RESEARCH ARTICLE

Genetics in Trauma Response: Identifying Differentially Expressed Genes Linked to PTSD History

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Abstract

Over 70% of people worldwide have experienced a traumatic event at least once in their lives.[1] This study analyzes transcriptomic alterations in prefrontal deep-layer pyramidal neurons of individuals with a history of childhood abuse using data from Gene Expression Omnibus. The data consisted of 58,126 genes spread between individuals with a history of child abuse (N=24) and control groups (N=21). Through a differential expression analysis, 20 genes were identified as most significant in predicting a history of child abuse, being linked to various physiological functions such as neural development, immune system response, and sensory processing. Among the results, the CALML5 gene was found to be severely downregulated in abuse groups as a gene responsible for muscle contraction and relating to the Innate Immune System pathway. The downregulation of genes SPRR2E and SPRR1A between cases and controls suggested altered nervous system development due to child abuse. KIF4CP's upregulation was responsible for adrenaline and stress hormones, suggesting potential health complications later in life. These findings suggest a physical link to child abuse and provide valuable insights into the genetic factors of trauma response, potentially informing the development of novel & personalized therapeutic interventions for individuals based on genetic analysis.

Keywords

Cellular And Molecular Biology; Genetics; Epigenetics; Trauma Response; Differential Gene Expression; Transcriptomic Alterations

Introduction

The Growing Youth Mental Health Crisis

Psychological trauma is defined as a lasting emotional response that results from experiencing a traumatic event or series of stressful events.[3] The causes of trauma vary vastly, ranging from a single traumatic incident such as a car accident to the death of a loved one, or assault. It can also arise from long-term chronic exposure to traumatic experiences, such as childhood neglect, sexual, or physical abuse.[4] The impact of trauma can be long-lasting and may manifest in a range of mental health conditions, including post-traumatic stress disorder, depression, and anxiety.

It is critical to analyze the causes and effects of trauma, especially in light of the growing youth mental health crisis that continues to deteriorate. In 2013, it was reported that young people aged 15 to 24 are more likely to experience mental illness and/or substance use disorders than any other age group.[5] Moreover, this alarming disparity has only been further exacerbated as a result of the recent COVID-19 pandemic, which has forced children to be isolated in their homes, often with limited proper access to mental health services and resources. In particular, many mental health surveys and studies of youth

students have reflected a significant increase in the prevalence of mental health issues including distress, anxiety, and depression.[6]

Based on the ever-growing need for proper mental health care, it is imperative to investigate the genetic factors of trauma response in order to best equip medical professionals to deal with trauma experiences and develop efficient treatments for individuals. With COVID-19's amplification of the mental health crisis, targeted intervention based on unique human responses to trauma also becomes as important as ever.

The pandemic has been a source of trauma for many due to widespread anxiety about contracting the virus, constantly changing public health instructions, and measures for confinement through social and physical distancing.[7] Furthermore, the pandemic increased the likelihood of youth exposure to multiple complex traumatic experiences including physical, sexual, inter-parental, and psychological violence, as well as both physical and emotional neglect combined with other household stressors.[7] Moreover, child abuse rates have begun to climb at a rapid pace.[8] Children have been increasingly vulnerable to abuse and neglect due to school closures, isolation, and economic stressors related to the pandemic. Thus, investigating the trauma caused by child abuse could have various potential applications for ensuring good mental health for today's youth.

According to the U.S. Department of Health & Human Services, child abuse can be defined as "any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation."[8] In 2014, UNICEF reported that between 133-275 million children worldwide experience violence in the family.[9] With the number of children who experience abuse, it is pertinent that we understand more about the physical and mental effects caused by child abuse.

The Role of Genetic Factors

One key factor in assessing a child's response to abuse is by using their gene expression. Environmental stressors have previously been linked to changes in an individual's genetic expression profile.[10] In a 2006 study, Booij et al. reported that increased methylation of the serotonin transporter was specifically observed in the depressed group receiving selective serotonin reuptake inhibitors (SSRIs).[10] This suggests that the development of stress-related brain alterations could be linked to interactions between epigenetic factors, such as DNA methylation, and the physiological gene environment. Another study conducted in 2017 linked PTSD to 5-HTTLPR, a serotonin-transporter-linked promoter region[11]. Simons et al. found that individuals with low expression alleles of 5-HTTLPR had stronger ties to childhood traumatic stress and PTSD.

While previous studies have linked genetic expression to depression and PTSD, there has been limited research on the specific effects of child abuse on genetic expression. Furthermore, most of the research focuses on the effects of trauma on serotonin transporters. However, with child abuse, there may be other effects on genetic expression due to the physical nature of which some abuse occurs.

In this study, we explore various gene expressions of 58,126 separate genes and how they affect children's responses to child abuse in order to establish a better understanding of the impacts of genetics on trauma response in youth and create opportunities for better trauma therapy treatment.

Methods

Dataset GSE157197 was obtained from the Gene Expression Omnibus[2] to investigate the correlation between 58,126 genes and a history of childhood abuse. The dataset reports read counts of transcriptomic alterations to prefrontal deep-layer pyramidal neurons in individuals with a history of childhood abuse (N=24) compared to controls (N=21). Data originates from the usage of a laser capture microdissection followed by RNA sequencing in a study conducted by the Department of Psychiatry of McGill University, submitted in 2020.[2]

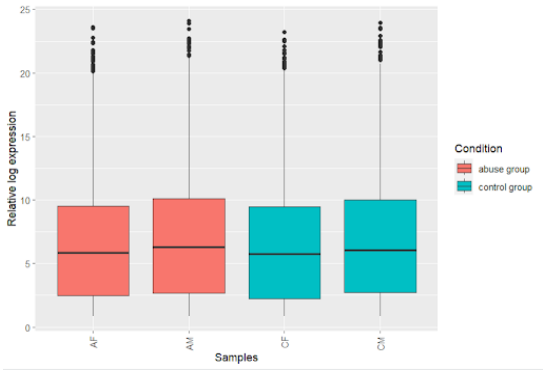

Figure 1. Visualization of RLE values for sample groups. RLE values were used to normalize the data. Shown above is the variance of RLE values with 4 different groups that we performed statistical analysis on, with the red groups representing those who experienced abuse and the blue groups representing those who have not experienced abuse (AF, AM, CF, CM = abuse female, abuse male, control female, control male respectively).

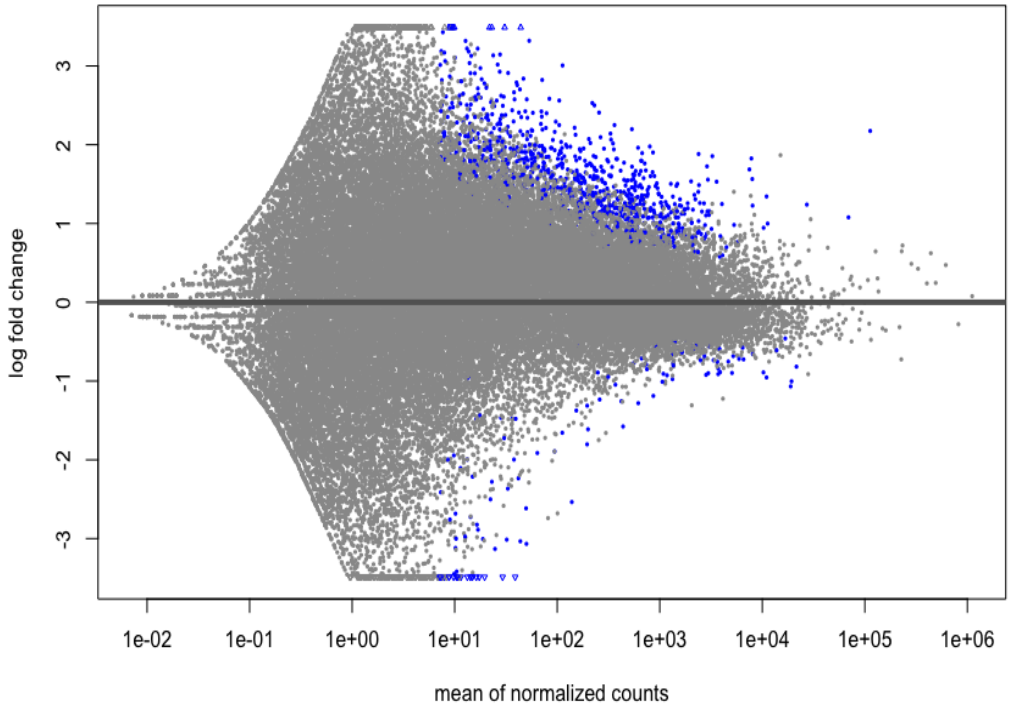

Figure 2. MA plot of the raw data obtained from individuals with a history of child abuse and individuals without. This plot explores the relationship between the log ratio and mean values of the data. The blue dots represent genes that are differentially expressed at a significant level (adjusted p-value < 0.05) between conditions of child abuse and control (no child abuse).

The data was normalized prior to regression analysis through the visualization of relative log expression (RLE) (**Figure 1**) and the elimination of RLE values outside the interquartile range. Then, genes predicting a history of childhood abuse for both male and female groups were identified through differential expression analysis, using the DESeq2 package in the R language. Samples were collected randomly, and therefore amenable to statistical analysis.

Ratios of gene expression (RGE) were taken from log2FoldChange values, which measure the expression levels of genes between control and treatment groups **(Figure 2)**. Commonly used in

RNA-sequencing experiments, log2FoldChange is important for determining differential changes in gene expression rather than absolute values. A positive value for the log2FoldChange indicates an upregulation of a gene (increase in expression) while a negative value for the log2FoldChange suggests downregulation (decrease in expression).

In the analysis of the study, the metric log2FoldChange along with other indicators was used to measure the expression levels of genes in the individuals who experienced childhood abuse compared to those who did not. Our results (**Table 1)** include evaluations of test statistics, p-values, and their expression levels in addition to log2FoldChange. The p-value is a statistical measure that measures the strength of evidence against the null hypothesis. The stat column refers to the value of the test statistic for whether the expression level for the respective gene is significantly different from zero. The magnitude of the test statistic reflects the magnitude of the difference between the observed fold change and zero, relative to the standard error.

Table 1. Prominent genes in individuals with a history of child abuse (in decreasing order of RGE).

Gene	Ratio of gene expression	Stat	p-value
CALML5	-25.69208177	13.06385	2.41E-41
KIF4CP	6.152609958	-3.30545	0.000948
SETP3	-5.804228895	3.85349	0.000116
OR52M2P	-5.803409736	2.797718	0.005147
NPM1P36	-5.673055039	3.691532	0.000223
OR2W6P	-5.665441846	3.969057	7.22E-05
RP11-376O6.2	-5.581969006	3.59878	0.00032
AC007559.1	-5.533650606	2.449538	0.014304
RPL29P32	-5.447326022	3.886609	0.000102
OR4D12P	5.42172608	-1.94811	0.051402
CTD-2071N1.2	5.383477129	-3.05763	0.002231
RP5-967N21.2	-5.305117402	3.344836	0.000823
LCE1C	-5.273281106	3.664468	0.000248
OR5AL2P	5.27083689	-2.93965	0.003286
KRT17P4	5.26361838	-3.39206	0.000694
QRSL1P1	-5.190422375	2.895392	0.003787
WBP2P1	-5.170528701	2.227522	0.025912
CTAGE14P	-5.087071751	3.873348	0.000107
SPRR2E	-5.085257179	3.747898	0.000178
SPRR1A	-5.068032502	2.223593	0.026177

Notes: The data was sourced from the Gene Expression Omnibus. The data consisted of 58,126 genes spread between individuals with a history of child abuse (N=24) and control groups (N=21). Using the DESeq2 package we narrowed the genes to 20 of the most differentially expressed genes.

Results and Discussion

Of the 58,126 genes tested, 20 were found to be significant in predicting a history of childhood abuse (**Table 1**). The ratio of gene expression here suggests that both the upward regulation (expressed as a positive ratio of gene expression) and downward regulation (expressed as a negative ratio of gene expression) of specific genes affect the child's trauma. Following the initial results, we investigated the link between the genetic expression of specific individuals and their hierarchical clustering groups which we organized into a heatmap (**Figure 3**).

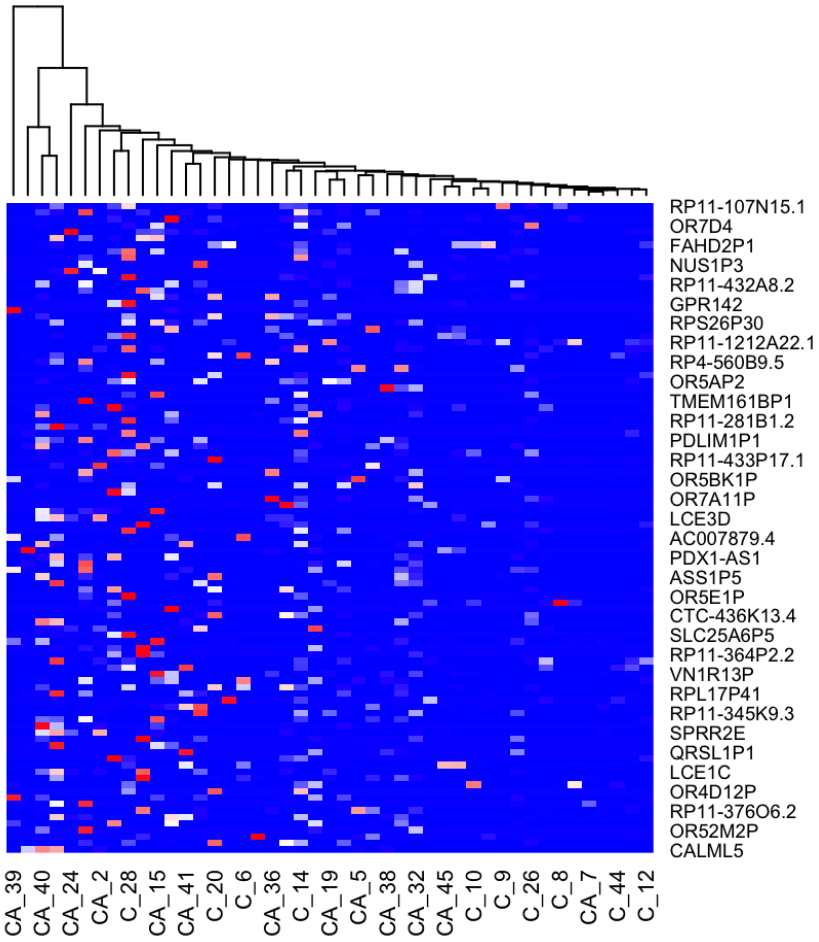

Figure 3. Heatmap representation of the prominent gene expression patterns in victims of child abuse. Along the bottom x-axis, the gene expression for various people is shown, with individuals with a history of abuse (CA) and individuals from the control group (C). The top x-axis shows the hierarchical clustering groups samples with similar gene expression profiles together, with the dendrogram showing how samples are clustered based on their similarity. The genes are arranged along the y-axis. The upregulation is shown as a measure of the colour, with the red rectangles representing genes that are the most upregulated and the blue rectangles representing genes that are the most downregulated in abuse victims.

Differential Expression Analysis

Different gene expression ratios have been found for each of the 20 significant genes. The differential expression analysis revealed that out of the 20 genes identified as affecting trauma response, 5 genes (KIF4CP, OR4D12P, CTD-2071N1.2, OR5AL2P, and KRT17P4) were upregulated in individuals with a history of childhood abuse compared to the control group, while the remaining 15 genes (CALML5, SETP3, OR52M2P, NPM1P36, OR2W6P, LCE1C, QRSL1P1, RP11-376O6.2, AC007559.1, RPL29P32, RP5-967N21.2, WBP2P1, CTAGE14P, SPRR2E, and SPRR1A) were downregulated **(Figure 4)**. It is important to note that some of the genes that were downregulated or upregulated were found to be pseudogenes. These pseudogenes structurally resemble a functioning gene but cannot code for a protein.[12] In most cases, this is a result of many mutations that have occurred over time, causing the pseudogene to lose its ability to code protein.[12]

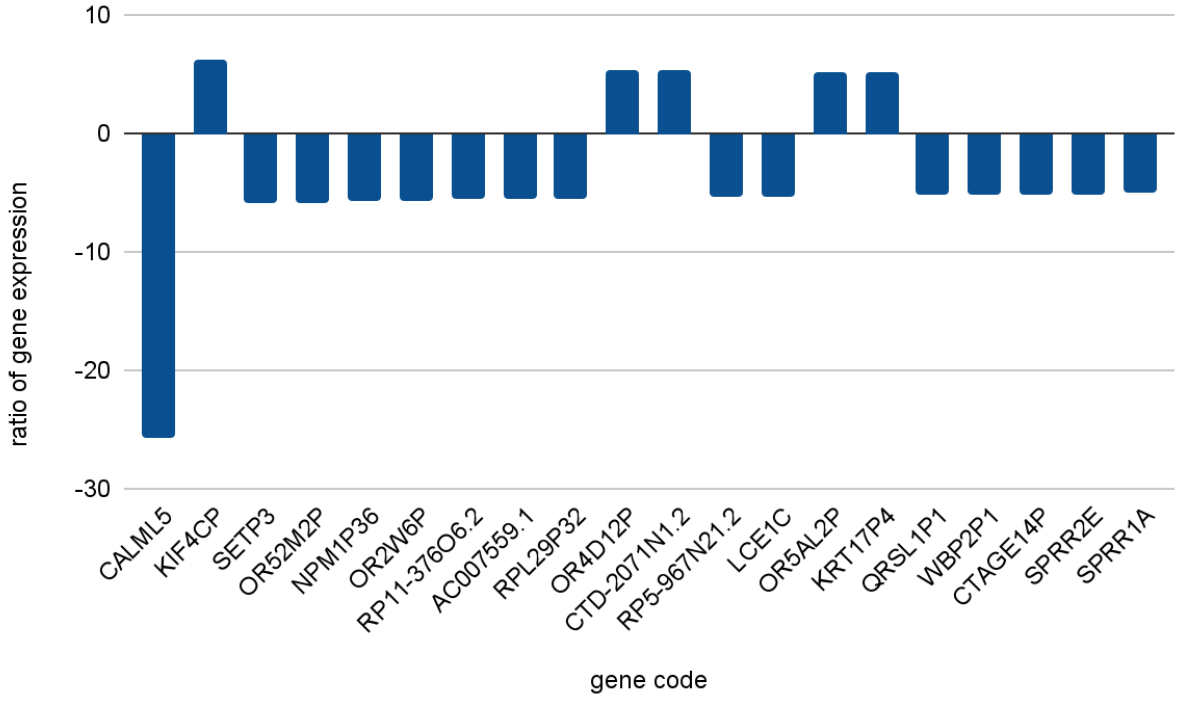

Figure 4. 20 significant genes were variably expressed in abuse victims when compared to their respective control groups.

Most notably, the gene CALML5 was found to have extreme significance considering the RGE and stat values. It was downregulated between cases and controls with an RGE value of approximately -25.692 **(Table 1)**. The rest of the genes, on the other hand, had an absolute variation of 1.084577456 (from 6.152609958 to -5.068032502), revealing minor discrepancies in expression levels.

In addition to the findings related to gene expression ratios and differential expression analysis, further analysis was conducted to explore the potential clustering patterns of individuals based on their genetic expression profiles. Hierarchical clustering groups were generated to examine the similarities and differences in gene expression among individuals with a history of childhood abuse **(Figure 3)**. This analysis provides insights into the potential subgroups and patterns within the study population, shedding light on the relationship between genetic expression and trauma response, which we used to better understand the link between genetic expression and the response of each individual to child abuse. It is clear that most of the individuals from the control group (C) have minimal changes to their gene expression. Contrarily, individuals with a history of child abuse (CA) had significant changes to their gene expression profiles. There is also more variation with individuals who have experienced child abuse, as

can be seen through the hierarchal branching patterns in the heatmap. This suggests that there are varying factors that cause varying effects on victims of child abuse.

Downregulation of CALML5

Although there is a mental link between trauma and resilience, a physical link also exists. The most significant genes have been linked to neural development, the immune system, and motor functions. Most notably, the CALML5 gene was severely downregulated as shown in the ratio of gene expression and highly significant. This gene indicates a physical response as it is responsible for muscle contraction, enzyme activity, and gene expression.[13] CALML5 is also related to the Innate Immune System pathway.[13] It is highly concentrated in the brain, indicating its important role in brain function and development. CALML5 has been linked to several neurological disorders such as schizophrenia and Huntington's disease. Furthermore, it is significant in the calcium cycle as it is part of the calmodulin family.[14] Ca^{2+} (Calcium) spike patterns at glutamatergic synapses encode information. These biochemical and cellular changes are necessary for long-term memory formation.[14] A significant lack of this gene would lead to cognitive deficits, worsening memory, and lesser brain function. With its high stat and extreme downregulation in individuals who have experienced child abuse, the CALML5 gene could be utilized to facilitate a more personalized treatment strategy, thereby increasing the likelihood of successful therapeutic outcomes.

Upregulation of KIF4CP

The upregulation of KIF4CP suggests that the pseudogene was caused by the overactivation of a sister gene, KIF4A,[15] which is responsible for regulating adrenaline and stress hormones.[16] The upregulation can be explained due to the intense psychological effects children experiencing abuse face. When KIF4A is upregulated, it may lead to increased cell proliferation, migration, invasion, and tumour growth.[15] This is significant to our findings as the overproduction of this gene in many young children suggests that their exposure to child abuse could lead to health complications later on in life. The intense psychological effects experienced by abused children may trigger dysregulation in genes involved in stress response, such as KIF4A. By understanding the relationship between the pseudogene (KIF4CP) and the functional gene (KIF4A), we can gain insights into the biological responses to childhood abuse, with potential therapeutic targets and interventions for individuals who have experienced trauma and upregulation of KIF4CP.

Downregulation of SETP3

The downregulation of genes such as SPRR2E and SPRR1A suggests that genes related to nervous system development[17,18] are altered due to child abuse. These two genes are expressed in the brain and spinal cord, particularly with involvement in sensory processing and motor control. Specifically, the SPRR family has been identified as a set of keratinocyte differentiation markers.[19] This family of genes is mostly found in the dorsal root ganglion (DRG), linking it to sensory messaging such as pain and temperature.[20] The SPRR1A specifically has been identified as a regeneration-associated gene.[19] A severe downregulation of SPRR1A could be an indicator of recent injuries and the inability to regenerate or repair neurons within the DRG.[19]

Role of Pseudogenes in Trauma Response

The olfactory receptors family, including OR52M2P, OR2W6P, OR4D12P, and OR5AL2P pseudogenes, are most important in cases of physical child abuse. While 2 of these genes (OR52M2P and OR2W6P) are downregulated, the other 2 (OR4D12P and OR5AL2P) are upregulated. This mix of up and downregulation would lead to a lack of olfactory sensory and overwhelming stimulation. This can be explained by the heightened senses that victims may have as a survival response. Blunt trauma to areas of the body such as the head or the nose can cause permanent damage to the olfactory nerves present in the area. These olfactory receptor proteins are members of a larger group called the G-protein-coupled receptors (GCPR).[21] These receptors share a 7-transmembrane domain structure which is responsible for the recognition and conversion of odorant signals via G protein-mediated transduction. Consequently,

losses of taste and smell may present themselves, directly impacting the ways in which the brain is able to process information. Lack of smell and taste in post-traumatic brain injury has various other effects as well such as increased memory loss and depression.[22]

The SETP3 gene is a crucial gene that codes for the protein called SET domain-containing protein 3.[23] It is typically involved in the regulation of gene expression and chromatin structure. Notably, it has been linked to the development of several cancers, including breast cancer and pancreatic cancer. SETP3 was also significantly downregulated for victims of child abuse. Since SETD3, the neighbouring gene, was responsible for regulating gene expression and chromatin structure, this downregulation of SETP3 could lead to altered regulation of gene expression and chromatin structure,[23] which could lead to the development of cancer and other diseases. It is important to note that SETP3 is a pseudogene. At one point, this gene may have had an important function, however, due to mutations, it no longer has any function within the body.

The presence of pseudogenes among the differentially expressed genes has profound implications for our understanding of trauma response. Pseudogenes are non-functional genes, which are not capable of producing functional proteins. Traditionally thought of as nonessential, our findings show that they may play an intricate role in regulatory functions and epigenetics processes

Limitations

Limitations of this study were mainly derived from two main factors: using secondary source data, and the statistics from the examined study depicted results of an adult population speaking to traumatic experiences as a youth. While this may have been done to ensure objectivity and separate the event from childish perception, the time between the original traumatic event and the time of study is too great to ignore. During this time frame, other events may have happened to alter the gene expression profile or the individual's perception of the original event. Regarding the first limitation, as aforementioned, although widespread research was conducted to ensure our findings were corroborated with those of other professionals in the field, our main source of data came from the Department of Psychiatry at McGill due to the time constraint. Consequently, our direct analysis is confined to the data from their studies and trials. Furthermore, a portion of the genes analyzed were pseudogenes: nonfunctional segments of DNA that resemble functional genes but are unable to code for proteins.

While our research has identified significant genes being implicated in child abuse victims, it does not show causation between the gene's up or downregulation and whether trauma these individuals have occurred. Our conclusion presents potential hypotheses to explain the differential expression of genes, which warrant further exploration and investigation. More analysis needs to be conducted with a larger dataset.

Furthermore, research needs to be conducted on each of these genes to find the specific effects that it has on the individual. In the future, these findings can be used to ameliorate and optimize trauma diagnosis and treatment. By conducting similar genetic tests, or assessing an individual's genetic history, medical professionals are able to more efficiently identify to what extent an individual may require therapy for trauma, or if other alternatives such as medicinal-based methods would work best given each person's unique situation. Additionally, assessments may be used to predict the likelihood of an individual undergoing a severely traumatic experience, and preventative measures may be put in place should the time come.

Conclusion

In this study, we investigated the correlation between genetic variation and post-traumatic stress disorder. Through transcriptomic analysis of prefrontal deep-layer pyramidal neurons, we identified significant alterations in gene expression associated with neural development, immune system response, and sensory processing among individuals with a history of child abuse. The downregulation of genes such as

CALML5, SPRR2E, and SPRR1A, along with the upregulation of pseudogenes like KIF4CP and olfactory receptors, highlights the multifaceted impact of trauma on biological pathways.

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