns may allow researchers to relate different symptoms to the underlying biology. Before using genetic and epigenetic tests in medicine, doctors must think about ethical matters such as unexpected test results and how these can influence decisions on having children.

All things considered, how genetics, epigenetics and the environment interact in ASD is important for research about neurodevelopment and can greatly shape diagnosis, treatment and prevention. Continued in-depth research brings the community closer to recognizing autism not just as an observed behavior but as a group of disorders with specific causes, genes and therapies.

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Conflicts of interest

The authors have no conflicts of interest to declare

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