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The Genetics and Epigenetics of PTSD: Overview, Recent Advances, and Future Directions

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Abstract

This paper provides a brief summary and commentary on the growing literature and current developments related to the genetic underpinnings of posttraumatic stress disorder (PTSD). We first briefly provide an overview of the behavioral genetic literature on PTSD, followed by a short synopsis of the substantial candidate gene literature with a focus on genes that have been meta-analyzed. We then discuss the genome-wide association studies (GWAS) that have been conducted, followed by an introduction to other molecular platforms used in PTSD genomic studies, such as epigenetic and expression approaches. We close with a discussion of developments in the field that include the creation of the PTSD workgroup of the Psychiatric Genomics Consortium, statistical advances that can be applied to GWAS data to answer questions of heritability and genetic overlap across phenotypes, and bioinformatics techniques such as gene pathway analyses which will further advance our understanding of the etiology of PTSD.

Introduction and History of Genetics of PTSD

The classification of posttraumatic stress disorder (PTSD) within the category of “trauma- and stressor-related disorders” of the Diagnostic and Statistical Manual (DSM-5 [1])

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highlights a continued, unique challenge for genetic and epigenetic investigations of PTSD, given the diagnostic requirement of exposure to a traumatic event [2], and thus, both cases and controls in genomic studies must be exposed to a traumatic event. While the prevalence of trauma exposure is high (50-60% of the US adult population will be exposed to at least one traumatic event in their lifetime), the lifetime prevalence of PTSD is comparatively low (ranging from 7-30% depending on population and trauma type [3]), pointing to the importance of individual differences in response to trauma. While numerous psychosocial factors are related to risk for PTSD [4], evidence from family, twin, and molecular studies suggest genetic differences are also an important etiologic source of variability in risk [5, 6]. This review opens with a brief summary of behavioral genetic studies of PTSD, which provide the basis for molecular studies aimed at identification of specific genetic variation, followed by an overview of the growing molecular genomic literature, concluding with a discussion of new developments in the field.

Early work provided evidence for familial influences on PTSD. Over 100 studies of parental and offspring PTSD in trauma-exposed samples have been conducted (see recent meta-analysis [7] and review [8]). Although this line of research suggests that PTSD ‘runs in families,’ these parent-offspring designs are complicated by shared genetic and environmental risk. A second behavioral genetic design, twin studies, affords the ability to disentangle shared environmental influences from heritable influences. Twin studies (see review [9]) have demonstrated that PTSD is moderately heritable (even after controlling for genetic influences on exposure to trauma itself [5]; i.e., gene-environment correlation, rGE [10]) and that genetic influences on PTSD are shared with those for other phenotypes (e.g., complete overlap with major depression [11]). Sex differences in heritability have not been formally tested, as samples including both males and females (e.g., [12]) have not been sufficiently powered. However, examination of the pattern of findings across studies suggests that sex effects may be present (i.e., estimates of heritability differ by population, ranging from approximately 30% in male Veterans [5] to 72% in civilian women [6]). Thus, the heritability for PTSD may be nearly two to three times higher for females than males; however, a well-powered twin study of both sexes would need to be conducted to determine if there is a significant difference.

While twin studies have demonstrated latent genetic influences for PTSD, molecular genetic studies aim to identify *specific genetic variation* that may account for increased risk (see [13**] for a review and primer on genetic studies). Although a new endeavor, over 100 studies searching for genetic markers of PTSD have been published since 1991. Despite increased growth of this literature, the molecular architecture of PTSD remains largely uncharted. Following, we provide an overview of molecular genetic risk for PTSD identified to date, including candidate gene and genome-wide association studies (GWAS [14, 15**]). Other genomic platforms (i.e., gene expression and methylation) will be briefly discussed, with recent reviews highlighted.

Molecular Genetics

The majority of the extant molecular genetic studies have utilized a candidate gene design, examining either main effects or interactions with environmental variables (e.g., trauma

load) in gene by environment (G×E) designs. More recently, GWAS studies have been conducted, with eight published to date. Another exciting direction in the field of molecular genetics of PTSD is that of the formation of the Psychiatric Genomics Consortium PTSD workgroup [15**], discussed in the future directions section.

Candidate Gene Studies

In the candidate gene approach, selection of the gene(s) is informed by existing biological evidence, with candidate approaches targeting polymorphisms within and around the gene region of interest. The most commonly studied genetic variation in molecular studies of PTSD is single nucleotide polymorphisms (SNPs), in which a location in the genome has variation in a single nucleotide sequence. A wide variety of polymorphisms within genes selected from different candidate systems have been studied in relation to PTSD (see Figure 1a); to date there have been polymorphisms within 52 genes studied in relation to PTSD. This literature, similar to that of other psychiatric phenotypes, has had a number of independent replications as well as published studies that have failed to replicate initial findings. As an exhaustive discussion of the vast PTSD candidate gene literature is beyond the scope of this review, readers are directed to comprehensive reviews for further details [14-17*] and we focus our presentation of the candidate gene literature on those polymorphisms that have been meta-analyzed, and briefly highlight a few markers in a system that has gained increased interest.

Of those meta-analyzed, the serotonin transporter (*5-HTTLPR*; [18, 19]) represents one of the most highly studied polymorphisms. Both meta-analyses (including 13 and 12 studies, respectively, of which five in each were significant) found no overall association with PTSD, although suggested the importance of potential G×E with level of trauma exposure. A meta-analysis of the Val⁸⁸Met SNP in the brain-derived neurotrophic factor (*BDNF*) gene [20] (including six studies, two of which were significant), found an association only when restricting to trauma-exposed controls. A more recent meta-analysis [21] (including nine studies, four significant) found only trend-level support for an association. A meta-analysis of dopaminergic system genes [22] resulted in significant overall associations for *DRD2* (rs1800497; five of six studies significant) and *SLC6A3* (3' UTR variable tandem repeat polymorphism; five of five significant), but no effect for *COMT* Val¹⁵⁸Met, likely due to different directions of effect across the five included studies). These meta-analyses represent one way of summarizing existing evidence, highlight important factors such as differing directions of effect and utilizing a proper trauma-exposed control group, and represent a useful direction for continued efforts as the number of studies for additional polymorphisms increase.

Specifically, there are numerous genes and gene systems that have yet to be meta-analyzed (i.e., five of 52 genes studied in candidate approaches have been meta-analyzed to date) yet appear to be promising. For example, genes involved in regulation of the hypothalamic pituitary adrenal (HPA) axis system serve as useful exemplars (Figure 1b), given the HPA-axis' biological plausibility in the context of systems involved in PTSD risk (i.e., stress response; see [23*]). Two such candidate genes include the *FK-506* binding protein (*FKBP5*, modulates the glucocorticoid receptor) given its relevance with G×E (childhood

trauma) interactions [24] and *PACAP* (pituitary adenylate cyclase-activating polypeptide, coded by *ADCYAP1* gene, associated with estrogen response) given evidence of sex effects [25].

Genome-wide Association Studies

Despite the still-growing candidate gene literature, there has been a shift away from this design within the field [14], in part due to limitations of candidate gene studies more broadly (e.g., confines of existing knowledge of etiologic processes, small sample sizes, and variability in study quality; see [26] for a cogent overview). Instead, the use of more agnostic approaches has gained momentum since the first PTSD GWAS was published in 2013 [27]. GWAS uses a hypothesis-free approach that permits examination of common SNP variation across the genome. While this literature will undoubtedly continue to grow and shift, four overall conclusions can be drawn at this time. First, although two studies failed to identify SNPs that met genome-wide significance [28, 29], the majority of GWAS have identified significant hits [27, 30-34*], some of which have been internally replicated. Attempts at external replication by other groups (e.g., the *RORA* variant identified in [27]) have been successful in some [e.g., 35*], but not all [36], samples. Second, GWAS have identified novel variants that had not previously been included in candidate approaches, supporting the unique contributions of this methodology. Third, novel loci identified appear to lie in pathways identified in biologic studies of PTSD (e.g., immune system function [31, 33, 34]). Fourth, despite novel and biologically relevant findings, there has yet to be replication of identified loci across separate GWAS.

Notably, the two most recent, and largest, GWAS to date [33*, 34*] have utilized recent statistical innovations and moved beyond standard analyses to use multi-ethnic/racial meta-analysis techniques and to examine shared genetic overlap between PTSD and other phenotypes. The first study [33] conducted GWAS analyses individually within four ancestral groups, and then meta-analyzed the separate GWASs. The meta-analysis identified a novel loci, rs6482463, in the *PRTFDC1* gene, and showed support for replication in an independent sample. In a cross-disorder analysis leveraging existing GWASs of other psychiatric phenotypes, evidence of some genetic overlap was found with bipolar disorder. The second study [34] found genome-wide significance in one sample for rs159572 in *ANKRD55* (associated with autoimmune and inflammatory disorders) in African Americans and rs1108537 in *ZNF626* (thought to be involved in the regulation of RNA transcription) in European Americans (EA). However, these findings were not replicated across ancestry groups, in the other sample, nor in the combined transancestral meta-analysis. A cross-disorders analysis did not find any significant genetic overlap with a number of psychiatric conditions but did find evidence of shared genetic overlap for a number of immune-related disorders in the EA sample.

Although GWAS permit examination of many genes, the approach is not without limitations: large samples are needed for adequate power, adjustments for multiple testing must be employed, and identified loci are not necessarily disease-causing polymorphisms but may be in high linkage disequilibrium with the ‘causal’ SNP, which may demonstrate small effects.

Thus, efforts to increase sample size will be important for identifying new PTSD genes and the need for large collaborative science is being increasingly recognized [15**].

Other Genomic Platforms

The molecular genetic research evidence has pointed to the importance of examining ways environmental experiences (i.e., trauma exposure) impact outcomes of DNA through changes to the epigenome, and in turn confer risk for PTSD. Epigenetic processes have been proposed as one way the environment may “get under the skin” [37]. Epigenetic changes such as DNA methylation modify DNA structure to permit molecular adaptability (e.g., [38]) and complexity [39], with functional changes in DNA products. Although most epigenetic investigations of PTSD have focused on methylation, it is one of numerous epigenetic processes of likely relevance. As with candidate gene studies, differential methylation in a number of genes and systems has been implicated in the pathogenesis of PTSD, including *NR3C1*, *CRHR1*, and *FKBP5* (stress response), *SLC6A3* and *SLC6A4* (neurotransmitter activity), and *IGF2* (immune regulation), among others, with about 20 conducted to date (see reviews [40* and 41] and Figure 2). A few studies have also examined epigenome-wide (EWAS) markers. This approach is promising as it offers a more agnostic method of examining epigenetic influences and allows for the potential to identify novel candidate genes and biological pathways implicated in PTSD. Moreover, sample size requirements for EWAS are substantially smaller than for GWAS; while there does not appear to be a specific threshold, published studies have generally included approximately 100 cases, as opposed to the thousands required for GWAS (see [42] for review of EWAS design and power considerations). EWAS have suggested the relevance of methylation of genes involved in immune system functioning (e.g., [43, 44]), as well as promising work in the domain of methylation age (i.e., a model of cellular age using methylation levels, based on theory that chronic stress may accelerate cellular aging; for review see [45]) associated with trauma exposure and PTSD [46, 47].

Epigenetic processes may exert effects through their impact on gene expression [48]. Clear differences in expression patterns between trauma-exposed individuals with and without PTSD have been identified. Specifically, expression within genes involved in HPA-axis [49], immune function [43], and transcription of neural and endocrine proteins [50] differentiate those with and without PTSD. Limited work has examined the link between SNPs implicated in association studies of PTSD and the expression of those same polymorphisms (e.g., *PAC1* [25]). Although this work is still in its infancy, these promising genomic platforms have the potential to clarify the biological mechanisms by which trauma exposure impacts propensity for PTSD.

Challenges/Considerations for Genetic Studies of PTSD

In addition to the limitations previously discussed with regard to candidate gene and GWAS designs, unique considerations in genomic studies of PTSD include variations in trauma exposure among cases and controls, differing methods of assessing exposure and symptoms, and variability in considerations such as time elapsed since the trauma that may affect replication success, or lack thereof, across studies. Convergence of agnostic and candidate

approaches, particularly those that factor in these considerations, offer new avenues for understanding the etiology of PTSD, including nuances such as how gender, ancestry, age at trauma, trauma type, and post/peri-trauma environments may be critical considerations in the biological underpinnings of PTSD development. Rapid advances in technology and analytic approaches, as well as the development of consortia and large available datasets, provide exciting opportunities in genomic research. It will be important for researchers to continue to conduct investigations that adopt the large-sample, agnostic approach *while simultaneously* examining more carefully phenotyped smaller sample investigations, as these methods have great potential to be mutually informative and iterative in value. Researchers have pointed to heterogeneity among populations diagnosed with PTSD and genomic studies may provide a way to understand this heterogeneity if PTSD subtypes are appropriately modeled (e.g., [51]).

Conclusions and Future Directions

Converging lines of evidence from genetic epidemiologic and molecular genomic studies underscore the importance of gaining a more thorough understanding of the genetic architecture of PTSD to fully understand its etiology. As the field of psychiatric genomics has increasingly recognized the need for large collaborative science to achieve greater statistical power, great strides have been made through the formation of the Psychiatric Genomics Workgroup (PGC). In 2013 the PTSD workgroup of the PGC was founded [15**], and now includes over 100 members. The current sample size for GWAS meta-analysis is around 20,000 and by October of 2016 it is expected that the group will have approximately 25,000 PTSD cases and nearly double that amount of trauma-exposed controls. The PTSD workgroup of the PGC has also formed numerous other workgroups, including EWAS and gene expression workgroups, which will likely soon yield important breakthroughs in their respective areas.

Another exciting area of development that will benefit the field of genomics of PTSD broadly is that of novel statistical innovations that can be applied to existing GWAS data. For example, analytic techniques are now available that allow for determination of SNP-based heritability (e.g., genome-wide complex trait analysis [GCTA; <http://cns.genomics.com/software/gcta/>] and LD score regression [<https://github.com/bulik/ldsc>] wherein researchers can determine the heritability of their phenotype using measured genes in unrelated individuals. Additionally, techniques such as polygenic risk scores (PRS; <http://prsize.info>) and cross-trait LD score regression are allowing researchers to ask novel questions about the degree of molecular overlap between phenotypes. Further, as we enter the ‘post-GWAS era’, bioinformatics approaches such as gene enrichment and gene pathway analyses will become critical to advance our understanding of the etiology of PTSD.

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Highlights

- Over 100 candidate gene studies have been conducted to date
- Candidate gene studies of the HPA-axis system appear to be promising
- Genome-wide association studies have identified novel variants of risk
- Recent developments include large-scale collaborative efforts for future GWAS
- New approaches examine heritability in unrelated individuals and molecular overlap between phenotypes

Figure 1.

Figure 1a. Molecular Genetic Studies of PTSD conducted to date. *Figure 1b.* Specific candidate genes studied within the HPA axis. System = neurotransmitter system of interest; Gene = HPA axis related gene; GWAS = genome-wide association study.

Note: These counts are not exhaustive of all PTSD association studies and only include those that primarily examined an association and had a control comparison group. Counts for this figure were derived from review articles (Almli et al., 2013 and Voisey et al., 2014) as well as an updated review of the literature by author ML. *COMT* has been categorized within the dopaminergic system.

Figure 2.

Figure 2a. Epigenetic Studies of PTSD conducted to date. *Figure 2b.* Specific candidate genes studied within the HPA axis. System = neurotransmitter system of interest; Gene = HPA axis related gene; EWAS = epigenome-wide association study.

Note: These counts are not exhaustive of all PTSD epigenetic studies and only include those that primarily examined an association and had a control comparison group. Counts for this figure were derived from review article by Zannas and colleagues (2015) as well as an updated review of the literature by author CS.