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HUMAN EPIGENETIC RESPONSES TO TRAUMA: A STUDY OF DNA METHYLATION ALTERATIONS FOLLOWING STRESS EXPOSURE

Supervisor
Professor Cristina Giuliani

Candidate
Greta Gandini
Student ID number: 2079634

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ABSTRACT

DNA methylation is an epigenetic mechanism which, in humans, involves the addition of methyl groups to CpG dinucleotides, potentially altering gene expression without changing the gene's nucleotide sequence. In recent years, several studies have shown that traumatic events can induce changes in DNA methylation, with biological effects that may manifest both in the long term and across generations. The aim of this work is to examine the existing literature regarding DNA methylation changes induced by exposure to various types of traumas, identifying the most commonly involved genes and analyzing the presence of shared biological mechanisms among different trauma categories. Through a systematic search on the PubMed database, articles that addressed the role of DNA methylation in relation to various forms of trauma were selected, including studies on both human and animal models. The analysis allowed the studies to be grouped into 8 main trauma categories: physical trauma, alcohol exposure, early-life adversity, maltreatment, maternal trauma, genocide exposure, undernutrition, and combat trauma. For each study, significant genes were extracted and analyzed to identify genes shared across different types of traumas as well as mechanisms specific to individual categories. In conclusion, the analysis of the collected data highlighted frequently involved genes, suggesting the existence of recurrent and shared epigenetic and biological mechanisms in response to different types of traumas.

1. INTRODUCTION

1.1. Epigenetics and DNA Methylation

Epigenetics refers to alterations in chromatin structure and DNA that are inherited by other cells and by future generations and affect phenotypic traits, but are not caused by changes in the nucleotide sequence itself and are reversible (1). The main epigenetic modifications affecting gene regulation are histone modifications, chromatin remodeling and DNA methylation.

Histones are protein components around which the DNA lies, in order to form the fundamental subunit of chromatin, the nucleosome. Nucleosomes are composed of around 200 bp of DNA wrapped around the histone octamer, which consists of two copies of each core histone, H2A, H2B, H3 and H4. Regions known as histone tails are often subjected to modifications involving the removal or addition of acetyl, phosphate or methyl groups, as well as to other modifications such as mono-ubiquitylation, sumoylation and ADP-ribosylation (2). Many of these histone modifications have known roles in chromatin assembly, replication, splicing, transcription and DNA repair.

Another epigenetic modification is chromatin remodeling, which refers to the reorganization of the chromatin structure through action of proteins called chromatin-remodeling complexes that interact directly with specific regions on DNA and shift the position of nucleosomes, with the goal of enabling transcription factors to bind to promoters and start transcription (1). However, remodeling can also prevent transcription of genes by repositioning nucleosomes onto fundamental promoter sequences, rather than away from them. Chromatin remodeling is an ATP-dependent mechanism during which chromatin-remodeling complexes use ATP hydrolysis to provide the energy needed for the process (2).

DNA methylation was the first epigenetic modification to be discovered and it involves the addition of a methyl group at specific sites. In eukaryotes, its main known function is associated with transcription control and regulation (2).

1.1.1. Molecular mechanisms of DNA methylation

DNA methylation primarily occurs on cytosine bases adjacent to guanine nucleotides–known as CpG sites, where p denotes the phosphate group in the DNA backbone. In eukaryotes, methylation mainly occurs at CpGs in the 5’ regions of genes and, in particular, at the fifth carbon position of the cytosine, resulting in the formation of 5-methylcytosine (5mC) (2).

The enzymes involved in the methylation process are DNA methyltransferases (or DNMTs) containing methyl-CpG-binding domains which add methyl groups to the 5th position of the cytosine, and demethylases which instead remove methyl groups (2).

Two types of DNA methyltransferases have been discovered based on their activity. De novo methyltransferases act on unmethylated DNA in order to establish new methylation patterns. Maintenance methyltransferases act on hemimethylated sites (sites where one DNA strand is methylated and the other is not) to convert them to fully methylated sites after replication (2).

In mammals, DNMT1 is the maintenance methyltransferase keeping DNA methylation status across cell divisions, while DNMT3a and DNMT3b are de novo methyltransferases having different target sites, both fundamental in developmental stages (2).

Over the decades, researchers have also investigated the role of DNMT2, a human protein that present high sequence similarity to that of the other DNA methyltransferases. DNMT2 contains all the sequence motifs that are conserved among methyltransferases, but neither methyltransferase activity nor changes in DNA methylation have been observed in studies experimenting on mice embryonic stem cells, showing how its biological function is still not completely known (3).

Regions rich in CpGs are called CpG islands (CGIs), which present a CG content higher than 50% and are commonly found within or close to transcription start sites (1). In mammalian genomes, these regions usually extend for 300-3000 base pairs and, in normal cells, are mostly unmethylated and can be considered good predictors of active or potentially active promoter regions (4).

In normal somatic cells, these CGIs are generally unmethylated, allowing for transcriptional competency of associated genes. When methylation does occur at these regions, particularly at transcription start sites (TSSs), it is commonly associated with transcriptional repression. Such methylation events can obstruct transcription factor binding directly or promote the recruitment of chromatin-modifying complexes that enforce a repressive chromatin state. This mechanism plays a well-established role in epigenetic phenomena such as X-chromosome inactivation and genomic imprinting (5). In contrast, CpG-poor promoter regions exhibit more dynamic methylation patterns that can vary depending on the developmental stage or cellular context. In primordial germ cells (PGCs)—the embryonic precursors of gametes—genes with non-CGI promoters that are transcriptionally active typically remain unmethylated at their transcription start sites (TSSs). Conversely, genes predominantly expressed in embryonic stem cells (ESCs) or those with tissue-specific expression often display promoter methylation in sperm, while remaining unmethylated in oocytes and in the somatic tissues where they are actively transcribed. Furthermore, certain tissue-

specific genes maintain methylation at their promoters in both sperm and ESCs, with demethylation occurring only within the specific differentiated tissues in which gene expression is required. These observations illustrate the precise and context-dependent regulation of DNA methylation throughout development (5).

DNA methylation is also frequently observed within gene bodies, which are often densely methylated and contain various repetitive and transposable elements. While most of these regions lack a high CpG content, CpG islands (CGIs) can also be located within gene bodies, not just at promoter regions. Interestingly, CGIs situated within gene bodies may exhibit high levels of methylation without suppressing transcription; in fact, they are often associated with actively transcribed genes. Beyond CGIs, gene body methylation has been observed to be implicated in the repression of intragenic repetitive elements, thereby preventing inappropriate transcriptional initiation. Additionally, methylation in these regions seems to play a significant role in the regulation of RNA splicing as well (5).

In addition to its roles at promoters and within gene bodies, DNA methylation also influences the function of distal regulatory regions, such as enhancers and insulators. Despite typically having a low density of CpG sites, these elements are highly responsive to methylation changes. Methylation at enhancer regions is commonly linked to diminished regulatory activity, whereas methylation at insulator sites can interfere with chromatin loop formation and boundary maintenance, ultimately leading to alterations in gene expression regulation (5).

1.1.2. Role of DNA methylation in trauma exposure

As we stated previously, in adult individuals DNA methylation is maintained across cell divisions through the action of DNA methyltransferase 1 allowing to maintain tissue-specific gene expression. However, the epigenome can be influenced and modified by exposure to many environmental factors, such as diet, climate, stress, environmental compounds and pathogens, and by exposure to physiological and pathological conditions, such as ageing and tumor conditions (6).

Factors such as diet, nutrition, disease, hypoxia, environmental pollution, chemical contamination, exposure to behavioral toxicants, deprivation, and psychosocial stress can be grouped as immediate environmental influences that directly impact physical growth. The significance of these factors can vary depending on the specific context, as well as the individual's age and developmental stage—whether in infancy, childhood, or adolescence. In contrast, broader influences such as cultural norms, societal structures, behaviors, socioeconomic status, poverty, and the political economy function as

more indirect yet powerful structural determinants. These distal factors shape patterns of growth and body size throughout all stages of development during childhood and adolescence (7).

Extensive research has established a link between traumatic experiences and alterations in DNA methylation, shedding light on potential mental, behavioral, and physical health consequences as well.

For instance, a study by Cicchetti and colleagues (8) examined DNA methylation patterns in children from low-income backgrounds, comparing those with a history of maltreatment to children living under similar socioeconomic conditions but without maltreatment history. The results revealed distinct methylation differences in genes associated with several major health conditions, including various cancers, cardiovascular and hematological diseases, immune system dysfunctions, and psychiatric disorders such as schizophrenia, bipolar disorder, and depression. These findings from a genome-wide epigenetic analysis highlight how trauma may contribute to elevated vulnerability to both psychological and physical illnesses, underlining the long-term implications of adverse experiences on health (8).

Additional studies on childhood trauma provide evidence that adverse experiences during early stages of life can lead to lasting alterations in DNA methylation, which may persist into later stages of life. Marinova et al. (9) investigated DNA methylation differences in a group of elderly individuals who, as former child laborers, had experienced severe childhood adversity, compared to a demographically equal control group without such adverse experiences. The study revealed significant methylation differences in genes related to cell signaling and neuronal development. Notably, several of these genes had previously been implicated in responses to traumatic stress, further supporting their relevance in the long-term biological impact of early-life trauma (9).

Numerous studies using mouse models have also been conducted to explore the impact of environmental stressors on DNA methylation patterns. One such study by Weng et al. (10) focused on male mice subjected to malnutrition, aiming to assess the epigenetic consequences of a nutrient-deficient diet. Nutrition plays a critical role in proper development and growth, particularly during early life stages. The researchers observed significant alterations in DNA methylation within the hippocampus and thalamus of malnourished mice compared to those receiving a normal diet. These changes were predominantly found in genes involved in neuronal development and maturation. Furthermore, their findings suggest that postnatal malnutrition may elevate the risk of developing neuropsychiatric disorders, including Alzheimer’s disease, schizophrenia, and bipolar disorder (10).

Two historical phenomena of the past, the Great Chinese Famine (1959-1961) and Dutch Famine (1944-1945), draw attention to the importance of a correct nutrition especially in early stages of development. Many studies explored the consequences that these two phenomena might have had on the epigenome of the affected individuals. For instance, a gene-candidate study by Wang et al. (11) investigated the differences in DNA methylation between individuals prenatally exposed to the Chinese Famine and those who weren't affected. In particular, Wang and colleagues focused on the methylation of the insulin receptor (INSR) gene encoding for the insulin receptor, mediating the effects of insulin and regulating glucose homeostasis. Their data showed higher DNA methylation levels in the insulin receptor gene of individuals subjected to fetal exposure to the famine compared to the gene of the non-exposed group. Increased DNA methylation level in the intragenic enhancer region of INSR was associated with higher triglycerides and lower HDL-C levels, suggesting a predisposition to metabolic problems (11).

Research conducted on cohorts exposed to the Dutch Hunger Winter (Dutch Famine) and the Chinese Famine has provided compelling evidence that undernutrition, especially during prenatal or early developmental periods, is associated with persistent changes in DNA methylation. These epigenetic alterations have been implicated in adverse metabolic outcomes later in life, as well as in disrupted developmental trajectories following in utero exposure.

1.1.3. Intergenerational and transgenerational inheritance of trauma

In the past, it was believed that epigenetic modifications resulting from environmental exposures affected only the individual directly subjected to the stimulus. However, more recent studies have challenged this view by demonstrating that changes in DNA methylation can be passed down to subsequent generations, beginning with the initially exposed individuals (6).

It is fundamental to make a distinction between transgenerational and inter-generational inheritance of epigenetic changes when mentioning inheritance of epigenetic alterations. In fact, inter-generational effects arise when an individual develops a DNA methylation-related phenotype due to indirect exposure to an environmental factor—for example, through in utero exposure affecting both the offspring and its developing germ cells. In contrast, transgenerational effects refer to the persistence of epigenetic changes, in generations that have never been exposed to the original environmental trigger. This indicates that specific DNA methylation patterns can be transmitted through the germline and evade the usual reprogramming events that occur both in the zygote and during germ cell development (6).

Numerous studies have demonstrated that DNA methylation alterations resulting from traumatic experiences of various kinds and associated stress can be inherited by subsequent generations, leaving epigenetic marks of the trauma that may persist across several generations.

A study by Yehuda et al. (12) investigated transgenerational methylation changes of holocaust survivors and their offspring. They examined a cohort of Holocaust survivors and their offspring and a cohort of control individuals and their offspring who were not exposed to the genocide. This study presents novel evidence that extreme stress experienced prior to conception may lead to epigenetic alterations not only in directly exposed individuals but in their offspring as well. Specifically, both Holocaust survivors and their children exhibited methylation changes at the same site within intron 7 of the FKBP5 gene, a region known to contain a functional binding site for the glucocorticoid receptor (GR) (12). This study constitutes evidence that in adult humans preconception exposure to extreme stress can be linked to epigenetic modifications in both the directly affected individuals and their descendants.

A recent study by Mulligan et al. (13) investigated the transmission of DNA methylation changes in three generations. The study examined methylation alterations in Syrian refugees who were pregnant during either the 1980 Syrian conflict or the 2011 conflict and were therefore exposed to violence and war stress, as well as in their children, who were indirectly exposed prenatally, and their germline. The findings revealed that 14 differentially methylated positions (DMPs) were linked to germline exposure to violence, while 21 DMPs were associated with direct personal exposure to violence. 32 of these methylation sites demonstrated consistent directional changes in DNA methylation across all three forms of exposure—germline, prenatal, and direct exposure—indicating the potential presence of a shared epigenetic pattern related to violence experienced at different developmental stages (13).

Evidence of transgenerational inheritance of DNA methylation in animal models was provided by Guerrero-Bosagna et al. (14) in a study of F0 pregnant mice exposed to vinclozolin. Effects were examined in the F3 generation which was not directly exposed to the stress. Their findings provide some of the first direct molecular evidence that environmental exposures can lead to epigenetic alterations in the sperm epigenome that persist across multiple generations even in the ones not exposed to the stress.

Transgenerational inheritance research is still constrained by ethical and methodological limitations especially in human models. These include the requirement for extended multigenerational follow-up, challenges in accessing relevant tissues (particularly germ cells) and the need for precise

molecular tools. Additionally, distinguishing epigenetic inheritance from genetic variation remains a fundamental challenge due to their intricate interplay (15).

2. METHODOLOGY

2.1. Data collection

2.1.1. Research articles selection from literature

Our work aims at collecting and analyzing research papers of studies already present in the scientific literature in order to gather evidence on the fundamental role that DNA methylation plays in trauma exposure and trauma inheritance and search for genes commonly affected by these changes among the different types of traumas.

To reach this goal, we conducted a search on PubMed, which is a freely accessible platform designed to help users search for and retrieve scientific literature in the biomedical and life sciences fields, with the goal of enhancing both individual and global health. The database hosts over 38 million citations and abstracts from scientific publications, primarily in medicine, biology, and related disciplines. While it typically does not provide the full text of journal articles directly, it often includes links to full versions available through external sources, such as journal publishers or PubMed Central (PMC). Launched online in 1996, PubMed is developed and operated by the National Center for Biotechnology Information (NCBI), a division of the U.S. National Library of Medicine (NLM), which is part of the National Institutes of Health (NIH).

On PubMed we used the query “Trauma exposure and DNA methylation changes” to identify relevant literature exploring the relationship between traumatic experiences and associated alterations in DNA methylation.

We applied broad inclusion criteria to capture a comprehensive range of studies examining the association between trauma exposure and DNA methylation modifications. The search strategy for literature articles was designed to be inclusive, and no a priori exclusion criteria were applied with respect to the type of trauma, the characteristics of the study population (age, sex, clinical status), or the biological model employed (human or animal subjects). This approach was intended to encompass the full scope of relevant findings and to facilitate the identification of convergent epigenetic patterns across diverse trauma exposures and populations.

2.1.2. Genes affected by DNA methylation alterations

From the literature articles we collected, we conducted a search to identify all the genes affected by changes in DNA methylation in each study.

For each eligible study, we analyzed the main text, supplementary materials, and associated data tables to identify all genes reported as showing trauma-related DNA methylation changes. All identified genes were systematically recorded. We compiled the extracted data into a structured Excel sheet, categorizing genes according to the corresponding study, the type of trauma investigated, and the methodological approach employed (genome-wide vs. gene-candidate). This organization facilitated subsequent analysis and interpretation of shared epigenetic patterns across different studies and trauma contexts.

2.2. Data visualization

2.2.1. Identification of common affected genes

Analyses for common genes shared across trauma categories were conducted using R (version 4.3.3, released February 29, 2024) in the RStudio environment. We used the rJava package to establish an interface between R and Java, enabling the use of the xlsx package for the reading of Excel files. The stringr package was employed to clean and standardize data extracted from Excel files. This included removing whitespace and detecting inconsistent entries in gene identifiers, which could otherwise interfere with set operations. To ensure clean and analyzable data, the dplyr and tidyr packages were used for data processing and restructuring. The dplyr package was employed to filter out rows with missing or empty values in key columns such as gene identifiers and trauma categories. It was also used to identify and remove duplicate gene–trauma pairs. The tidyr package was used to reshape the dataset from a long to a wide format using pivot_wider(), allowing each trauma type to become a separate column. This transformation produced a binary matrix indicating the presence or absence of each gene across trauma types, which was essential for visualizing gene set intersections using the ComplexUpset package. ComplexUpset package was used to create an UpSet plot for analysis of intersections of sets and visualization of genetic overlap, especially powerful when dealing with many categories.

3. RESULTS AND DISCUSSION

3.1. Research articles selection from literature

The selection of articles for our work includes clinical trials, reviews, meta-analyses, and randomized controlled trials involving both human and animal models—particularly mice—to gain a comprehensive understanding of the shared epigenetic mechanisms across mammalian species.

A total of 119 original research studies and 23 review articles were included in our analysis. The review papers were primarily consulted to provide contextual background, helping to illuminate the development of the field, the variety of trauma types explored in previous research, and broader trends identified in the existing literature. However, our primary focus was on the original research studies, from which we extracted specific data on genes exhibiting trauma-associated DNA methylation changes, which were published between 2008 to 2025.

In our selection both genome-wide and gene-candidate studies were included. Genome-wide studies take into consideration the whole genome without focusing the attention on a particular gene a priori and assess DNA methylation variations at hundreds of thousands to millions CpG sites across the entire genome. Gene candidate studies, in the contrary, examine methylation at specific CpG sites in a pre-selected gene of interest hypothesized to be involved in relevant findings.

We divided our research studies into 8 trauma categories based on the type of stressful experience the individuals in the studies were subjected to. The 8 trauma categories are: physical and mechanical trauma, alcohol exposure, early-life adversity, maltreatment, maternal trauma, genocide exposure, undernutrition and combat trauma.

In the physical and mechanical trauma category, we included human and mice studies examining changes in DNA methylation among individuals who experienced physical trauma, such as traumatic injuries, as well as mechanical trauma, including surgical procedures.

In the alcohol exposure category, we included human studies that investigated the impact of prenatal alcohol exposure on DNA methylation patterns in children born to mothers who consumed alcohol during pregnancy. In mouse models, we grouped studies that examined both the effects of prenatal alcohol exposure through maternal consumption during gestation, as well as the impact of preconception paternal alcohol exposure, where male mice consumed alcohol prior to mating, despite the mothers having no direct exposure.

The early-life adversity category comprised a broad variety of studies examining, both in human and mice models, traumatic experiences in early stages of life such as childhood abuse, neglect, post-natal

maternal separation and isolation, violence exposure, childhood labor, and their effects on DNA methylation changes which are investigated later in life in adulthood. This group also included studies on prenatal adversities, specifically examining how maternal exposure to trauma (such as war trauma and sociocultural stress) occurring during pregnancy may leave epigenetic marks on the developing fetus. In these studies, the DNA methylation assessment of the newborn was conducted postnatally or samples for methylation alterations were extracted from the umbilical cord.

The maltreatment category includes human studies that investigate the effects of abuse and violence on DNA methylation alterations and studies on mice in which they are subjected to maltreatment such as chronic social defeat stress and induced exposure to environmental toxicants. DNA methylation changes are examined while the individuals are still actively experiencing these forms of trauma providing insight into the immediate epigenetic impact of ongoing maltreatment.

Although certain types of traumatic experiences appear in both the maltreatment and early-life adversity categories, we opted to differentiate these groups based on the temporal context of DNA methylation analysis. Specifically, studies classified under early-life adversity assessed DNA methylation patterns in adulthood, in relation to traumas experienced earlier in life, thereby reflecting long-term epigenetic consequences. Conversely, the maltreatment category includes studies in which DNA was extracted and differentially methylated regions were identified during the period of active trauma exposure.

In the maternal trauma group, we categorized human studies conducted on children of women who experienced stressful traumatic events before becoming pregnant (preconceptionally). Even if the trauma occurred years earlier, the mother could still carry biological memories of the traumatic experience which shape the fetal environment. Therefore, even if the child is indirectly affected by these events, long-term alterations in DNA methylation in the child epigenome can be seen.

Figure 1 illustrates the timing of methylation assessment relative to the occurrence of traumatic events across the early-life adversity, maternal trauma and maltreatment categories, in order to facilitate a clearer understanding of the temporal relationship between trauma exposure and DNA methylation changes.

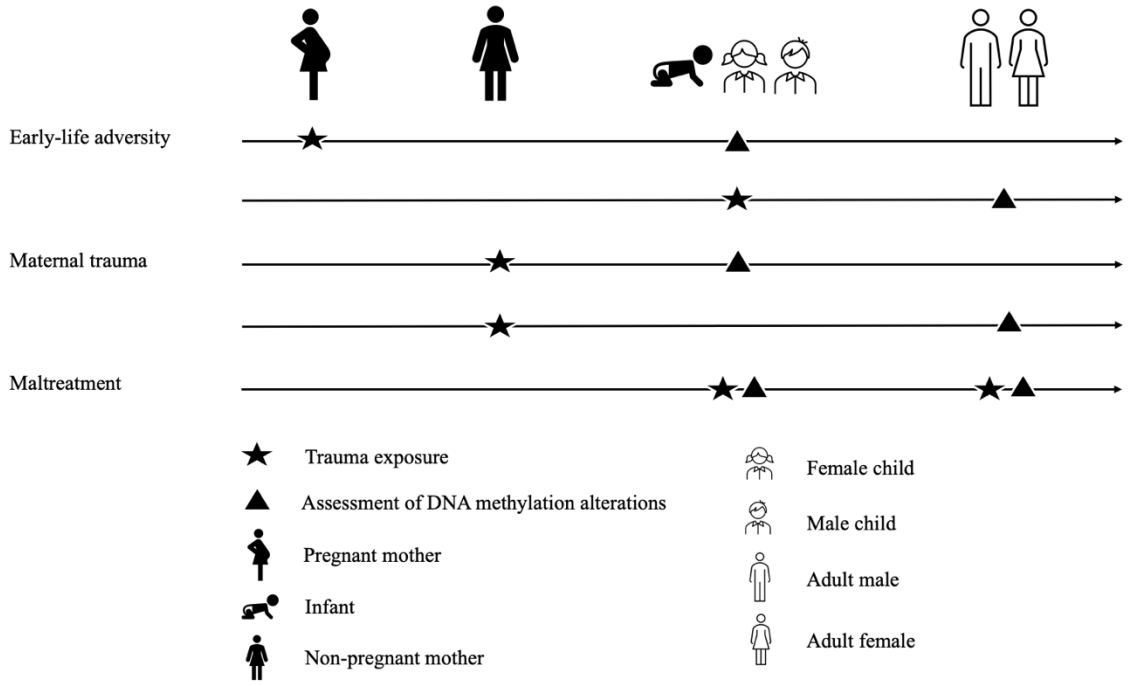

Figure 1. Timing of DNA methylation changes assessment in relation to the timing of trauma exposure in early-life adversity, maternal trauma and maltreatment categories.

The next category is genocide exposure, in which we included studies on human individuals investigating the effect of the exposure to the genocide that happened in Rwanda in 1994 against the Tutsi and the Holocaust which occurred between 1941 and 1945. These studies examined DNA methylation patterns in both survivors and their offspring, including individuals exposed to trauma in utero or whose parents were exposed prior to conception, in order to assess the potential intergenerational effects of genocidal trauma on the epigenome.

The undernutrition category groups human studies investigating DNA methylation changes in individuals prenatally exposed to food restriction mainly due to two main historical events, the Chinese famine of 1959-1961 and Dutch Hunger Winter (or Dutch famine) of 1944-1945.

Animal studies conducted in this group examined DNA methylation alterations in mice exposed to prenatal caloric restriction. Dams were subjected to either caloric restriction or folate-deficient diets during gestation, and epigenomic modifications were subsequently analyzed in the offspring.

The final category encompasses combat-related trauma, including studies that investigated DNA methylation changes in war veterans with a history of exposure to combat and war-related stress, as well as active-duty personnel undergoing DNA methylation assessments while still in deployment.

Table 1 summarizes the number of articles analyzed for each trauma category in both human and animal models.

Trauma type	N. Articles on human models	N. Articles on animal models
Mechanical/physical trauma	5	13
Alcohol exposure	5	10
Early-life adversity	25	7
Maltreatment	9	2
Maternal trauma	6	
Genocide exposure	6	
Undernutrition	12	7
Combat trauma	12	

Table 1. Total articles analyzed for each of the 8 trauma categories.

3.2. Genes affected by DNA methylation alterations

We found a total of 3445 affected genes in mice and 5076 affected genes in human studies. These numbers represent unique genes identified across the different studies within each trauma category, with each gene counted only once per category.

3.2.1. Identification of common affected genes

Using the ComplexUpset package in R, we generated two intersection plots to visualize gene overlap across trauma categories. One plot displays gene intersections across categories in the full dataset, including both human and mouse studies, while the other focuses exclusively on gene overlap within the human subset.

Figure 2 illustrates the UpSet plot including both human and mouse data. The highest gene overlap was observed between the maltreatment and alcohol exposure categories, with 251 genes commonly affected in both. This substantial overlap may reflect the high number of affected genes identified individually within each of these two trauma categories.

Among the genes analyzed in the human and mice plot, BDNF (Brain-Derived Neurotrophic Factor) gene was found to be shared across seven trauma categories: alcohol exposure, undernutrition,

physical trauma, early-life adversity, combat trauma, genocide exposure, and maternal trauma. BDNF plays a critical role in neuronal survival and growth, synaptic plasticity, brain development and function, and the response to stress and trauma.

GNAS gene, was found to overlap across six trauma categories: maltreatment, alcohol exposure, physical trauma, early-life adversity, combat trauma, and genocide exposure. GNAS encodes the alpha subunit of G proteins, which are essential components of G protein–coupled receptor (GPCR) signaling pathways, playing a key role in cell signaling and hormonal regulation.

Figure 3 illustrates the UpSet plot of gene intersections in human studies only. The RPTOR (regulatory associated protein of MTOR complex 1) gene showed overlap across the highest number of trauma categories, being shared among five trauma types: maltreatment, early-life adversity, alcohol exposure, combat trauma and undernutrition. RPTOR encodes for a component of a signaling pathway which regulates cell growth in response to nutrient and insulin levels.

In the human plot, several additional genes were found to overlap across multiple trauma categories. Notably, two of these, BDNF and GNAS, were also identified in the combined human and mouse analysis, reinforcing their potential as common epigenetic targets of trauma.

BDNF was shared among maternal trauma, genocide exposure, combat trauma, and early-life adversity. GNAS was found to overlap in maltreatment, early-life adversity, combat trauma, and genocide exposure.

NR3C1, encoding the glucocorticoid receptor, was shared across maltreatment, early-life adversity, undernutrition, and genocide exposure. SDK1, encoding the Sidekick Cell Adhesion Molecule 1, overlapped across maltreatment, early-life adversity, physical trauma, and combat trauma.

The left side of the plot in figure 3 shows the highest degrees of gene overlap with many genes being shared between pairs of trauma categories, including combinations such as maltreatment and early-life adversity, maltreatment and physical trauma, and maltreatment and alcohol exposure. The maltreatment category displays a notably high number of affected genes, which may partly explain its frequent involvement in overlapping gene sets.

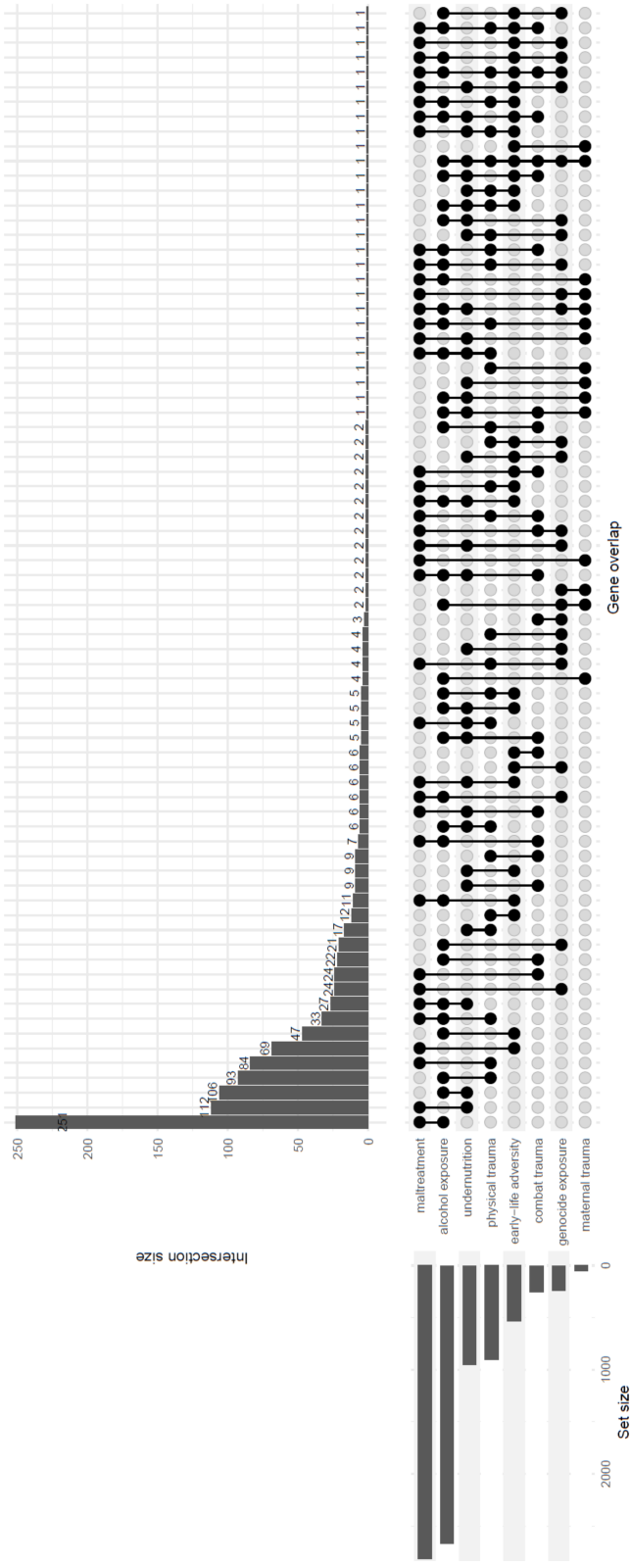

Figure 2. UpSet plot of gene overlaps in human and mice studies.

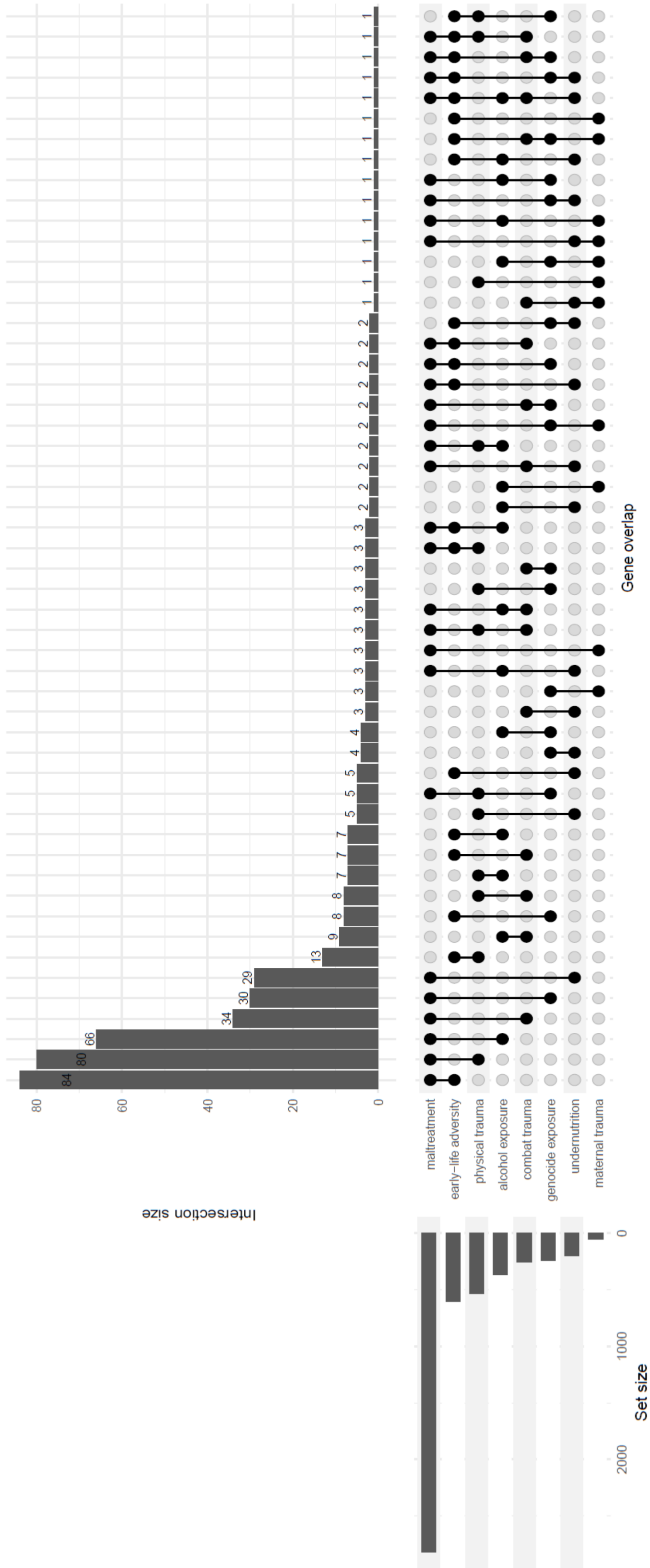

Figure 3. UpSet plot of gene overlaps in human studies.

4. CONCLUSION

Although no gene was found to be shared across all trauma categories, our results demonstrated that several genes were recurrently affected by DNA methylation alterations across multiple forms of trauma.

In human studies, we found significant overlap across trauma categories of genes such as RPTOR, BDNF, GNAS, NR3C1 and SDK1, which indicates that certain biological pathways may be commonly disrupted, regardless of the specific nature of the trauma.

RPTOR encodes a protein involved in a signaling pathway that responds to nutrients and insulin levels to regulate cell growth. BDNF encodes a neurotrophic factor involved in neuronal development and plasticity. GNAS encodes a component of GPCRs therefore playing a fundamental role in cell signaling and hormonal regulation. NR3C1 encodes the glucocorticoid receptor, which is involved in inflammatory responses, cellular proliferation, and differentiation in target tissues. SDK1 encodes the Sidekick Cell Adhesion Molecule 1, involved in cell-cell adhesion especially in the nervous system.

The pattern we found in these genes suggests the presence of shared epigenetic and molecular mechanisms that may underlie the biological response to diverse traumatic exposures. These findings support the hypothesis that different forms of trauma may converge on similar epigenetic targets, leading to potentially comparable long-term biological effects.

Furthermore, the studies we analyzed reveal that trauma-related epigenetic alterations can persist long after the initial exposure. In several cases, such changes were detected years later, even in adulthood, following trauma experienced early in life. This temporal persistence highlights the potential for trauma to exert a lasting, and possibly lifelong, impact on the epigenome.

Importantly, these DNA methylation changes are not limited to individuals who directly experience the trauma. Emerging evidence suggests that such alterations may be transmitted across generations, indicating that the biological effects of trauma can extend beyond the affected subject to affect descendants, potentially shaping their vulnerability to stress and disease.

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