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# Epigenetics: The Impact of Trauma on Gene Expression and Transgenerational Transmission

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**Abstract**

This study examines the relationship between childhood trauma and epigenetic changes in genes that regulate the stress response. Traumas such as violence or lack of control experienced at an early age can disrupt the long-term regulatory mechanisms of the hypothalamic-pituitary-adrenal (HPA) axis, leading to impaired stress responses. Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs play an important role in the stress response by regulating gene expression without altering the DNA sequence. Genes such as FKBP5, MAOA, and NR3C1, which are important in stress regulation, are sensitive to childhood trauma; changes in their methylation and transcription levels affect neuronal function, synaptic plasticity, and emotional regulation. These modifications have been associated with increased psychiatric risks such as depression, post-traumatic stress disorder (PTSD), and antisocial behaviors. In addition, the intergenerational transmission of trauma is also considered; epigenetic changes that occur at an early age can be passed down through generations, increasing children's susceptibility to stress. The tissue specificity of epigenetic changes and the interaction between genetic and environmental factors are also important factors. Understanding these mechanisms provides a foundation for understanding the biological memory of childhood trauma and its impact on long-term health outcomes. At the same time, it suggests potential targets for early interventions and therapeutic strategies and provides guidance in understanding the psychological and physiological effects of trauma.

**Keywords:** epigenetics, trauma, genetic changes

## 1. Introduction

Trauma can affect individuals within a generation and future generations (transgenerationally) through biological and environmental influences. Recent studies suggest that environmental stressors can induce long-lasting epigenetic modifications that influence stress responsiveness and may contribute to the intergenerational transmission of trauma [1], [2]. The term epigenetics was first proposed by Conrad Hal Waddington in 1940. It refers to changes in gene expression without changes in the underlying DNA sequence. These changes are permanent but reversible. These changes occur through multiple molecular mechanisms (Figure 1), such as DNA methylation, hydroxymethylation, histone modifications, nucleosome positioning, 3D genome organization, and non-coding RNAs (ncRNAs). Collectively, all of these mechanisms biologically link stress-related genes to the ability to regulate gene expression, mediating long-term effects of trauma, and influencing health outcomes [3]. Early-life adversity has been shown to alter epigenetic regulation of stress-response genes, thereby increasing vulnerability to psychiatric disorders later in life [2], [4].

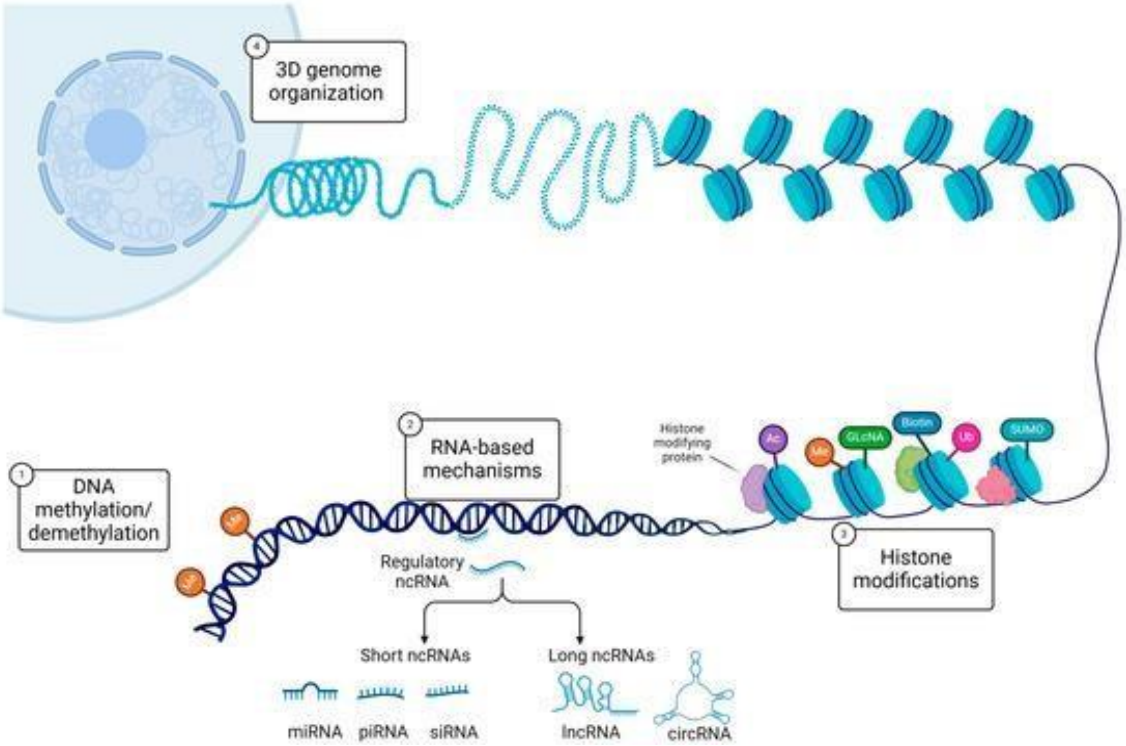


**Figure 1.** Epigenetic mechanisms in gene regulation: (1) DNA methylation and dimethylation. The addition or removal of methyl groups to the cytosine nucleotide, (2) RNA-based mechanisms, (3) Histone modifications are modifications that occur during translation, (4) 3D genome organization [5].

The mechanisms that regulate gene activity (epigenomes) change throughout life. Epigenetic marks are erased and re-established during early development. In adults, these genes change in response to environmental influences, for example, during inflammation and infection in immune cells, epigenetic changes cause genes to be activated or silenced. Research over the past decade has shown that exposure to environmental toxins and nutritional deficiencies can, in some cases, cause epigenetic changes that can be passed down through generations [5].

## 2. Epigenetic Mechanisms

### 2.1. DNA Methylation

DNA methylation is the most common epigenetic mechanism. This mechanism is the covalent attachment of methyl groups to the C-5 position of the cytosine ring of DNA by DNA methyltransferases. In plants, cytosines are located both symmetrically and asymmetrically, and methylation occurs here. In mammals, DNA methylation occurs predominantly at cytosines within CpG dinucleotides, although non-CpG methylation can also occur in specific cell types such as embryonic stem cells and neurons. More than 98% of methylation occurs in somatic cells. This also occurs at CpG dinucleotide in somatic cells. A quarter of all methylation appears in a non-CpG context in embryonic stem cells [6].

It was first discovered by Hotchkiss in 1944. When DNA methylation occurs in the promoter region, it usually acts as a repressor of gene transcription. DNA methylation represents one of the most extensively studied mechanisms through which environmental experiences become biologically embedded and influence long-term gene expression patterns [3]. DNA methylation is a key player in processes such as X chromosome inactivation, regulation of gene expression, and silencing of retroviral elements. During the process, the Tet enzyme (translocation) accelerates the formation of 5hmC (5-methylcytosine). It is then hydroxylated by Tet. It is then deaminated by AID/APOBEC enzymes. The deaminated molecule is removed by Tet enzymes by BER, which removes damaged or altered nucleotides and incorporates molecules (Thy, 5hmU, 5Fc, 5caC) that will be replaced by cytosine. Methylated cytosines are read by MBD (methyl-CpG) proteins and UHRF proteins, and either silence gene expression or enhance methylation during replication [7].

### 2.2. Non-Coding RNAs (ncRNAs)

Each of the RNA classes has specific cellular functions. Some of these functions involve chromatin remodeling during or after transcription in gene expression. The types of RNA that cause epigenetic modifications are microRNA (miRNA), small interfering RNA (siRNA), promoter-associated RNA (PAR), enhancer RNA, and non-coding RNA. The most common types of non-coding RNA are ncRNA and lncRNA. MiRNA and siRNA are involved in the regulation of approximately 50% of gene expression by degrading mRNA. PAR has been shown to have activating effects. This type of RNA enhances transcription [7].

### 2.3. Histone Modifications

Histone protein is a molecule that causes DNA to be transformed into nucleosomes and chromatin. Changes in histones affect chromatin structure. Histone modifications include acetylation, deacetylation, histone methylation, and histone phosphorylation. Histone acetylation occurs at lysine amino acids. Lysines in the histone core and tail can be acetylated. Histone acetylation generally relaxes chromatin structure, increasing DNA accessibility and promoting gene transcription. In the deacetylation process, chromatin is condensed by HDAC, and gene expression is repressed. Finally, histone phosphorylation occurs at serine and tyrosine residues located in the histone tail [8].

### 2.4. Stress and the HPA Axis

Trauma, especially childhood trauma, affects health. So why does it affect? Stress is classified into 3 categories: “good stress”, “tolerable stress”, and “toxic stress”. The central biological pathway that responds to stress is the hypothalamic-pituitary-adrenal (HPA) axis. Walter Cannon proposed the fight-or-flight model of stress response in 1914. Recent studies suggest that changes in the HPA axis are related to the process of coping with stress. Stress and trauma experienced during childhood alter the HPA axis. Stress also causes epigenetic effects on genes. These genes are as follows:

FKBP5 encodes FK506-binding protein 51 (FKBP51), a co-chaperone that regulates glucocorticoid receptor sensitivity and HPA-axis feedback. Gene expression is affected by genetic variants of FKBP5. For example, SNP rs1360780, which is associated with a change in the three-dimensional structure of a genetic locus, affects the physical contact between the transcription start site and hormones located in intron 2. These changes cause different variants of the FKBP5 gene to alter the sensitivity of the glucocorticoid receptor. Thus, HPA axis activity produced differences in the regulation of neuronal function and synaptic plasticity. Studies demonstrate that the rs1360780 risk allele (T) is associated with childhood trauma and increases the risk of many psychiatric disorders [9]. Allele-specific demethylation of FKBP5 following childhood trauma has been shown to alter glucocorticoid receptor regulation, providing a molecular explanation for gene–environment interactions in stress-related disorders [10].

The MAOA gene is located on the X chromosome and encodes MAO A and B, which break down dopamine, serotonin, and noradrenaline, genes related to the effects of childhood trauma. MAOA and MAOB regulate the degradation of monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, thereby influencing cognition, emotion, and behavior. Brunner syndrome is caused by a point mutation in exon 8 of the MAOA gene and is characterized by aggressive behavior.

Different health outcomes seen after stressful life events have been associated with a variable number of tandem repeats (VNTRs) in the MAOA gene. VNTR is a short repeat of 20−100 nucleotides and is involved in the regulation of gene expression.

There are CCCCTCCCCCG and CTCCCTCCCCCG VNTRs located near the transcription start site of MAOA, which are associated with antisocial behavior in women after childhood trauma. Additionally, children who have the risky MAOA u-VNTR genotype and are maltreated in childhood are more likely to develop psychiatric disorders such as conduct disorders, antisocial personality, and violent crime in adulthood.

The NR3C1 gene is one of the genes studied in the HPA axis. Childhood trauma and stress alter the methylation of this gene. NR3C1 encodes the glucocorticoid receptor. Childhood trauma in humans increases NR3C1 methylation. One of the landmark studies in this field demonstrated increased methylation of the glucocorticoid receptor gene (NR3C1) in the hippocampus of suicide victims with a history of childhood abuse, suggesting long-term epigenetic programming of stress-response pathways [11].

In salivary DNA samples from a specific type of childhood trauma, parental loss, hypermethylation of CpGs near the NGFI-A binding site in the NR3C1 gene was observed in association with the L-allele (3 or 5 repeats) of the MAOA u-VNTR. Stress during adolescence further increases methylation of the NR3C1 gene. It has become clear that methylation within the NR3C1 gene promoter can be gender-specific. Increased methylation of the NR3C1 promoter has been associated with altered glucocorticoid receptor expression and dysregulated stress responses. Among survivors of the Rwandan genocide, men had a lower risk of PTSD [9]. Collectively, evidence indicates that childhood adversity influences stress-response pathways through epigenetic modifications of genes such as FKBP5 and NR3C1. These alterations contribute to dysregulation of the HPA axis and increase susceptibility to depression, anxiety, PTSD, and other psychiatric disorders [4], [12].

## 3. Transmission of Trauma from Generation to Generation

According to epidemiological studies, 70% of people have experienced at least one traumatic event in their lifetime, and 30% have experienced four or more. These statistics have caused concern, and researchers have investigated the causes, pathophysiology, and transmission mechanisms of trauma to address this concern.

There are two important mechanisms to explain the intergenerational transmission of trauma:

1. Socio-environmental transmission (parenting styles, discrimination, etc.)
2. Biological conditions (epigenetic inheritance) (Figure 2)

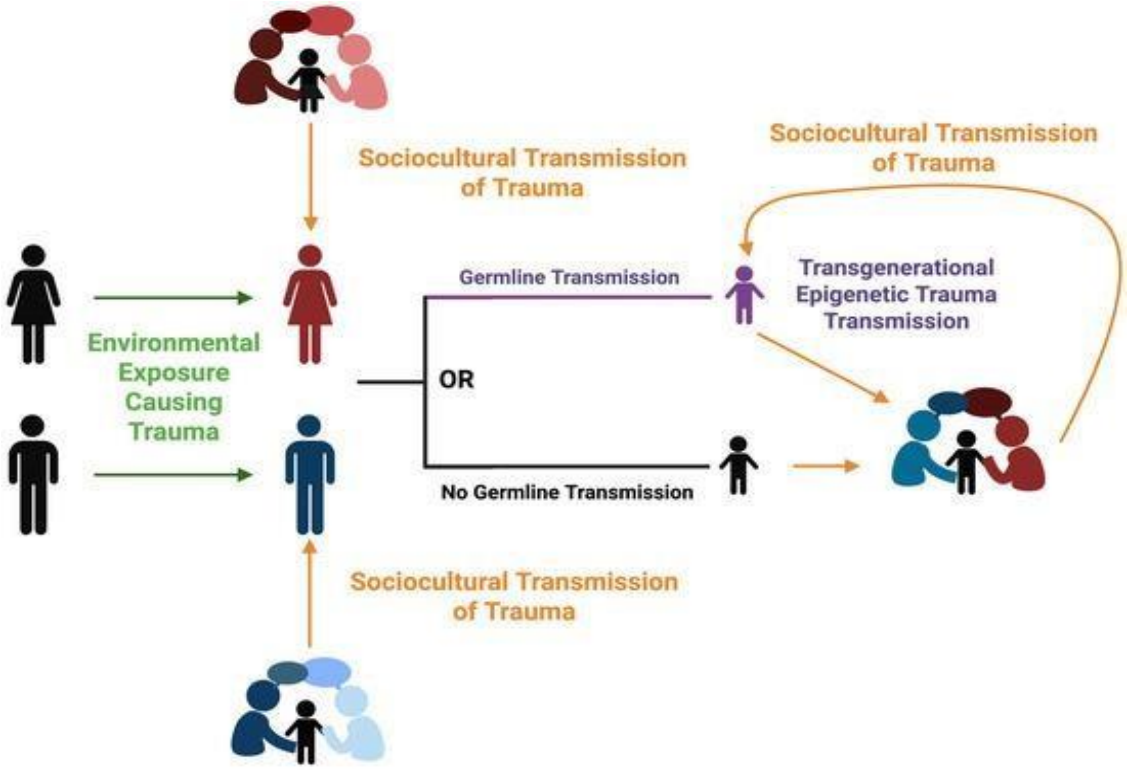


**Figure 2.** The rise and transmission of intergenerational trauma [13].

Studies have found that adults' maladaptive attachment styles increase the risk of transmitting trauma to their children. One of the important elements of the transmission of social trauma is the environment and external factors. These factors increase vulnerability to trauma and hinder the ability to cope with adversity. Factors such as poverty, discrimination, exposure to violence, and lack of social support increase the risk of trauma and limit the resolution of the issue. If such conditions persist frequently, their effects can be preserved across generations and passed on to other generations. For example, a child growing up in an area with high crime rates is more likely to experience trauma, such as being bullied, being sexually abused, etc. Such conditions create obstacles to trauma resolution. Unresolved traumas are more likely to be passed down from generation to generation [13].

The terms intergenerational and transgenerational have been proposed to more fully describe epigenetic inheritance. Intergenerational epigenetics are epigenetic changes that occur in both parents and offspring after exposure to environmental stressors. For example, if a pregnant woman drinks alcohol, both the fetus and the ovaries are exposed to the alcohol (Figure 3).

Transgenerational epigenetic transmission is the transmission of epigenetic modifications that cannot be caused by environmental exposure. These epigenetic changes must be transmitted directly from the parent's epigenome to the embryo.

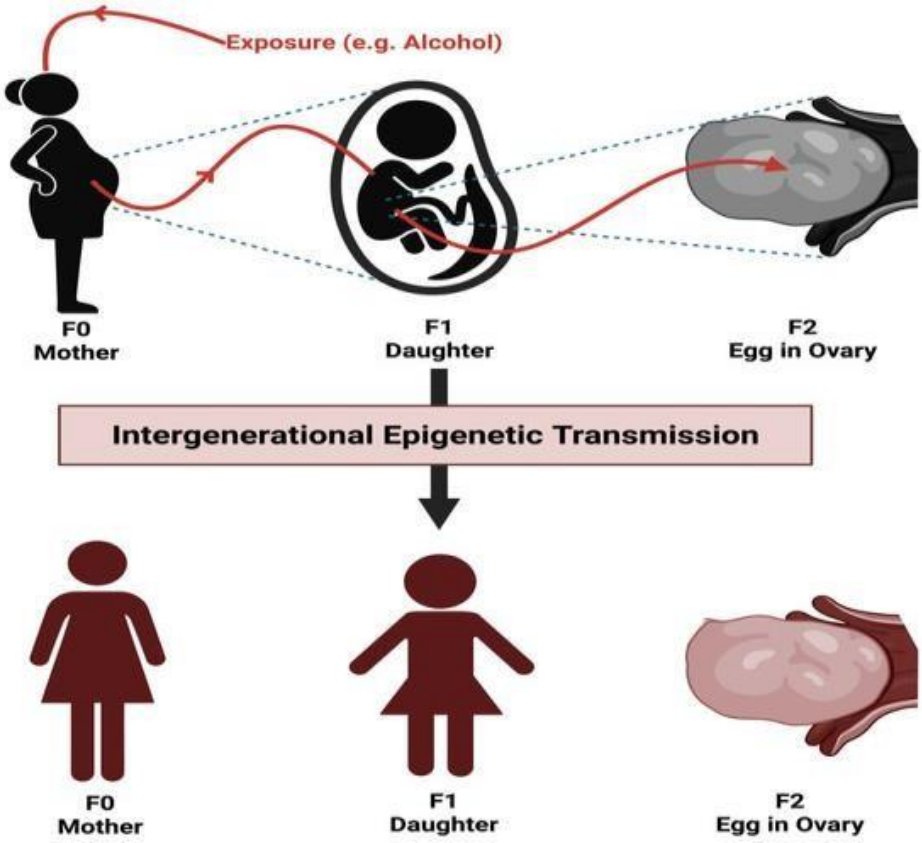


**Figure 3.** Mechanism of transmission of epigenetic trauma [13].

One of the most widely studied examples of intergenerational trauma involves Holocaust survivors and their descendants. Previous studies have shown that children whose parents survived the Holocaust are more likely to experience mental health difficulties than individuals without a family history of Holocaust exposure. The psychological effects of this trauma may persist across multiple generations. In addition to psychosocial influences, biological mechanisms have also been investigated. Yehuda et al. demonstrated altered methylation patterns of the FKBP5 gene in Holocaust survivors and their offspring, suggesting that severe trauma may affect epigenetic regulation of stress-response pathways across generations. These findings provide evidence that trauma transmission may involve both environmental and biological mechanisms [13], [14]. Although evidence supports epigenetic contributions to trauma transmission, environmental influences such as parenting behaviors, family dynamics, and social conditions also play significant roles in shaping outcomes across generations [15].

## 4. Conclusion

This review provides information on the effects of trauma on genes and the transmission of these effects to generations. Childhood traumas and stresses affect living organisms epigenetically and cause changes in gene expression. DNA methylation, dimethylation, histone modifications, and non-coding RNAs, particularly in genes such as FKBP5, MAOA, and NR3C1 that regulate the HPA axis, are involved in shaping stress responses and behavioral mechanisms. These changes have been linked to psychiatric disorders, stress sensitivity, and other health problems. The effects of trauma on genes are being investigated, and the processes involved in the mechanism of transmission from generation to generation are being identified. The mechanism

of epigenetic transmission is influenced by the interaction of living things with the environment, nutrition, age, and gender. Understanding epigenetic mechanisms offers important opportunities for the prevention of trauma-related diseases and the development of effective interventions. Future research should focus on studying in more depth the transmission of these mechanisms from generation to generation and their specificity in different tissues and cells. Epigenetic mechanisms are increasingly recognized as central contributors to the pathophysiology of stress-related psychiatric disorders, including depression, anxiety disorders, and PTSD [16]. Future longitudinal and multi-omics studies integrating epigenomics, transcriptomics, and environmental exposure data will be critical for elucidating the mechanisms underlying trauma-associated biological inheritance and for developing precision-based therapeutic interventions.

## Author Contributions

Sama Akbarli conceptualized the study, conducted the literature review, and wrote the original manuscript. Chilanay M. Alakbarova reviewed and edited the manuscript. Both authors read and approved the final version of the manuscript.

## Conflict of Interest

The authors declare no conflicts of interest.

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## Abbreviations

Hypothalamic-Pituitary-Adrenal (HPA), Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), Single Nucleotide Polymorphism (SNP), Variable Number of Tandem Repeats (VNTRs).

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