Differentially Expressed Genes and Pathways Involved in the Development of PTSD in World Trade Center Responders

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ABSTRACT: Post-traumatic stress disorder (PTSD) is a chronic psychological disorder that develops due to exposure to environmental trauma, resulting in debilitating impacts on cognitive function, emotions, and psychological recovery. The differential expression of key genes in the human genome is involved with the progression of PTSD and contributes to PTSD-related symptoms. Epigenetic alterations control the expression levels of specific genes by altering DNA methylation and histone acetylation patterns on them. Since genetic expression markers have been linked with the development of PTSD, our study aims to 1) confirm previous genetic expression markers, 2) identify new genetic expression markers, and 3) identify the biological and pathological pathways that are involved in the onset and progression of PTSD. Using the Gene Expression Omnibus (GEO) database provided by National Center for Biotechnology Information (NCBI), we retrieved a sample of 324 World Trade Center responders, who were sorted into three cohorts: PTSD patients, former PTSD patients, and non-PTSD patients. Using RNA sequencing technology, transcriptome-wide RNA expression patterns were determined for each participant. Genes were analyzed using DESeq2 to outline a variety of genetic expression markers that are prime targets for PTSD symptoms. Additionally, neurological, immune, and metabolic pathways were explored to reveal the associations between PTSD and other comorbid disorders.

KEYWORDS: Computational Genomics; PTSD; Gene expression; Transcriptome; Epigenetics; RNA-sequencing; Biomarkers.

Introduction
Post-traumatic stress disorder (PTSD) is a disabling mental condition characterized by flashbacks, avoidance, and hyperarousal symptoms that produce adverse changes in cognition, mood, and personal functioning as a response to a traumatic event. Although 60-90 percent of people are exposed to at least one traumatic incident during their lives, only 3.9 percent of US population has a PTSD diagnosis. The psychological trauma associated with recurring images of past traumatic or life-threatening events leads to flashbacks, nightmares, insomnia, and intrusive thoughts for many PTSD patients, often over extended periods of time. PTSD is linked with considerable morbidity, and patients with PTSD have a greater risk of suicidal conduct than the general population. PTSD is also highly associated with other mental disorders such as depression, drug addiction, and panic disorder. These disorders place an even greater burden on a patient’s emotional and physical well-being. Contemporary methods of intervention include several psychological treatments, predominantly eye movement desensitization and reprocessing (EMDR) and trauma-focused cognitive behavioral therapy (TF-CBT).

Despite PTSD becoming one of the most diagnosed disorders among mental health professionals, the full scope of its prevalence is not understood. Since PTSD is directly impacted by environmental trauma factors, the function of non-genetic variables in the condition has been of interest. Various studies have shown that following differentiation, cells exhibit altered gene expression patterns, which are transferred during cell division to the daughter cells. This concept makes up the emerging field of epigenetics, which involves the effect of heritable mechanisms on gene expression, the changes of these factors throughout development, and the transmission of these factors to the offspring. In all of these scenarios, the genome and genetic information are not being altered; rather, the expression of these genes are being controlled by epigenetic factors, namely DNA, RNA, proteins, and chemical groups.

One of the most thoroughly studied mechanisms of epigenetic inheritance is DNA methylation. Put simply, methylation of a specific part of the genome is associated with gene silencing. Methylation occurs on silent genes and functions as a cellular lock, preventing transcriptional factors from binding to the promoter region of these genes, thereby influencing gene silencing. Studies have shown that the patterns of methylation are influenced by the DNA sequence itself, by how tightly packed the DNA strands are, and by other epigenetic factors which all coalesce to form a complex mechanism of gene expression.

Studies have confirmed the connection between genetic expression patterns and the pathophysiological development of PTSD. Specifically, PTSD appears to develop from a combination of inherited genetic and epigenetic risks as well as acquired epigenetic marks that result from childhood and adult trauma exposure. To better understand the etiology of PTSD, we need to understand the role of environmental influences, genetic interactions, allele types, and epigenetic modifications. The current study utilizes a promising approach to investigate the biological and pathological pathways that are involved in the onset and progression of PTSD.
methodology to explain the gene expression differences underpinning PTSD, a transcriptome-wide design.

Many of the current transcriptome-wide gene studies that have been conducted on PTSD have generally relied on small sample sizes (N < 40). Notably, Mehta et al.¹⁰ used a 169-participant sample of participants who were abused as children with 61 PTSD cases, and attributed differential gene expression to specific DNA methylation patterns that developed as result of the maltreatment. Tylee et al.¹¹ analyzed 50 PTSD and control samples and using the 23 full-length transcripts was able to predict PTSD with a 70% accuracy. Logue et al.¹² studied 115 PTSD participants and 28 controls and identified 41 differentially expressed, though only 1 gene remained after multiple testing correction. Bann et al.¹³ utilized RNA-seq, miRNA, and DNA methylation data and found an inverse relationship between differential expression and miRNAs; the study also concluded that inflammation in PTSD may be the result of epigenetic factors. Even studies with larger sample sizes (>40) that have investigated key candidate genes related to PTSD have produced inconsistent results, which may be a result of a lack of statistical power or methodological errors.¹⁴

The current study aims to expand the current understanding of how PTSD develops using a large and relatively homogeneous sample. We made use of a publicly available RNA sequencing dataset of 324 World Trade Center responders. Previous studies on PTSD and gene expression patterns have included PTSD and non-PTSD cohorts, but no study to date has included a “past” cohort in which participants were previously diagnosed with PTSD but recovered. A past cohort would allow us to gain insight into what it means to recover from PTSD as well as understand the gene expression changes that occur when a person overcomes PTSD. In this study, the past cohort (N = 42) will be compared to PTSD and non-PTSD cohorts to allow us to better understand the transcriptomic changes that occur during PTSD recovery. This research will not only contribute to our current understanding of how PTSD develops, but it will also highlight the target genes and pathways that are driving its development.

### Methodology

The participant gene expression data utilized in this study was collected by Dr. Kuan of the University of Wisconsin and her colleagues.¹⁵ The researchers recruited a total of 324 participants from the Stony Brook World Trade Center Health Program: 201 subjects did not have PTSD, 81 had PTSD at the time of the study, and 42 previously had PTSD but did not at the time of data collection. All participants were World Trade Center responders who experienced a single major traumatic event — that is, the World Trade Center terrorist attack on September 11, 2001. This constraint limited the heterogeneity of the environmental exposure for PTSD development in the sample. To ensure that differential expression patterns were primarily due to PTSD, females were excluded from the study as females express significantly different gene expression patterns from males.¹⁶ To categorize the participants into the past, never, and current groups, the researchers used the Posttraumatic Stress Disorder Checklist (PCL-C) developed by psychology professor Frank Weathers¹⁷ that assesses the severity of the symptoms experienced by the participants related to the trauma.

### Table 1: Demographics of all three cohorts depicting age and race clinical data.

A one-way ANOVA was performed for age in all samples and a chi-squared test was used to compare race between the cohorts.¹⁵

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Never (N = 201)</th>
<th>Current (N = 81)</th>
<th>Past (N = 42)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.36</td>
<td>51.57</td>
<td>51.36</td>
<td>0.331</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>2.20</td>
<td>2.76</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>69 (65.2%)</td>
<td>33 (78.6%)</td>
<td>27 (80.0%)</td>
<td>0.100</td>
</tr>
<tr>
<td>Other</td>
<td>22 (14.8%)</td>
<td>9 (21.4%)</td>
<td>6 (16.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Blood tissue was collected by Dr. Kuan and her colleagues, which was later profiled using RNA sequencing (RNA-seq) at the Roswell Park Cancer Institute Genomic Shared. Specifically, Dr. Kuan’s team conducted transcriptome-wide expression analysis using RNA sequencing for the 324 participants. RNA sequencing is used to detect the transcriptome of RNA in each sample.¹⁸ RNA was isolated using the Paxgene Blood Collection kit (Qiagen) and purified. Abundant amounts of rRNA were removed from the sample using the rRNA depletion process.¹⁹ After the ribosomal RNA was removed, the remaining RNA was fragmented to allow for measurable sizes in the sequencer. RNA was then converted into complementary DNA (cDNA) to allow for a more stable form of molecule that can be easily modified and amplified as needed.²⁰ Multiple indexing adapters were ligated to the ends of the cDNA fragments to allow for the fragments to hybridize onto the flow cell and so the sequencing machine can recognize the fragment pieces.²¹ The fragments are then amplified, and added onto a HiSeq Flow Cell, and then sequenced using a HiSeq2500 Sequencer (Illumina Inc., San Diego, CA).

We retrieved the raw data from Kuan et al.¹⁵ via the Gene Expression Omnibus (GEO) database provided by the National Center for Biotechnology Information.²² The raw data is freely accessible with accession number GSE97356. In order to analyze the data, we used the DESeq2 software²³ provided via the R programming language. Using the DESeq2 library, we normalized the data, accounting for differences in terms of library size in the collection of the samples (also known as sequencing depth) and RNA composition. In order to allow the program to run faster and eliminate some genes that were highly unlikely to be differentially expressed, all the lowly expressed genes (<10 transcripts) were excluded from the dataset. Out of the original 25,830 genes accounted for, 24,547 remained after the manual exclusion of these lowly expressed genes. The DESeq2 library, after calculating dispersion estimates and fitting dispersion models to the data, excluded outliers that are unlikely to be differentially expressed and adjusted dispersion estimates based on its algorithm to minimize the likelihood of false positives. Once normalized, we used DESeq2 to complete a differential gene
analysis and create generalized linear models (GLMs) based on a negative binomial distribution for each gene. To test for statistical significance, we performed a Wald Test, calculated by dividing the log fold change (LFC) by its standard error. This results in a z-statistic that can then be compared to a normal distribution to obtain a p-value for each gene.

Since we used a p-value of less than 0.05, with a dataset of over 20,000 genes, we can expect over 1,000 false-positive results. This is known as the multiple testing problem and it arises from the fact that for each of the 25,830 genes, a p-value was calculated. Thus, we made use of a multiple test correction technique Benjamini-Hochberg correction to reduce the false discovery rate (FDR). With FDR < 0.05, we should expect less than 5% of those genes found to be differentially expressed after adjustment to be false positives. Therefore, we determined differential gene expression for those genes whose adjusted p-value was less than 0.05.

The DAVID Bioinformatics Resource was used to perform a KEGG analysis of the differentially expressed genes in the comparison between the never and current groups. KEGG is a set of databases containing information about genomes, biological pathways, and diseases that report the pathways likely to be involved in the observed differential gene expression. Using this platform, probable correlations between the differentially expressed genes and certain diseases and biological pathways were determined.

Results

After conducting the Benjamini-Hochberg correction, we made separate comparisons between the three groups (never, current, and past). When comparing the never and current groups, a total of 1051 genes were differentially expressed, with 516 genes being under expressed and 535 genes being overexpressed in subjects with PTSD. The volcano plot (Figure 1) depicts participant-wide expression patterns by showing the relationship between the log fold change and -log₁₀ of the adjusted p-value after multiple testing corrections. Each point on the volcano plot is representative of a gene, with differentially expressed genes (FDR < 0.05) at the top in red. A total of 238 genes displayed an LFC > 1.1 and 309 genes an LFC < 0.9. A total of 53 genes showed an LFC > 1.2 and 36 genes an LFC < 0.8.

![Figure 1: Volcano plot depicting all differentially expressed genes based on their log₂ fold change (LFC) and their transformed FDR. Genes who remained differentially expressed after multiple testing corrections (FDR < 0.05) are depicted in red.](image1)

Our data has confirmed previously identified genes with a direct correlation to PTSD, such as FKBP5, SOX5, NOS1AP, C9orf84 (SHOC1), and NFKB1. Violin plots with embedded box plots are displayed in Figure 2 for each of these genes, with the normalized count being depicted for all samples in the current and never groups. It should be noted that extreme outlier values were filtered out of the plots to make the violin plots easier to observe.

![Figure 2: Violin plots with embedded box plots displaying the normalized counts in the current and never groups for a variety of genes that have been previously identified in the literature.](image2)

A heat map is depicted in Figure 3 that compares the 283 samples for the never (N = 201) and current group (N = 81) to the DE genes with average expression mean > 50, FDR < 0.05, and log₂ FC > 0.3 (Figure 3). The color gradient identifies the z-statistic between that gene and the sample, with the extrema representing higher differential expression. The scaling occurred across the rows, and therefore no meaningful comparisons can be made between genes, but instead between samples.

When comparing the past and never groups, 138 genes were differentially expressed but only 3 remained significant after correction (and a few others with a p-value slightly above 0.05). As for the past and current groups, there was no differential gene expression, and the gene with the lowest FDR
has an FDR of 0.16. For a more detailed discussion of these groups, please see the Discussion section.

The KEGG analysis results from the DAVID resource are depicted in Table 2.

### Table 2: Pathways identified by KEGG pathway analysis. For each pathway, the number of genes differentially expressed are shown as well as the adjusted p-value.

<table>
<thead>
<tr>
<th>KEGG pathway</th>
<th>Gene Count (percent of total)</th>
<th>Benjamini Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>29 (2.8%)</td>
<td>3.1E-4</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>33 (3.2%)</td>
<td>3.8E-4</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>24 (2.3%)</td>
<td>7.6E-3</td>
</tr>
<tr>
<td>Oxidative phosphorylation</td>
<td>19 (1.9%)</td>
<td>7.0E-3</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease (NAFLD)</td>
<td>19 (1.9%)</td>
<td>3.0E-3</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>20 (2.0%)</td>
<td>3.6E-3</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>17 (1.7%)</td>
<td>8.0E-3</td>
</tr>
<tr>
<td>Ubiquitin mediated proteolysis</td>
<td>16 (1.6%)</td>
<td>1.3E-3</td>
</tr>
<tr>
<td>Neurotrophin signaling pathway</td>
<td>12 (1.2%)</td>
<td>7.0E-1</td>
</tr>
<tr>
<td>HIF-1 signaling pathway</td>
<td>10 (1.0%)</td>
<td>8.6E-1</td>
</tr>
<tr>
<td>Pymitamine metabolism</td>
<td>10 (1.0%)</td>
<td>9.0E-1</td>
</tr>
<tr>
<td>ErdB signaling pathway</td>
<td>9 (0.9%)</td>
<td>9.0E-1</td>
</tr>
<tr>
<td>NF-kappa B signaling pathway</td>
<td>9 (0.9%)</td>
<td>9.0E-1</td>
</tr>
</tbody>
</table>

### Confirmatory Results:

Our findings confirmed a variety of genes and biological pathways that have been previously identified. Below, these confirmed pathways are listed with respective references to the studies that have identified them.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene of Interest</th>
<th>Fold Change</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid Pathway</td>
<td>FKB5</td>
<td>1.27</td>
<td>Szeshko et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kong et al.</td>
</tr>
<tr>
<td>NF-kB Pathway</td>
<td>NFKB1</td>
<td>1.05</td>
<td>O’Donovan et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Guardado et al.</td>
</tr>
<tr>
<td>Systemic Lupus</td>
<td>Antibodies</td>
<td>——</td>
<td>Roberts et al.</td>
</tr>
<tr>
<td></td>
<td>Erythematosus</td>
<td>——</td>
<td>Case et al.</td>
</tr>
</tbody>
</table>

#### Neurotrophin Signaling Pathway:

The KEGG analysis concluded that 12 differentially expressed genes within our data were associated with the neurotrophic signaling pathway. This pathway is responsible for neuroplasticity and maintaining the integrity of the hippocampus. Given that this pathway is involved in moderating fear responses as well as the physiological response to stress, its downregulation exhibited in the PTSD group (with the majority of genes in the pathway being under expressed in PTSD patients) appears to contribute to the symptoms experienced by those affected by PTSD.
ErbB Signaling Pathway:

Pathway analysis found 9 differentially expressed genes within our data that are components of the ErbB signaling pathway. Among these genes is the MTOR gene, which codes for the mTOR protein, which plays a key role in the cellular response to stressors. This gene (fold change = 1.06) plays a key role in the development of fear memories. Fifield et al. concluded that the mTOR pathway was associated with the formation of oxidative stress.}

Chen et al. also confirmed these results by concluding that the ErbB4 gene (a part of the ErbB signaling pathway) was responsible for fear conditioning, and the inhibition of this gene resulted in impaired fear conditioning function in mice. These findings coupled with the results of the KEGG analysis for our dataset seems to suggest that the ErbB signaling pathway is involved in the deteriorating ability of PTSD patients to cope with fear and fear memories.

Wnt Signaling Pathway:

Previous studies demonstrated that the development of PTSD may be mediated by the Wnt signaling pathway due to malfunctions in synaptic transmission in the brain that are associated with trauma development. This pathway plays a critical role in regulating synaptic plasticity and memory formation. We identified the SYT1 gene as a possible genetic expression marker as it was upregulated in the PTSD cohort with a fold change of 1.26. The upregulation of the SYT1 gene and its interactions with Wnt pathways modulates subsequent neurotransmitter release in synapses. More recently, mice models have shown that increased expression levels of the SYT1 gene may be due to the hyperacetylation of H3K9 and H3K14, which are promoter regions for SYT1.

Major Depressive Disorder:

Previous studies have noted overlapping gene expression patterns between PTSD and major depressive disorder (MDD) patients. Our data showed that the DOCK10 gene showed around an 8% increase in expression in the PTSD cohort. Similarly, the GLS and CD47 genes were differentially expressed, though after Benjamini-Hochberg correction, there was no statistical significance (with adjusted p-values of 0.09 and 0.19, respectively). These three genes were categorized as relevant biomarkers for tracking and predicting depression. The SOX5 gene (previously associated with mood disorders) was also differentially expressed between the current and never cohorts, with expression levels 30% higher in the PTSD group (FDR < 0.05). Lastly, our results identified the C9orf84 (SHOC1) gene as a genetic expression marker for PTSD as it displayed a fold change of 1.31. This gene has been linked to MDD pathways and is therefore a gene of interest for the development of PTSD.

Schizophrenia:

Our study also found ties between PTSD and schizophrenia. Seow et al. indicated that PTSD and schizophrenia share neurological risk factors and superficial symptoms. The NOS1AP gene was identified as overexpressed by a fold change of 1.61. Overexpression of NOS1AP was found in postmortem samples of schizophrenia patients.

The protein this gene encodes binds to synapsin and disrupts the signal transduction of the N-methyl d-aspartate receptor complex, which plays a role in memory formation. The G allele of this gene has been associated with PTSD and severe depression. Our findings substantiate the connection between schizophrenia and PTSD with relation to the NOS1AP gene.

Parkinson’s Disease:

The KEGG analysis found 17 differentially expressed genes within the PTSD cohort that are associated with Parkinson’s disease (PD). There is a comorbid association between PTSD and PD but the exact biological mechanisms behind the association are yet unknown. We identified the TRIM11 gene as a possible genetic expression marker with a fold change of 0.93. TRIM11 is a protein known to restore cell viability as it prevents the formation of protein aggregates and deposits that interact with the TRIM SUGO ligase to degrade proteins that are malfunctioning. The downregulation of this gene is likely linked with neurodegeneration and may explain the connection between PTSD and PD.

Alzheimer’s Disease:

Studies have shown that individuals with PTSD have a greater chance of developing Alzheimer’s disease (AD). Our analysis of KEGG pathways found 20 genes that were implicated in the progression of AD. Specifically, the NDUFA1 gene was significantly downregulated in the PTSD cohort with a fold change of 0.81. The connection is likely due to a missense mutation which results in significant neurodegenerative side effects. The hypermethylation of the NDUFA1 sequence has been linked to under expression of the gene, indicating that epigenetic factors may be involved in this gene’s downregulation. Given the decreased expression of the NDUFA1 gene in PTSD patients, and the correlation of the gene to the development of neurodegenerative disorders, the gene should be further researched for possible associations with PTSD development.

Metabolic Pathways:

Non-alcoholic fatty liver disease (NAFLD) is a condition associated with excessive fat storage in the liver. NAFLD is a comorbid condition with PTSD and other mental disorders, due to the common pathogenesis of oxidative stress pathways and lack of mitochondrial function. Individuals with mitochondrial dysfunction have the capacity to execute needed daily life needs but have deficient mitochondrial capacity to respond to traumatic exposure. The downregulation of the NDUFA1 gene (fold change = 0.81) has been associated with the development of reactive oxygen species (ROS), which is generated by oxidative stress within cells. The formation of ROS is linked to the development of NAFLD. Therefore, the pathological connection of 19 DE genes with the NAFLD pathway from our KEGG analysis seems to derive from the differential expression of genes linked to oxidative stress.

Future Studies and Limitations:

Since the expression patterns of these samples were of blood tissue, predicting neurological associations in brain tissue is a possible limitation of our paper. However, studies have noted that blood expression patterns are accurate predictors of gene
expression in the brain. For instance, blood gene expression patterns were highly predictive (with 85 to 90 percent accuracy) of neurodegenerative gene expression patterns in the brain as well as disease progression.⁵⁴ This underscores the importance of studying blood expression patterns, since studying brain tissue would require deceased participants. Nevertheless, it is important to note this limitation as differences in genetic expression in other tissues besides blood may be present. Future studies should aim to study other tissues as well as verify the validity of using blood in understanding the development of PTSD. Another limitation of our work is that all participants were males and many of them were of the Caucasian ethnicity. Therefore, these findings may not generalize to females or other ethnicities, and future research needs to be done for these populations.

While studies have shown that psychotherapy can reverse a few epigenetic modifications made after trauma exposure⁵⁵ and help PTSD patients cope with their symptoms, these behavioral changes are not permanent and some patients experience a relapse of symptoms after treatment, often resulting in increased alcoholism and drug intake.⁵⁶ Since epigenetic marks were the cause of the altered expression levels that resulted in phenotypic differences in PTSD patients, one could theoretically reverse these marks to alleviate the symptoms. However, the field of epigenetics is in its infancy and the possibility of modifying the epigenome is but a mere contemplation. Thus, future research should begin considering whether modifying the epigenome would be a plausible and practical treatment.

■ Conclusion

In this paper, we have outlined a variety of gene expression markers that are potential prime targets for epigenetic alterations. We have also presented a variety of neurological, immune, and metabolic pathways that are associated with PTSD and other stress-related and depressive disorders. Undoubtedly, other pathways allowing for PTSD progression may exist, especially considering the complex and highly interconnected nature of this disorder. In the immediate future, it is crucial to continue validating (or challenging) the existing literature and the biomarkers and pathways identified. This will allow for future treatments to be highly calibrated and precise to the specific regions of interest and for diagnostic and screening tools to detect abnormalities before the onset of severe symptoms.

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