

# Genetic and Epigenetic Aspects Linked to The Etiology of Autism

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## Article Info

### Article Notes

Received: April 04, 2025

Accepted: June 12, 2025

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### Keywords

Autism

Genetic

Epigenetic

Environment

Social Interaction

Synaptogenesis

## Abstract

Autism is a childhood-onset neurodevelopmental disorder characterized by high heritability, a complex genetic basis, and a wide range of phenotypic expressions. Its etiology is identified in a significant proportion of cases and may involve chromosomal abnormalities, pathogenic variations in several genes, or environmental factors. However, in many cases, the underlying causes remain unexplained, even after comprehensive genetic testing in accordance with ACMG (American College of Medical Genetics and Genomics) guidelines.

The complex phenotype of autism includes a "core triad" of symptoms—impaired social interaction, restricted and repetitive behaviors—often accompanied by additional conditions such as language impairments, intellectual disability, epilepsy, hyperactivity, anxiety, and various other comorbidities.

In this paper, I aim to explore the interplay between genetic, epigenetic, and environmental factors to better understand the potential pathogenic mechanisms underlying this disorder, which continues to show a rising global prevalence.

## Introduction

**Autism Spectrum Disorder (ASD)** is a neurodevelopmental disorder of childhood, classified in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. It affects approximately 1% or more of the preschool population.<sup>1</sup>

The core symptoms of ASD include deficits in social communication and interaction, as well as restricted, repetitive patterns of behavior, interests, or activities. These are often accompanied by other medical and developmental conditions, such as language disorders, cognitive impairment (in over 40–50% of cases), epilepsy (in approximately 30% of cases), gastrointestinal issues, hypo- or hypersensitivity to sensory stimuli (including auditory, tactile, and gustatory sensitivities), sleep disturbances, depression, anxiety, attention-deficit/hyperactivity disorder (ADHD), and self-injurious behaviors, among others.<sup>2 3</sup>

ASD is four times more prevalent in boys than in girls. However, girls and women with ASD may be better at masking or compensating for their symptoms, particularly in social communication—a phenomenon clinically referred to as *camouflaging*.<sup>4</sup>

For many years, ASD has been suspected to have a strong genetic basis, as evidenced by studies of monozygotic twins, which show concordance rates approaching 90% across various cohorts.<sup>5,6</sup>

More recently, research has increasingly focused on epigenetic mechanisms, including DNA methylation at CpG sites, histone

modifications (such as methylation and acetylation), and the regulatory role of non-coding RNAs (ncRNAs), which influence gene expression without altering the DNA sequence. These mechanisms may contribute to the genetic and epigenetic load associated with ASD.<sup>7</sup>

The etiology of ASD includes a variety of chromosomal disorders, such as Down syndrome, Pallister-Killian syndrome (tetrasomy 12p), Wolf-Hirschhorn syndrome (4p-), Cri du Chat syndrome (5p-), DiGeorge syndrome (22q11.21 deletion), 47,XXY syndrome, Angelman and Prader-Willi syndromes (15q11-q:13), and Smith-Magenis syndrome (17p11.2 deletion), among other chromosomal aneuploidies and copy number variants (CNVs) or structural chromosomal abnormalities.<sup>8,9</sup>

In addition, numerous cryptic chromosomal anomalies—detectable only via chromosomal microarray analysis (CMA)—have been associated with ASD, as well as hundreds of pathogenic gene variants identifiable through next-generation sequencing (NGS) techniques. Many of these genetic findings have only been recognized in recent years due to improved accessibility and availability of advanced genetic testing.<sup>10</sup>

Environmental factors have also been implicated in the development of ASD. These include prenatal infections, inflammatory conditions with prolonged fever, maternal diabetes, eclampsia, prematurity, and exposure to teratogenic substances such as valproic acid, misoprostol, alcohol, tobacco (particularly heavy smoking), cannabis, heavy metals, pesticides, and insecticides, among others.<sup>11,12</sup>

### Pathogenic Mechanisms related with ASD

The symptoms of Autism Spectrum Disorder (ASD) typically emerge in early childhood, a critical period that coincides with an intense phase of brain development. During this time, neurons proliferate and differentiate, inhibitory and excitatory signaling systems mature, axons undergo myelination, and synaptic plasticity is activated through the orchestration of intricate molecular pathways influenced by environmental factors and learning experiences.<sup>10</sup>

Disruptions in any of these processes may potentially contribute to the onset of ASD symptoms. As previously mentioned, ASD begins in childhood, persists throughout life, and exhibits considerable variability in its clinical presentation over time.

These phenotypic variations may be modulated by epigenetic factors, including therapeutic interventions, behavior-modifying medications, and environmental influences. Although ASD has a strong genetic foundation more so than many other neurobiological disorders, genetic sequence alterations remain an area of active investigation.

Variants in genes such as *NRXN*, *NLGN*, *SHANK3*, *TSC1/2*, *FMR1*, *MECP2*, *SYNGAP1*, *ADNP*, *ANKK2*, *PTEN*, *RELN*, and *UBE3A*, among many others, have been implicated.<sup>9</sup>

There is growing evidence for the involvement of imprinted genes and paternal transmission patterns in ASD, which, combined with the lack of clearly defined genetic markers, has brought increased attention to the role of epigenetic mechanisms in the possible etiopathogenesis of the disorder.<sup>11</sup>

### Study of Epigenetic Mechanisms

Epigenetics is defined as “the study of modifications in gene expression caused by chromatin remodeling that do not involve alterations to the underlying DNA sequence.”<sup>12</sup> These processes are recognized as complex chemical reactions that modify how DNA is transcribed, ultimately influencing an organism’s response to environmental stimuli.

Many genetic conditions in which autism is a prominent feature are associated with disruptions in specific epigenetic patterns, helping to elucidate the pathogenesis of ASD.<sup>13</sup>

Key epigenetic mechanisms include:

- DNA cytosine methylation
- The interaction of *MECP2* with target genes
- Post-translational modifications of histone proteins within nucleosomes
- Genomic imprinting
- MicroRNA (miRNA) synthesis
- Chromatin organization and spatial distribution within the cell nucleus<sup>14,15,16</sup>

We will now examine each of these processes in detail.

### DNA Methylation

DNA methylation is the most extensively studied and well-understood epigenetic mechanism. Through an ATP-dependent reaction, methionine is converted into S-adenosylmethionine (SAM), the universal methyl group donor in cells. This process requires various micronutrients and vitamins, including folate, vitamin B6, vitamin B12, choline, and methionine.

Many gene promoters contain CpG dinucleotide islands, where methyl groups are added to the 5-position of the cytosine ring, forming 5-methylcytosine. These methyl groups bind covalently and remain stable through cell divisions (mitosis). This reaction is mediated by a family of enzymes known as DNA methyltransferases (DNMTs), which cause the DNA to adopt a closed chromatin conformation, thereby suppressing gene transcription.<sup>12,13</sup>

CpG islands are not randomly distributed throughout the genome; they are most found in gene promoter regions. As such, methylation at these sites can significantly alter the level of gene transcription. Approximately 80% of CpG dinucleotides are methylated. The specific methylation sites depend on the gene in question, the type of cell or tissue, and even the developmental stage or age of the individual. Active chromatin regions—those capable of gene expression—tend to be hypomethylated, whereas hypermethylated regions are tightly packed, forming transcriptionally inactive chromatin.<sup>15</sup>

For example, the expression of protocadherins (*Pcdhs*)—including *Pcdha*, *Pcdhb*, and *Pcdhg*—which play critical roles in neuronal migration, is regulated by specific methylation patterns. *Pcdh* expression is stochastic; different promoters generate various isoforms through distinct methylation profiles.<sup>16,17</sup>

Once DNA methylation marks are established, a group of “reader” proteins recognize and bind to these methyl groups, protecting and interpreting the epigenetic code.

Methylation plays a key role in memory formation, with the cerebral cortex and hippocampus being essential regions for the encoding and storage of memories.

Just as methylation can be added, it can also be removed in a process known as demethylation, which may occur either passively or actively. This is particularly important during early embryonic development, when germ cells must erase previous epigenetic marks to reset for a new round of cell fate determination. Demethylation is mediated by enzymes known as “erasers,” including TET1, TET2, and TET3. Later in the central nervous system, these enzymes also contribute to neuronal dedifferentiation, synaptic plasticity, and the regulation of memory and fear responses.<sup>18</sup>

An example of CpG island hypermethylation in a pathological context is Fragile X syndrome, a condition associated with the X chromosome, which will be discussed in detail later.

### Function of the MECP2 Protein

MeCP2 (methyl-CpG-binding protein 2) is one of the best-known proteins involved in transcriptional repression. It contains a critical domain known as the methyl-CpG-binding domain (MBD), which consists of 85 amino acids and binds specifically to DNA regions containing one or more symmetrically methylated CpG dinucleotides.

MeCP2 interacts with histone deacetylases (HDACs), enzymes involved in chromatin remodeling, which regulate the accessibility of transcriptional machinery to DNA—either by promoting or inhibiting gene expression.<sup>16,19</sup>

DNA is closely associated with histone proteins that

help regulate its transcriptional activity. It wraps around histone octamers—composed of H2A, H2B, H3, and H4 forming nucleosomes. Each nucleosome contains approximately 147 base pairs of DNA wrapped around these core histones. The N-terminal tails of histones (ranging from 19 to 39 amino acids) are subject to various post-translational modifications, such as acetylation, methylation, phosphorylation, and ubiquitination.<sup>19,20</sup>

These modifications do not occur simultaneously on a single histone tail, but a given nucleosome may exhibit multiple types of modifications. This pattern of histone modifications—often referred to as the “histone code”—plays a key role in regulating the accessibility of DNA to transcription factors. Specific proteins “read” these modifications by binding to the modified histone tails, influencing the transcriptional state of the underlying DNA.

Methylated DNA regions are commonly recognized by proteins like MeCP2, which belongs to a family of methyl-CpG-binding proteins that bind specifically to methylated DNA sequences. MeCP2 is a highly expressed nuclear protein that mediates gene silencing by recruiting co-repressors. In association with the transcriptional repressor Sin3A, MeCP2 facilitates the recruitment of histone deacetylases. This leads to deacetylation of lysine residues on histones H3 and H4, resulting in chromatin condensation and reduced accessibility of DNA to the transcriptional machinery.

However, gene repression is not MeCP2’s only role. It is now believed to function as a transcriptional modulator, capable of both enhancing and repressing the transcription of active genes—extending its influence beyond promoter regions.

MeCP2 plays an essential role in central nervous system (CNS) development. Deletions or mutations in the *MECP2* gene are responsible for Rett syndrome (RS), a severe neurodevelopmental disorder primarily affecting girls. Alterations in MeCP2 function are also associated with other CNS conditions observed in both sexes, including autism, epilepsy, and intellectual disability.

While MeCP2 is crucial in neurons, its role in glial cells appears to be even more significant. Abnormal MeCP2 levels are considered critical in the pathogenesis of Rett syndrome and related disorders, as will be discussed further.<sup>21</sup>

### Histone Modifications

#### Histone Acetylation / Deacetylation

Histone acetylation typically occurs on lysine residues and represents a reversible modification mediated by two main enzyme families: histone acetyltransferases (HATs) and histone deacetylases (HDACs). During acetylation, the positive charge of lysine (K) is neutralized, causing

chromatin to adopt a more open conformation that facilitates transcription and replication. Thus, histone acetylation is a key mechanism for regulating gene expression.<sup>19,20</sup>

### Histone-Methylation

Lysine residues on histones can also undergo methylation, which often antagonizes acetylation. This process may involve the addition of one, two, or three methyl groups referred to as mono-methylation, di-methylation, and trimethylation, respectively—each with distinct functional consequences for gene regulation.

### Histone Ubiquitination and Phosphorylation:

The addition of other molecules, such as ubiquitin or phosphate groups (typically on serine residues), can also occur on histone tails. These chemical modifications of histone amino acids play a key role in regulating chromatin structure, allowing it to be transcribed, replicated, or repaired as needed.

### Other Epigenetic Mechanisms Include:

#### Genomic Imprinting

Certain genes exhibit a unique feature known as *genomic imprinting*. These genes, which are scattered across various chromosomes, are characterized by *monoallelic expression*, meaning that only one allele—either maternal or paternal—is transcribed, in contrast to the typical *biallelic expression*. In other words, gene expression depends on the parental origin of the allele.

Genomic imprinting is established in the gametes *prior to fertilization*, during gametogenesis. In male and female gonads, these genes are “marked” as either paternal or maternal, depending on whether they arise in the testis or ovary. Unlike the general epigenetic reprogramming of methylation patterns that occurs in early embryonic development to confer pluripotency, the imprinting marks remain unchanged. These marks define the specific expression pattern of imprinted genes and are preserved throughout development.

Currently, approximately 200 imprinted genes have been identified in autosomes. If a deletion or mutation affects the *active* allele in one of these regions, the individual may experience pathological consequences due to the total absence of transcription from the *imprinted* (and thus silent) allele.<sup>22</sup>

#### The Role of microRNAs

MicroRNAs (miRNAs) are small RNA molecules transcribed by RNA polymerase II, with over 1,000 identified in humans to date. Their expression is tightly regulated in both time and space. As non-coding RNAs, miRNAs regulate various aspects of gene expression, including cell proliferation, apoptosis, and differentiation.

miRNAs can silence chromatin, degrade target mRNAs, or inhibit their translation. Due to these functions, they play a significant role in the pathogenesis of cancer as well as in neurological and behavioral disorders, including those affecting memory.<sup>23</sup>

### Epigenetics, the Brain, and Developmental Disorders

The proper functioning of the genome is closely tied to its epigenomic regulation. *Epimutations*—modifications to normal epigenetic patterns that occur despite an unchanged DNA sequence—can lead to neurodevelopmental disorders. Disorders that do not follow Mendelian inheritance patterns can often be partially explained by epigenetic abnormalities. Several key theories help illustrate this connection:

- The epigenetic landscape is significantly more dynamic than the DNA sequence itself, making it susceptible to modifications triggered by environmental influences, developmental processes, or random (stochastic) events.<sup>8,9</sup>
- Certain epigenetic marks can be inherited transgenerationally alongside the DNA sequence, contributing to clinical traits or disorders observed across multiple generations.<sup>14,17</sup>
- Epigenetic regulation is crucial for maintaining genomic stability and function. Taken together, these factors support interpretations that align with the epidemiological, clinical, and molecular characteristics of complex conditions such as neurodevelopment disorders.

As previously noted, methyl groups selectively bind to CpG dinucleotides and are maintained by the DNA methyltransferase (DNMT) family of enzymes. Additionally, hydroxyl-methyl-cytosine recently recognized in Purkinje cells and other brain cell types contributes to epigenetic patterns that regulate neuronal function.<sup>19,20</sup>

Histone proteins, modified by histone acetyltransferases (HATs) and histone deacetylases (HDACs), determine whether genetic material is active or repressed. The N-terminal methyl-CpG-binding domain (MBD) of the MeCP2 protein binds to methylated DNA regions and, in conjunction with corepressors such as SIN3A, influences gene transcription.

Phenotypic differences observed in monozygotic twins can be better understood through the lens of these epigenetic mechanisms. It is well established that epigenetic variation accumulates gradually over time and becomes more pronounced with increasing divergence in the twins' environments and lifestyles.<sup>6,24</sup>

Epidemiological studies have frequently reported sex-

based differences in the prevalence of certain psychiatric disorders. These disparities may, in part, be due to the epigenetic effects of sex hormones.

Another factor to consider is the age of onset of various conditions. One hypothesis suggests that symptoms emerge once accumulated epigenetic changes surpass a threshold, triggering the manifestation of disease. There is compelling evidence demonstrating that epigenetic mechanisms play a key role in neuronal development, cell differentiation, synaptic communication, and synaptic plasticity—processes that are fundamental to the biological underpinnings of memory and learning.<sup>8</sup>

### Disrupted Epigenetic Mechanisms and Associated Clinical Entities (Genetics & environmental)

The following section outlines key epigenetic disruptions implicated in specific neurodevelopmental and psychiatric conditions, with a focus on autism spectrum disorder (ASD) as a recurring behavioral phenotype.

#### Some of these genetic pathologies, associated with ASD are described in detail below:

##### Fragile X Syndrome (FXS)

**Core phenotype:** Autism spectrum disorder, hyperactivity, intellectual disability, seizures. *Classic physical features:* macrocephaly, elongated face, prominent jaw, large ears, mitral valve prolapse, post-pubertal macroorchidism, and scoliosis.

**Genetic bases:** FXS is the most common inherited form of intellectual disability and is frequently associated with ASD and learning disorders. It results from a CGG trinucleotide repeat expansion within the 5' untranslated region of the *FMR1* gene, located at Xq28. This expansion leads to gene silencing via hypermethylation of the CpG island in cases of full mutation (>200 CGG repeats). Based on the number of CGG repeats, alleles are classified as:

- **Normal:** 5–40 repeats
- **Intermediate (Gray Zone):** 45–54 repeats
- **Premutation:** 55–200 repeats
- **Full mutation:** >200 repeats

The full mutation affects approximately 1 in 4,000 males and 1 in 6,000 females. Premutations are more common, affecting 1 in 260–800 males and 1 in 260 females. Due to X-inactivation, females often present with a milder phenotype.

Approximately 21–50% of individuals with FXS exhibit features consistent with ASD, with prevalence increasing alongside the severity of intellectual disability. Around 90% of males with the full mutation display autistic-like behaviors, although not all meet strict diagnostic criteria based on instruments such as the ADI-R and ADOS.<sup>25,26,27</sup>

The *FMR1* gene encodes FMRP, an RNA-binding protein that regulates synaptic plasticity, mRNA trafficking, and dendritic spine maturation, particularly in the glutamatergic postsynaptic compartment. FMRP binds mRNA at polyribosomes located at the base of dendritic spines and acts as a translational repressor. Its absence results in unchecked protein synthesis and excessive synaptic plasticity, a hallmark of FXS pathophysiology.<sup>28,29,30</sup>

Knockout mouse models of *FMR1* demonstrate exaggerated metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD). mGluRs, particularly subtypes 1 and 5, stimulate protein synthesis at the synapse and contribute to LTD in the hippocampus. The antagonistic interaction between mGluR activity and FMRP function is central to the “mGluR theory” of FXS. According to this hypothesis, reducing mGluR signaling in *FMR1*-deficient mice can normalize synaptic protein synthesis and restore aspects of synaptic function.<sup>28</sup>

Supporting this theory, *Fmr1* knockout mice show reduced levels of AMPA and NMDA receptors, impaired dendritic spine maturation, and increased susceptibility to epileptiform discharges. *Drosophila* models (*dfmr1* knockout) exhibit altered courtship behavior and anatomical defects in the mushroom body—an insect brain region involved in learning and memory—further illustrating the behavioral and structural consequences of FMRP deficiency.<sup>30</sup>

#### The Role of MECP2 in Neurodevelopmental Disorders:

Pathogenic variant in the gene encoding methyl-CpG-binding protein 2 (MeCP2)—a critical epigenetic regulator in the developing brain—are primarily responsible for classic Rett syndrome (RS).

Mutations in *MECP2* are central to Rett syndrome (RS), a severe X-linked neurodevelopmental disorder. Clinically, RS presents with an initial period of apparently normal development, followed by regression, intellectual disability, features of autism spectrum disorder, motor abnormalities (including ataxia), epilepsy, microcephaly, poor eye contact, bruxism, irregular breathing patterns, and scoliosis. Rett syndrome exemplifies how disruption of epigenetic regulation can lead to widespread and progressive neurodevelopmental deficits, underscoring the critical role of epigenetic mechanisms in brain development and function.<sup>31,32</sup>

Other variants of *MeCP2* are also implicated in a broader spectrum of neurodevelopmental disorders, including X-linked severe neonatal encephalopathy in males, developmental delays in both sexes, and, more rarely, autism spectrum disorder (ASD). This broad phenotypic variability underscores the complex and multifaceted role of MeCP2 in neurodevelopmental processes.<sup>33</sup>

**Table1.** Summary of Genetic Medical Conditions related to ASD and Epigenetic Mechanisms:

EPIGENETIC DEFECT	MEDICAL CONDITION (OMIM)	PATHOGENIC	CLINICAL PICTURE
DNA METHYLATION	<p>1.- <b>Fragil X MR S</b> (300624) <u>Gene:</u> FMR1 (309550)</p> <p>2.- <b>Heyn-Sproul-Jackson S.</b> (HSJ) (618724) <u>Gene:</u> DNMT3A (602769) Gain-of-function</p> <p><b>Tatton-Brown-Rahman S.</b> (TBR) (615879) <u>Gene :</u> DNMT3A (60276) Lost-of-function</p> <p>3.-<b>Phelan-McDermid S.</b> (606232) <u>Gene :</u> SHANK3 (606230)</p>	<p>1.- CGG repeat expansion &lt;200 repeats + methylation Gene FMR1 = Suppression of transcription and decreased protein level in postsynaptic neurons in brain</p> <p>2.-Pathogenic Variant of DNMT3 gene: altered chromatin binding specificity resulting. In significant DNA hypermethylation of many genes</p> <p>3.-Abnormal methylation status related with SHANK3 gene expression. a)22q13.2 deletion with SHANK3 haploinsufficiency b)Missense Mutation of SHANK3 in highly CG rich region wich affect methylation status.</p>	<p>Intellectual Dissability/ ASD/ ADHD/ Specific Phenotype</p> <p><b>HSJ:</b>Microcephalic Dwarfism /Global Developmental delay</p> <p><b>TBR:</b> Macrocephaly /Talla stature/ Dismorphic facial features /ID/ASD</p> <p>ID/ ASD/Epilepsy/ Schizophrenia / Bipolar disorder</p>
MECP2 Patogenic variants	<p>1.-<b>Autism Susceptibility X-linked 3-</b> (300496)</p> <p>2.-<b>Encephalopathy Neonatal severe-</b> (300673)</p> <p>3.-<b>Intellectual Developmental disorder X-linked Syndrome 23 –</b> (300055)</p> <p>4.-<b>Rett Syndrome-</b> (312750)</p> <p>5.-<b>Rett syndrome atypical-</b> (312750)</p> <p>6.-<b>Rett Syndrome preserved speach variant –</b> (312750) <u>Gene:</u> MECP2 (300005)</p>	<p>Mutations in the gene encoding MECP2 (methyl-CpG-binding protein 2, a transcriptional repressor that binds methylated DNA, associated with Rett syndrome and other developmental encephalopathies</p>	<p>Rett S.: Normal psychomotor development during the 6 to 18 months of life. Followed by a short period of stagnation then rapid regression.</p>
HISTONES MODIFICATION	<p>a) <b>Rubinstein-Taybi S.Type I.</b> (180849) <u>Genes:</u> CREBBP ( 600140) or EP300 (602700)</p> <p>b)<b>Niikawa-Kuroki S. type I (Kabuki make-up S.)</b> (147920) <u>Gene:</u> KMT2D: (602113)</p> <p>c) <b>Seckel S.type I</b> (210600) <u>Gene:</u> ATR(601215)</p>	<p>a)Histone Acetylation/De-acetylation : CREBBP -EP300 ↓Acetylation of histones ↑Hetrocromatine ↓Expression of essential developmental genes in brain, squeleton anf face</p> <p>b)Histone Methylation: KMT2D gene Abnormal metylathion of H3K27</p> <p>c)Histone Ubiquitination/ Phosphorilation Gene: ATR</p>	<p>Distintive facial features /Broad thumbs and halluces /Short stature/ Moderate to severe ID</p> <p>ID / Specific pheotype /Peculiar facies (Reminiscent of the make-up of actors of Kabuki)</p> <p>Michrocephaly /ID /Dwarfism / characteristic bird face</p>
GENOMIC IMPRINTING	<p><b>Angelman S. (105830) /Prader Willi S.</b> (176270) Gene:UBE3A (601623)</p>	<p>Maternal allele deletions 15q11.2 or imprinting defects, leading to exclusive paternal gene expression <u>Gene:</u> UBE3A</p>	
MicrRNA	<p>Autism Spectrum disorder</p>	<p>miR-137 miR-132 miR-181 Neurons Proliferations and Diferentiation</p>	<p>ASD ASD DI</p>

Importantly, mutations in *MECP2* are identified in approximately 96% of individuals with classic RS, yet they are infrequently found in other conditions such as autism.

Moreover, a consistent genotype–phenotype correlation is lacking, suggesting that the clinical manifestations of *MECP2* mutations may be modulated by additional genetic, epigenetic, or environmental factors.

MeCP2 is a nuclear protein that functions as a transcriptional regulator. It binds to methylated CpG dinucleotides in the DNA, allowing it to interpret epigenetic modifications and modulate gene expression accordingly—without altering the underlying DNA sequence. As such, its effects are epigenetic in nature: potentially reversible and generally non-heritable.

Recent studies have expanded the known functions of MeCP2 beyond methylated promoter regions, showing its involvement in broader chromatin remodeling activities. Notably, MeCP2 interacts with transcription factors such as CREB (cyclic AMP response element-binding protein), which plays a central role in cellular growth, differentiation, and function.

MeCP2 is widely expressed across various tissues, with particularly high levels in the central nervous system. Expression is developmentally regulated: it is low during early embryogenesis and increases postnatally, reaching peak levels in mature, post-mitotic neurons. This pattern indicates that MeCP2 plays a more prominent role in neuronal maturation and synaptic stabilization than in neurogenesis.<sup>30,31</sup>

Neuropathological analyses in girls with RS have revealed reduced neuronal size and dendritic complexity, indicating impaired neuronal maturation and deficits in synaptic connectivity and plasticity—processes essential for cognitive functions such as learning and memory. In addition to its role in neurons, MeCP2 is also expressed in astrocytes, which contribute to neuronal support and maturation. Disruption of MeCP2 in astrocytes has been shown to further exacerbate the neurodevelopmental deficits characteristic of RS.<sup>32</sup>

Interestingly, while MeCP2 deficiency leads to neurodevelopmental impairment, MeCP2 overexpression—as observed in MECP2 duplication syndrome—is also pathogenic. This rare condition is characterized by intellectual disability, autism, epilepsy, anxiety, and premature mortality, highlighting the necessity of tightly regulated MeCP2 expression for normal brain development and function.<sup>33</sup>

### Phelan-McDermid Syndrome (PMS)

**Core Phenotype:** tall stature, dolichocephaly, prominent brow, prognathism, prominent ears, and saddle nose. Global developmental delay, intellectual disability, autism spectrum disorder (ASD), epilepsy, and reduced sensory sensitivity.

**Genetic Basis:** 22q13 deletion, affecting the *SHANK3* gene. PMS is primarily caused by haploinsufficiency of chromosome 22q13, typically involving a deletion or structural variant affecting the *SHANK3* gene. This gene encodes a postsynaptic scaffolding protein essential

for synapse formation, maturation, and maintenance. It contains five CpG islands, which serve as sites for alternative splicing and methylation. The differential methylation status of these islands is associated with isoform-specific expression and has been implicated in autism pathophysiology. Furthermore, *SHANK3* has been linked to long non-coding RNAs (lncRNAs), especially within the cerebral cortex, further highlighting its complex role in transcriptional and epigenetic regulation.<sup>34,35</sup>

### Angelman Syndrome (AS)

**Core phenotype:** Severe intellectual disability, autistic traits, frequent unprovoked laughter, ataxia, tremors, motor incoordination, epilepsy, early feeding difficulties, gastroesophageal reflux, and sleep disturbances.

**Genetic Basis:** AS is caused by the loss of function of the maternally inherited *UBE3A* gene, which encodes the E3A ubiquitin-protein ligase. This gene is subject to genomic imprinting, with predominant maternal expression in neurons.<sup>37,38</sup>

The disorder can arise from:

- A 5–7 Mb deletion in the maternal 15q11.2–q13 region (most severe phenotype due to concurrent deletion of GABA receptor subunit genes),
- A point mutation in the maternal *UBE3A* allele,
- Paternal uniparental disomy (UPD) of chromosome 15,
- An imprinting defect preventing maternal allele activation.

Pathogenic variants and imprinting defects affecting *UBE3A* can also carry a significant risk of familial recurrence.

Functionally, *UBE3A* loss impairs synaptogenesis and limits activity-dependent synaptic remodeling. These disruptions in synaptic architecture are closely associated with the cognitive and behavioral phenotype observed in AS.<sup>37</sup>

### Other Conditions Related to Autism:

The scenario linked to autism involves the post-synaptic neuron, where proteins are interconnected in a very complex interaction. We could describe autism as a “synaptopathy” in which mGluR5 interacts with numerous postsynaptic proteins, many of which have already been identified as candidates for autism spectrum disorders. These include HOMER, SHANK, NEUROLIGIN, NEUREXIN, along with hundreds of other genes responsible for genetic syndromes that show a clearly higher incidence of autism, as we showed before.<sup>9</sup>

Finally, the observation of improved social behavior in autistic children during febrile episodes has been linked

to dysregulation in the Locus Coeruleus-Noradrenergic (LC-NA) system, which has a regulatory system closely associated with epigenetic control patterns. This finding leads us to suspect that in ASD, the neuronal network may be intact, but the epigenetic control mechanisms may be “temporarily modified” by environmental events such as a febrile episode.<sup>39</sup>

We know that the epigenome can be affected by positive experiences, such as supportive relationships and learning opportunities, or negative influences, such as environmental toxins or stressful life circumstances that leave a unique epigenetic “signature” on the genes. These signatures can be temporary or permanent, and both types affect how easily the genes are turned on or off.

### **Environmental Factors Capable of Modifying the Normal Epigenetic Pattern:**

In recent years, our understanding of the potential impact of environmental factors on health and disease has increased. It is known that many environmental factors can directly generate changes during embryonic development, leading to congenital malformations by disrupting normal embryonic mechanisms as cell division, differentiation, migration, or apoptosis (e.g., thalidomide and limb malformations). Conversely, some non-disruptive chemical factors can produce changes in the embryo and fetus that become evident when the fetus reaches youth or even adulthood (e.g., children born with low birth weight have a higher risk of suffering from coronary heart disease, stroke, type II diabetes, metabolic syndrome, and osteoporosis in adulthood).<sup>40,41</sup>

During embryonic development in mammals, mothers transfer environmental factors such as nutritional resources to their embryo or fetus through the placenta or breastfeeding. The size of the offspring is partly linked to the size of the mother; although other growth factors may also play a significant role. This includes growth factors that exhibit an imprinting pattern, which can be modified by genetic errors as well as environmental factors. Examples of this condition include Beckwith-Wiedemann and Silver-Russell syndromes.

Attention has been given to malnutrition during pregnancy and its association with diseases in youth or adulthood. However, this variable appears to be as important as overexposure to nutrients, which can also lead to potential diseases in adulthood. The periconceptional period has been identified as one of great vulnerability. Studies have shown that rats exposed to a low-protein diet before embryo implantation exhibited a higher rate of malformations than those fed normally, and those that were born had low birth weight and developed hypertension in adulthood.<sup>42</sup>

Some rats, as Agouti, display different coat colors

depending on environmental stimuli and the type of nutrition they receive, even though they are genetically identical in this trait. In humans, an increase in the incidence of hypertension in adulthood has been observed in relation to maternal dietary imbalances during pregnancy, which affect the angiotensin/renin axis and the proper functioning of the nephrons.<sup>43</sup>

Analysis of diverse epidemiological investigations indicates that certain environmental factors, including advanced parental age, preterm birth, delivery complications, and exposure to toxic metals, drugs, air pollutants, and endocrine-disrupting chemicals, are linked to an increased risk of ASD through various mechanisms such as oxidative stress, inflammation, hypoxia and its consequences, changes in neurotransmitters, and disruption of signaling pathways.

Studies have shown that exposure to bisphenol, and phthalates can disrupt normal immune function in the brain, leading to chronic or excessive neuroinflammation. This disruption of immune function can contribute to the development of neurological disorders, including ASD. Furthermore, these factors may activate microglia, increasing pro-inflammatory cytokine production and astroglia-mediated oxidative stress, exacerbating neuroinflammation. They may also modulate the epigenetic profile of cells through methyltransferase expression, thereby affecting neurodevelopment.<sup>9</sup>

On the other hand, pregnancy-related factors such as maternal diabetes, maternal obesity, and cesarean section show a weaker association with ASD risk. These findings highlight the importance of environmental factors in the etiology of ASD and emphasize that more focused research is needed to target the risk factors associated with ASD.<sup>44</sup>

Moreover, exposure to toxins such as alcohol, tobacco, cocaine, and marijuana influences the developing central nervous system (CNS). Although not all children display altered physical characteristics at birth, many studies indicate a higher rate of learning disorders and attention deficits in children, as well as a greater predisposition among young people to consume these toxins compared to the unexposed population.<sup>8,45</sup>

Diabetic pregnancies, whether pregestational or gestational, are associated with numerous complications. They are mainly linked to disturbed fetal growth, an increased rate of pregnancy complications, and postnatal growth and developmental issues such as learning difficulties, ADHD, and a slight increase in the risk of ASD.

**We describe some of the most relevant and well-known causes of epigenetic changes, triggered by environmental factors:**

**Fetal Alcohol Spectrum Disorder (FASD):** Orientation

phenotype: +/- microcephaly +/- intellectual disability +/- autistic behaviors +/- ADHD. Maternal consumption of alcoholic beverages (ethanol) can produce varied effects, with a frequency of 1 to 3 per 1,000 live births.<sup>46</sup> It is estimated that FASD is detected in 5-10% of those exposed, and some effects are related to the dose, duration, and timing of exposure, possible maternal malnutrition, and genes such as ADH/ALDH that could potentiate its deleterious effects. Its pathogenesis is linked to alterations in normal DNA methylation patterns, as it affects folate metabolism, reducing its bioavailability by decreasing S-adenosylmethionine (SAM). Mice exposed to alcohol showed alterations in the acetylation of certain histones (H3-H4) in the brain, with a reduction in the transcription of the underlying DNA. Non-coding RNAs are also compromised, and significant intracellular modifications have been observed that induce changes that ultimately result in neuronal apoptosis. Animal models have also shown that alcohol exposure causes alterations in the structure and activity of chromatin, indicating that ethanol can affect all epigenetic mechanisms.<sup>46,47</sup>

Several authors have analyzed the impact of maternal alcohol consumption on offspring, but the effect of paternal alcohol consumption has been poorly investigated. Further studies focusing on paternal consumption are needed to shift towards a paradigm that acknowledges the decisive paternal contribution to the deleterious transgenerational effects of alcohol intoxication, rather than solely considering maternal consumption as the cause.

**Cannabis: Possible Neurodevelopmental Defects +/- Autism:** In recent years, particular attention has been paid to epigenetic changes that, due to lifestyle and environmental factors, modulate gene expression without altering the DNA sequence, thus creating conditions for potential disease susceptibility.<sup>48</sup>

The endocannabinoid system affects reproduction at multiple levels in both sexes, influencing the production of high-quality gametes and pregnancy outcomes. Moreover, the possible transmission of deregulated epigenetic marks to the embryo via parental gametes has recently been reported; thus, the contribution of the male gamete to the embryo has been revised with the introduction of paternal epigenetic inheritance.

In the gonads, the endocannabinoid system mediates spermatogenesis progression and folliculogenesis, including oocyte maturation and ovulation in females. In reproductive tracts, it also controls sperm maturation, acrosome reaction, fertilizing ability, early embryo development, implantation, embryo growth, and delivery. Exposure to delta-9-tetrahydrocannabinol ( $\Delta$ 9-THC) during pregnancy has several adverse outcomes, such as low body weight at birth, as well as developmental and behavioral

issues, particularly neurodevelopmental, musculoskeletal, and cardiovascular defects, or deregulation of the immune system, or congenital/teratogenic defects in children. However, the ability of cannabis to heritably impact the sperm epigenome has been poorly studied but is highly relevant.<sup>49,50</sup>

Some active ingredients in cannabis, such as delta-9-tetrahydrocannabinol ( $\Delta$ 9-THC), which is the main psychoactive component in cannabis, and cannabidiol (CBD), can decrease sperm concentration and directly alter the methylation pattern of paternal DNA, potentially affecting the neurodevelopment of offspring.<sup>51</sup>

One concerning situation is the increase in drug consumption, particularly illicit drugs like cannabis, referred to as "recreational use," which romanticizes drug addiction, especially among young consumers. These drugs interfere with the normal production and quality of gametes in both sexes, affecting pregnancy as an endpoint. In this context, the ability of cannabis to heritably impact the sperm epigenome remains underexplored but is highly relevant, considering the higher rates of recurrent cannabis consumption in boys and men compared to women; the ongoing debate regarding cannabis legalization for recreational use; and the erroneous perception of recreational cannabis as "safe" for health.

Emerging evidence from both human and animal models indicates that cannabis and its psychoactive component, THC, directly affect the sperm epigenome at the DNA methylation level, with possible consequences for offspring health.

**Chronic Stress in Pregnant Mothers:** Chronic stress in mothers is associated with elevated blood levels of cortisol, which can alter the methylation patterns of embryonic DNA in specific regions of the CNS, such as the hypothalamus, and is linked to structural alterations in the amygdala, leading to neurodevelopmental disorders.<sup>52,53</sup>

Environmental factors such as chronic prenatal stress have been shown to induce stable epigenetic modifications, particularly in hypothalamic cells. These alterations result in persistent changes in the methylation profile of genes regulating the hypothalamic-pituitary-adrenal (HPA) axis. Offspring exposed to sustained maternal stress exhibit an increased susceptibility to mood disorders such as depression and anxiety in adulthood, likely due to the aberrant transcriptional activation of stress-responsive circuits that, under normal conditions, would be epigenetically silenced via methylation.<sup>54</sup>

Numerous studies have connected a lack of maternal care, child abuse, and early life stressors to significant alterations in methylation patterns in CNS regions. Toxic stress also promotes changes in brain architecture, causing reduced brain volume and dysfunction of the

neuroendocrine and limbic systems, in addition to affecting structural and functional neuroplasticity.

The risk of neuropsychiatric and behavioral disorders, such as depression, generalized anxiety disorder, obsessive-compulsive disorder, increased risk of substance abuse, autism spectrum disorder, and attention-deficit/hyperactivity disorder also rises significantly. Research indicates that supportive and responsive relationships with caring adults early in life can prevent or reverse the harmful effects of the body's response to toxic stress.<sup>55</sup>

### Treatments that Act on Epigenetic Patterns

The potential to modify epigenetic patterns across a wide range of conditions—ranging from aging, oncological diseases, neuropsychological disorders, to other common adult conditions like hypertension, stroke, obesity, and metabolic syndrome—is currently the subject of significant research.

Techniques aimed at evaluating genome methylation patterns and other forms of epigenetic modifications in different individuals, diseases, ages, and tissues are being extensively developed. These studies promise to enhance our understanding and open a large field of research regarding possible preventive behaviors—dietary, pharmacological, and others—that could allow us to reverse pathological epigenetic processes.<sup>56</sup>

Certain pharmacological agents that influence the epigenetic landscape have demonstrated significant effects on long-term potentiation (LTP), a key mechanism underlying synaptic plasticity and memory formation in the mammalian brain. DNA methyltransferase (DNMT) inhibitors, such as zebularine, have been shown to impair LTP induction within the murine hippocampus. In contrast, histone deacetylase (HDAC) inhibitors—including sodium butyrate and trichostatin-A enhance synaptic plasticity by facilitating LTP in both the hippocampus and amygdala.

There are drugs that can control acetylation/deacetylation processes by selectively blocking the enzymes involved. These drugs have been successfully used in the treatment of certain tumors and neurological diseases.

Valproic acid and benzodiazepines, for example, are histone deacetylase (HDAC) inhibitors, allowing DNA to remain in an “active” state in specific regions of the CNS. There is extensive pharmacological development aimed at creating drugs that inhibit histone methyltransferase (HMT).

Other drugs with useful activity include histone demethylases, which would also allow the activation of tumor suppressor genes silenced by methylation. A non-selective monoamine oxidase inhibitor, such as

tranylcypromine, used as an antidepressant, has inhibitory functions against lysine methylation (lysine-specific demethylase, LSD).<sup>8,9</sup>

While most environmental factors do not affect DNA sequences, they do influence gene expression through modifications to normal epigenetic patterns. Epigenomic changes have been described in connection with environmental pollutants (agricultural chemicals such as vinclozolin), nutritional factors (folates), inorganic toxins (arsenic), and drugs (cocaine, alcohol, nicotine). Some of these changes affect somatic cells, while others alter the epigenetic patterns of germ cells, transcending defects trans generationally.

Therefore, we are not only the result of our genetic makeup (DNA) but also a consequence of the behaviors, habits, and environment of our parents, or even our grandparents.

Recognizing altered epigenetic factors in specific entities consistently associated with autism allows us to understand some of the mechanisms that could be triggering these disorders and possibly develop specific therapies for each in the future. Ultimately, this knowledge may provide keys to generating better lifestyle habits that lead to a reduction in the incidence of neuropsychiatric and oncological diseases, among others. Certain factors, such as maternal stress, can also produce effects during the adolescence of the unborn child.

**X Fragile Syndrome:** The feasibility of acting on altered epigenetic mechanisms has led to numerous therapeutic trials aimed at reversing the process and, consequently, the unwanted clinical defects. This includes studies promoting DNA demethylation of the FMR1 gene promoter (related to Fragile X Syndrome) using 5-azacytidine and 5-azadeoxycytidine (two drugs used in myeloid leukemia), which are still in the preclinical stage.<sup>57</sup>

There are currently several treatments under development targeting different biological mechanisms. Some are aimed at the mGluR5 pathway, which is overactivated because of the absence of FMRP, such as Mavoglurant and Basimglurant. Others have a GABAergic modulatory action, like Ganaxolone, and some agents are directly focused on the altered epigenetic mechanism, promoting demethylation of the gene promoter—these are still in the preclinical phase. Metformin, a drug used for type 2 diabetes, has also been tested, as there is some evidence it may help normalize certain dysregulated pathways in the condition. Finally, gene therapy aims to restore gene function and enable the production of the missing protein.

**Rett Syndrome treatment:** The discovery of MECP2 variants as the principal etiology for Rett syndrome by Amir et al. was fundamental in the expansion of clinical investigations.<sup>31</sup>

The current treatment options for the common clinical issues related to this pathology as many others, include specific pharmaceutical agents for epilepsy, gastroesophageal reflux, constipation, anxiety, sleep, muscle rigidity/hypertonia, pain, prolonged QTc, and health maintenance.

Specific agents directed at improving overall outcomes have been investigated, several pharmacologic agents have been testing over the past twenty years.

Initial clinical trials were ineffective, but other studies worldwide promoted significant interest from pharmaceutical firms resulting in several clinical trials. While some of these have been unrewarding such as Sarizotan, others have been quite promising including the approval of Trofinetide by the FDA in 2023 as the first agent available for specific treatment.

Blarcamesine has been trialed in phase 3 trials, 14 agents have been studied in phase 2 trials, and 7 agents are being evaluated in preclinical/ translational studies.

Gene replacement therapy has advanced through translational studies to two current phase 1/2 clinical trials (Taysha102 and Neurogene-401). Additional genetic therapies are also under study including gene editing, RNA editing, and X-chromosome reactivation. Taken together, progress in understanding over the past 40 years has been remarkable. This suggests that further advances can be expected.<sup>58,59</sup>

Angelman Syndrome treatment: At present, there is no cure for Angelman Syndrome, but several treatment approaches are available to manage symptoms and improve quality of life.<sup>61</sup>

These include physical therapy, occupational therapy, speech therapy, and behavioral interventions. Anti-seizure medications are commonly used to control epilepsy, which affects many individuals with the syndrome.

Additionally, promising therapies are under development. These include gene therapy and antisense oligonucleotide (ASO) treatments designed to activate the normally silent paternal copy of the UBE3A gene in neurons. One such experimental ASO treatment, known as GTX-102, is currently undergoing clinical trials. While these therapies are still investigational, they offer hope for targeting the root cause of the disorder in the future.<sup>60,61</sup>

Phelan-McDermid Syndrome treatment: Modification of the histone acetylation pattern in the SHANK3 gene (related to Phelan-McDermid Syndrome), mediated by a histone deacetylase inhibitor, Romidepsin, has shown encouraging results in mice deficient in this gene, promoting social development.<sup>62</sup>

## Conclusions

The interaction between genetic predispositions and

environmental exposures shapes the epigenetic landscape, affecting outcomes in conditions such as Autism Spectrum Disorder (ASD), intellectual disabilities, and related syndromes. Understanding these mechanisms opens new avenues for prevention, diagnosis, and treatment.

Epigenetics offers critical insight into the normal functioning of organisms, including regulatory processes, molecular interactions, and the influence of both genetic and environmental factors on neurodevelopment. Numerous genetic disorders involve disrupted epigenetic patterns, which can result in a broad spectrum of pathological conditions—many of which affect the central nervous system, as illustrated by the previously described syndromes.

A wide array of environmental factors is known to interfere with epigenetic mechanisms, thereby influencing neurodevelopment. While some of these factors produce clear and measurable outcomes, others have more insidious effects that may not be immediately apparent or easily correlated with specific time points. For instance, maternal stress during pregnancy can lead to neurodevelopmental consequences that emerge later in the offspring's adolescence.

Epigenetic reprogramming is particularly critical during embryonic and early postnatal development. Dysregulation during these sensitive periods has been associated with a variety of developmental disorders. Investigating the impact of environmental agents that alter normal epigenetic functioning allows for a deeper understanding of the dynamic relationship between genes and the environment across different life stages and contexts.

Importantly, many of these environmental influences may begin exerting their effects even before conception, through modifications in the epigenetic profiles of both male and female gametes. In certain regions—particularly agricultural areas—public health warnings have led to awareness campaigns regarding the indiscriminate use of pesticides and herbicides. In parallel, addressing the broader social determinants of health remains urgent: a significant portion of the global population lives under suboptimal conditions, facing basic nutritional deficiencies, inadequate prenatal care, and limited access to healthcare services.

Within this framework, early identification of subtle deviations in neurodevelopmental trajectories, combined with timely therapeutic intervention, may harness epigenetic mechanisms linked to brain plasticity. Evidence suggests that such interventions can lead to meaningful functional improvements, independent of the underlying etiology, thereby underscoring the importance of early action during critical periods of development.

Understanding and mitigating the epigenetic consequences of environmental exposures is vital not only for the prevention of disease but also for the promotion of optimal neurodevelopmental health. Public policies aimed at reducing exposure to harmful agents, ensuring equitable access to healthcare, and supporting early developmental screening and intervention should be integral components of a comprehensive public health strategy.

### Conflict of interest

None to declare.

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