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Recent Genetics and Epigenetics Approaches to PTSD

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Abstract

Purpose of Review Following a life-threatening traumatic exposure, about 10% of those exposed are at considerable risk for developing posttraumatic stress disorder (PTSD), a severe and disabling syndrome characterized by uncontrollable intrusive memories, nightmares, avoidance behaviors, and hyperarousal in addition to impaired cognition and negative emotion symptoms. This review will explore recent genetic and epigenetic approaches to PTSD that explain some of the differential risk following trauma exposure.

Recent Findings A substantial portion of the variance explaining differential risk responses to trauma exposure may be explained by differential inherited and acquired genetic and epigenetic risk. This biological risk is complemented by alterations in the functional regulation of genes via environmentally induced epigenetic changes, including prior childhood and adult trauma exposure.

Summary This review will cover recent findings from large-scale genome-wide association studies as well as newer epigenome-wide studies. We will also discuss future "phenome-wide" studies utilizing electronic medical records as well as targeted genetic studies focusing on mechanistic ways in which specific genetic or epigenetic alterations regulate the biological risk for PTSD.

Keywords PTSD · Genetics · Epigenetics · GWAS · DNA methylation

Introduction

Exposure to traumatic experience is common for most humans [1, 2•, 3]. A portion (5–15%) of the population is vulnerable to traumatic stress, does not recover, and shows persistent behavioral abnormalities like posttraumatic stress disorder (PTSD) [1, 2•, 3]. In contrast, another larger portion (> 75%) of the population remains resilient after multiple or severe exposures [1, 2•, 3]. Understanding the genetic and epigenetic underpinnings of behavioral vulnerability and resilience to traumatic stress is an active area of investigation as it would facilitate the development of preventive strategies and therapeutic interventions for PTSD [4]. In this review, we summarize research in this area, and discuss future opportunities for new discoveries.

Heredity is the transfer of certain characteristics from the parents to the offspring. At the molecular level, it primarily concerns the transmission of DNA-encoded genetic information to the next generation after sexual reproduction in humans and other mammals [5]. Apart from the inherited genetic code, there is another aspect to the genome, the epigenome, which can accommodate environmental influences in the form of chemical and protein modifications of chromatin (consisting of DNA, protein, and RNA) [6]. Epigenetic modifications can be long-lasting and alter gene regulation and expression. Such modifications include DNA methylation (mDNA) at cytosine sites, which can alter DNA binding to regulatory proteins, and histone acetylation and methylation at specific amino acids that alter chromatin availability for transcriptional activity [6]. These alterations originate from exposures during the sensitive periods of development, but have been described as a result of adult exposures too. Epigenetic inheritance is a recent exciting area of research, which investigates whether environmentally induced epigenetic alterations can pass in the next generations through the germline [7].

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Heritability

Twin Studies Twin study methodology allows researchers to identify and quantify the presence of genetic and environmental contributions to an observed trait by comparing samples of monozygotic and dizygotic twins. In the context of PTSD research, twin studies have identified a sizable genetic contribution to PTSD vulnerability, providing the impetus to use other genetic approaches in the study of PTSD. Twin studies have generally estimated the heritability for PTSD symptoms to be around 30% [8•, 9]. However, a general population study of both sexes has estimated the heritability of PTSD at 46% and an all-female study has estimated the heritability of PTSD at 71% [10, 11]. Note that these estimates of heritability are markedly higher than from large-scale genome-wide association studies (GWAS, estimating heritability of 10–20% in females and lower in males) [12••]. These lower estimates are likely due in part to the limitations of current GWAS, in that heritability estimates are limited to common single nucleotide polymorphisms (SNPs), and do not include other aspects of heritability captured by twin studies including rare variants, insertion/deletion events, potential effects of epigenetics, and gene × environment effects on heritability.

Because trauma exposure is a prerequisite for acquiring PTSD, some twin studies have also examined the heritability of likelihood of trauma exposure itself, hypothesizing that heritable personality traits put individuals at increased risk for experiencing traumatic events and consequently developing PTSD. Notably, one study has estimated a modest heritability of 20% for exposure to assaultive traumatic events [9]. Another study estimated a heritability of 60% for exposure to high-risk traumatic events [10]. Taken as a whole, these twin studies indicate the possible existence of both genotypes that predispose an individual to experience trauma and to develop PTSD.

Twin studies in PTSD were followed by candidate studies investigating limited panels of genetic variants or epigenetic marks based on a priori hypotheses for the involvement of particular genes with PTSD-risk. While most previous candidate gene studies are now questioned due to their apparent observations of high effect sizes and relatively low sample sizes relative to the large-scale GWAS effects outlined below, we will first describe a few examples that have been well-validated, either functionally or mechanistically.

Mechanistic Genetic and Epigenetic Studies

FK506 Binding Protein 51 A variety of glucocorticoid alterations associate with PTSD and predict or correlate with the treatment response [13]. These alterations have been demonstrated using brain measures and peripheral tissue, demonstrating a systemic glucocorticoid dysregulation [14, 15]. Among many genes related to HPA-axis functioning, the FK506 Binding Protein 51 (*FKBP5*) gene encoding FKBP5 protein, a co-chaperone of the glucocorticoid receptor (GR), has shown the strongest association with PTSD, albeit in interaction with presence of history of childhood traumatization [16•], and not as a main effect in predicting PTSD outcome. These variants are functional, affecting *FKBP5* expression and HPA-axis activity, as determined by a variety of in vivo and in vitro studies [17, 18].

Studies of mDNA have provided a more mechanistic understanding of how *FKBP5* variants and childhood maltreatment interact. In particular, in the presence of the minor allele of a SNP, rs1360780, childhood abuse survivors displayed increased PTSD risk. Additionally, it was found that they had decreased mDNA within a GR binding enhancer region (intron 7) of *FKBP5*, leading to increased gene expression [19••]. It was proposed that the affected mDNA sites may have been de-methylated during child development after exposure to excessive stress-induced glucocorticoids (one of the proposed culprits of childhood maltreatment). Interestingly, intron 7 de-methylation was also detected in Holocaust survivor offspring, a population at-risk for PTSD based on parental stress exposures [20]. Finally, mDNA in the promoter region was found to be correlating with reduced treatment response to psychotherapy [21]. Beyond the HPA-axis, translational studies have validated the functional role of FKBP5 in other neurocircuits relevant in PTSD pathophysiology, e.g., the amygdala-dependent fear extinction circuit [22].

Pituitary Adenylate Cyclase-Activating Polypeptide Type 1 Receptor A variant of *ADCYAP1R1*, encoding PACAP type 1 receptor (PAC1R), the receptor of pituitary adenylate cyclase-activating polypeptide (PACAP), and residing in a putative estrogen response element, has been associated with PTSD only in women [23•]. Further studies demonstrated that polymorphisms within *ADCYAP1R1* that reduce estrogen receptor (ER) binding altered *ADCYAP1R1* expression in an estrogen- and sex-dependent manner [24]. These were interesting findings in light of the higher prevalence of PTSD in women compared to men [25]. Additionally, mDNA within *ADCYAP1R1* was significantly associated with PTSD diagnosis and symptoms [23•], suggesting that, like *FKBP5*, it is regulated in both a genetic- and epigenetic way in regulating the trauma response. Furthermore, a series of interesting translational research studies suggest a crucial role of the PACAPergic system in the neural circuits that regulate stress and fear responses to trauma [26].

C-Reactive Protein There is accumulating evidence for immune dysregulation in PTSD, but it is unclear if it is related to a biological predisposition for PTSD or an outcome of the disorder or its comorbidities [27]. Some of the immune biomarkers of PTSD are robust and survive meta-analyses [28], in contrast to HPA-axis biomarkers [29], for example, which may be more sensitive to gene × environment interactions.

Analyses of peripheral blood biological markers in cohorts with pre- and post-deployment sampling design identified immune molecular alterations already in the pre-deployment samples of individuals that develop post-deployment PTSD [30–34]. Interestingly, a genetic variant of C-reactive protein (CRP) was significantly associated with increased PTSD symptom severity, including that of hyperarousal symptoms [35]. Using the top CRP-associated mDNA locus (transcription start site of the "*Absent in melanoma 2*" (*AIM2*)) gene [36], Miller et al. [37] found that the relationship between current PTSD severity and serum CRP was statistically mediated by mDNA at this locus. Multiple other studies have suggested that CRP may be a critical sensitive indicator of the inflammatory response, and may mark an "inflammatory subtype" of PTSD, depression, and other inflammatory and stress-related disorders [38]. However, whether CRP plays a causal role or is primarily providing a correlational readout of inflammation remains unclear.

Large-Scale Genetic and Epigenetic Discovery Studies

Genome-Wide Association Studies (GWAS) offer an unbiased approach to test the associations of common genetic variants across the whole genome with a trait of interest. Most GWAS test hundreds of thousands to several million SNP variants, with the requirement that this large number of genetic features would need a large number of samples. Some of the current and most successful human GWAS in PTSD are summarized in Table 1, in which 11 genome-wide studies are reported in chronological order [12••, 39, 40, 41•, 42, 43•, 44•, 45•, 46•, 47, 48]. SNP identification numbers and nearest genes are also recorded together with the sample sizes and the ancestry breakdown. In standard GWAS, the level of probability needed to reach "genome-wide significance" is simply the standard alpha = 0.05 divided by the approximate number of tests (~ 1,000,000 SNPs), for a derived multiple testing value of significance at $p < 5 \times 10^{-8}$. The majority of studies in Table 1 met genome-wide significance, except Wolf et al. 2014, which was a GWAS focused on dissociation [42]; Kilaru et al. [47], which used a different type of gene-based analysis, and thus arguably may not be required to meet the same GWAS level of statistical correction (since they were testing approximately 40,000 genes instead of 1 million SNPs); as well as Ashley-Koch et al. [45] and Melroy-Greif et al. [48].

Although it is still relatively early in the GWAS of PTSD field, many genes of interest have already been identified through these studies. The discoveries of *LINC01090* [41•], *BC036345* [44], and *ZNRD1-AS1* [47] underscore the potential significance of the non-coding genome in the development of PTSD (see [49] for a comprehensive review). *RORA* [39] encodes for the transcription factor RORα that regulates circadian genes [50], and *NLGN1* encodes Neuroligin 1 that is involved in synaptic processes and sleep/wake physiology [51]. Thus, discovering these gene as PTSD susceptibility genes highlight the potential importance of chronobiology in many mood and anxiety disorders, which all share sleeping-disturbance [52]. Similarly, *TLL1* encodes Tolloid-like protein 1, a metalloprotease with pleiotropic effects that has been implicated in processes that affect neurogenesis and neuroplasticity, and is regulated by glucocorticoids [40]. However, none of these GWAS signals have been formally replicated in an independent cohort, although many of the studies showed partial replication.

The Psychiatric Genomics Consortium (PGC) for PTSD (PGC-PTSD) Workgroup has been formed to conduct well-powered GWAS meta-analyses using the PGC analysis pipeline supplemented by secondary analyses tailored to PTSD research [53]. The first meta-analysis [12••] conducted by PGC-PTSD did not identify a loci passing 10^{-8} cut-off in the overall meta-analysis, but identified a significant SNP (rs139558732—close to Kelch-like protein 1 (*KLHL1*) gene) in the AA ancestry (Table 1). More interestingly, this study provided a SNP-based heritability estimate comparable to that of other major psychiatric disorders, and confirming the notion of higher heritability in women. Additionally, this study demonstrated a genetic correlation between schizophrenia and PTSD. The PGC-PTSD has currently over 72,000 samples consisting of nearly 20,000 cases and 52,000 controls. The PGC-PTSD samples have more ancestral diversity than the other PGC disorders, bringing benefit and additional samples to the overall PGC and cross-disorders analyses. Ongoing large studies from the PGC-PTSD, Million Veterans Program, and likely others offer great promise for the pending rapid elucidation of a large-scale, GWAS-based, "genetic architecture" of PTSD.

Epigenome-Wide Association Studies (EWAS) offer a distinct approach to examining epigenetic influences for potentially identifying novel candidate gene pathways implicated in various diseases. The sample size examined so far in EWAS studies to date is noticeably smaller than in GWAS. Most commonly, EWAS analyze mDNA sites since it is the most cost-effective epigenetic mark to measure in large-scale studies using commercial microarrays or sequencing-based methods. Some of the current human EWAS that have examined mDNA alterations in PTSD are summarized in Table 2. EWAS are listed in chronological order (2010–2017) [54•, 55, 56, 57•, 58, 59•, 60, 61]. The sites with differential mDNA together with the nearest gene are reported.

The findings generally comport with our current understanding of the etiology of PTSD, implicating many known pathways of the disorder. For example, the EWAS with the largest sample size to date identified epigenetic changes related to synapic plasticity, cholinergic signaling, oxytocin signaling, and inflammatory responses [61]. Smaller studies

Table 1 Genome-wide association studies (GWAS) in PTSD

Study	Sample size	Significant SNP(s)	Nearest gene	*p* value	Notes
Logue et al. [39]	Discovery: $N = 491$ European American Replication: $N = 600$ African American	rs8042149	RAR related orphan receptor A (RORA)	2.50E-08	
Xie et al. [40]	Discovery: $N = 1838$ European American $N = 3380$ African American Replication: $N = 1578$ European American $N = 744$ African American	rs6812849	Tolloid like 1 (TLL1)	3.10E-09	
Guffanti et al. [41•]	Discovery: $N = 413$ African American Replication: $N = 2541$ European American	rs10170218	LINC01090 (long non-coding RNA)	5.09E-08	
Wolf et al. [42]	Discovery: 484 Non-Hispanic White	rs263232	ADCY8 adenylate cyclase 8 (ADCY8)	6.12E-07	Outcome: Dissociation
Nievergelt et al. [43•]	Discovery: $N = 3494$ European American, African American, East Asian, Latin American Replication: $N = 491$ European American	rs6482463	Phosphoribosyl transferase domain containing 1 (PRTFDC1)	2.04E-09	
Almli et al. [44]	Discovery: $N = 147$ European American, African American, East Asian, Latin American Replication: $N = 2006$ African American	rs717947	BC036345 (long non-coding RNA)	1.28E-08	
Ashley-Koch et al. [45]	Discovery: 949 Non-Hispanic Black 759 Non-Hispanic White	rs7866350 Non-Hispanic White	TBC1 domain family member 2 (TBC1D2)	1.10E-06	
Stein et al. [46•]	Discovery: 5049 European American 1312 African American 1413 Latin American	rs159572	Ankyrin repeat domain 55 (ANKRD55)	2.34E-08	
	Replication: 4007 European American 667 African American 1242 Latin American	rs11085374	Zinc finger protein 626 (ZNF626)	4.59E-08	
Kilaru et al. [47]	Discovery: 3678 African American	N/A	Neuroligin 1 (NLGN1)	minSNP: 1.00E-06	Method: Gene-based
	Replication: $N = 205$ South African	N/A	ZNRD1-AS1 (long non-coding RNA)	VEGAS: 1.00E-06	
Melroy-Greif et al. [48]	Discovery: 254 Mexican Americans 258 American Indians	rs6681483 rs6667389 rs10888255 rs10888257	Olfactory receptor family 11 subfamily L Member 1 (OR11L1)	1.83E-06	
Duncan et al. [12••]	Discovery: 9954 European American 9691 African American 698 Latin American 387 South African	rs139558732 African American	Kelch-like protein 1 (KLHL1)	3.33E-08 LDSC = 0.36 s.e. = 0.12, $p = 3.00E-03$ GCTA = 0.21, s.e. = 0.09, $p = 1.90E-03$	 Method: SNP-based heritability Method: SNP-based heritability
	Replication: As in [46•]				

Table 2 Epigenome-wide association studies (EWAS) in PTSD

Study	Sample size	N of CpG tested	Significant CpG site(s)	Nearest gene	*P* value	Analysis cut-off	Validation	Highlights
Uddin et al. [54•]	*N* = 100	27 k	cg17709873	Lymphotoxin alpha (LTA)	3.00E − 3 (unadjusted)	Classified probes with beta < 0.2 as unmethylated, and probes with beta > 0.8 as methylated; averaged the methylation levels for each gene in each of the two groups and then determined the number of shared and uniquely methylated/ unmethylated genes	Pyro-sequencing and targeted DNA sequencing	Immune system functions were overrepresented among the uniquely unmethylated genes in subjects with PTSD.
			cg25831111	Coenzyme A synthase (COASY)	1.00E − 3 (unadjusted)			
Smith et al. [55]	*N* = 110	27 k	cg24577137	Translocated promoter region, Nuclear basket protein (TPR)	1.90E − 06	FDR < 0.05	Plasma cytokine measures	PTSD was associated with increased global mDNA and differential mDNA of genes associated with inflammation.
			cg08081036	Annexin A2 (ANXA2)	9.30E − 06			
			cg20098659	C-type lectin domain family 9 member A (CLEC9A)	4.30E − 06			
			cg07967308	Acid phosphatase 5, Tartrate resistant (ACP5)	8.00E − 06			
			cg07759587	TLR8 toll like receptor 8 (TLR8)	1.10E − 05			
Uddin et al. [56]	*N* = 100	27 k	118 CpG sites/116 genes		1.00E − 2 (unadjusted)			Socioeconomic position moderated the relationship between methylation levels of genes involved in neuronal function and PTSD symptoms.
Mehta et al. [57•]	*N* = 169	3958 CpG sites of differentially expressed genes	458 CpG sites/164 genes		< 5.00E − 2	permutation of regressor residuals test	Sequenom EpiTYPER	Compared with PTSD cases without childhood abuse, PTSD cases with childhood abuse showed distinct gene expression and mDNA profile
Mehta et al. [58]	Discovery: *N* = 211	450 k	cg26499155	Intergenic (43 kb from leucine-rich repeat containing 3B (LRRC3B))	7.94E-07		Expression analyses	Decreased mDNA was associated. with increased PTSD symptoms severity for the CpG in BRSK1, NGF, LCN8, and DOCK2. However, increased mDNA was associated with increased PTSD symptom severity in the intergenic CpG.
			cg02357741	BR Serine/Threonine kinase 1 (BRSK1)	2.24E-06			
	Replication: *N* = 115		cg09325682	Lipocalin 8 (LCN8)	3.28E-06			
			cg17750109	Nerve growth factor (NGF)	3.06E-06			
			cg16277944	Dedicator of cytokinesis 2 (DOCK2)	4.95E-06			
Rutten et al. [59]	Discovery: *N* = 93 Replication: *N* = 98	450 k	17 DMPs and 12 DMRs	Dual specificity phosphatase 22 (DUSP22) Histone cluster 1 H2A pseudogene 2 (HIST1H2APS2)	< 5.00E − 2	FDR or permutation-based cut-off	Pyro-sequencing	Emergence of PTSD symptoms over a deployment period to a combat zone was significantly associated with decreases in mDNA in ZFP57, RNF39 and HIST1H2APS2.

Table 2 (continued)

Study	Sample size	N of CpG tested	Significant CpG site(s)	Nearest gene	*P* value	Analysis cut-off	Validation	Highlights
				Hook microtubule tethering Protein 2 (HOOK2) Ninjurin 2 (NINJ2) Paired box 8 (PAX8) Ring finger protein 39 (RNF39) Zinc finger protein 57 (ZFP57)				
Hammamieh [60]	Training set: *N* = 99	27 k CpG islands	5578 differentially methylated CpG islands	3662 DMGs	< 5.00E − 2 (unadjusted)	Nominal significance	Targeted bisulfite sequencing	Majority of the CpG islands differentially methylated showed increased mDNA in PTSD cases and the respective DMGs were enriched for four functional clusters (somatic complications, endocrine signaling, nervous system development and nervous system functions).
	Test set: *N* = 60	27 k CpG islands						
	Merged *N* = 159	450 k		3339 DMGs				
Kuan et al. [61]	*N* = 473		cg05693864	Zinc finger DHHC-type containing 11 (ZDHHC11)	1.73E − 06	Nominal significance		Pathways significant in PTSD included a regulator of synaptic plasticity, oxytocin signaling, cholinergic synapse, and inflammatory disease pathways.
			cg06182923	CUB and sushi multiple domains 2 (CSMD2)	4.73E − 05			
			cg08696494	Collagen type IX alpha 3 chain (COL9A3)	5.39E − 05			
			cg25664402	Intergenic	5.80E − 05			
			cg05569176	Programmed cell death 6 Interacting protein (PDCD6IP)	7.82E − 05			
			cg09370982	TBC1 domain family member 24 (TBC1D24)	8.97E − 05			
			cg07654569	Family with sequence similarity 164, member A (FAM164A)	9.91E − 05			

CpG cytosine–phosphate–guanine, *DMG* differentially methylated gene, *FDR* false discovery rate, *kb* kilobases, *mDNA* DNA methylation, *PTSD* post-traumatic stress disorder

have implicated immune and inflammatory responses [54•, 55, 59•, 60], endocrine [60] and nervous system [56, 59, 60] pathways. One study has observed differential mDNA profiles in PTSD subjects with and without childhood abuse history [57•].

Unfortunately, most of these studies were underpowered to detect a signal that survives multiple-test correction. Additionally, all studies used DNA derived from blood which represents a bias toward detecting the involvement of certain pathways that are more active in blood cells, and epigenetic signals unique to the brain may be missed with these approaches. Within the PGC-PTSD, a special EWAS working group has been formed with the goal to create a large PTSD-focused mDNA data set meta-analyzed under a consensus pipeline with a current total $n = 1147$ of samples [62].

As the sample sizes increase and new consortia are built with combined datasets, the field is hopeful that the GWAS and EWAS combined data will be particularly powerful for elucidating genomic markers of risk and resilience in PTSD using integrated genetic-epigenetic analyses, as applied successfully in other environmentally induced diseases like type 2 diabetes [63].

Alternative Approaches

Alternative Phenotypes An alternative approach to traditional diagnosis-based GWAS is to consider psychiatric traits in terms of constellations of symptoms or endophenotypes, and to analyze these individuals jointly, rather than according to strict diagnostic boundaries [64, 65]. For example, one might consider grouping individuals on the basis of the presence of manic or psychotic episodes, rather than schizophrenia and bipolar disorder diagnoses [66]. These types of analyses have already been successful in studying shared genetic risk of bipolar disorder and schizophrenia [67, 68]. This approach can also be applied to PTSD that is comorbid with depression, traumatic brain injury, and a variety of psychiatric conditions [2•, 69] and physical health conditions [70].

Intermediate phenotypes (or endophenotypes) of disease are considered to be more proximal to genetic risk and have been recently applied to psychiatric genetic rirsk [71, 72], with limited success so far due to small sample size [73]. This is an approach that will be applied to PTSD by the PGC-PTSD psychophysiology working group that is aggregating data across ~2000 individuals, including cardiovascular measures, acoustic startle reflex, affective modulation of startle, conditioned fear and extinction, as well as skin conductance response.

eQTLs and Transcriptomic Imputation Large-scale GWAS have had substantial success in elucidating the genetic architecture of psychiatric disorders, but they rely on very large sample sizes. Additionally, even when successful, these types of results may be difficult to interpret biologically; in particular, it is difficult to translate large lists of associated loci into meaningful mechanisms for follow-up study. Finally, another complication is the effect of "winner's curse" in GWAS; that is, findings close to the genome-wide significance threshold are likely to be inflated, and consequently do not often replicate [74]. Successful, well-powered GWAS therefore may produce large lists of loci, but these have the risk of being uninformative and overly optimistic.

Expression quantitative trait loci (eQTLs) are SNPs that are directly associated with gene expression changes. Considering GWAS loci in the context of eQTLs might allow us to identify and prioritize interesting disease-associated variants. eQTLs provide a plausible link between genetic variants and disease through genetically regulated gene expression [75, 76•, 77, 78•], are enriched among GWAS loci [79], and explain a substantial proportion of the variance in gene expression [75, 76•, 77, 78•].

Methylation quantitative trait loci (mQTLs), a similar concept of genetic variants associated with specific differential mDNA, may be used to further contextualize GWAS loci [80•]. For instance, the PTSD-associated SNP, rs717947, is a mQTL of cg09242288 [44]. The data from this study identified a genome-wide significant polymorphism conferring risk for PTSD, which was associated with differential epigenetic regulation and with differential cortical responses to fear (via fMRI) in a replication sample. Identifying differential epigenetic regulation of gene pathways is another way of providing added support for understanding the possible function of genetic variants at the single nucleotide polymorphism level.

Multiple methods exist to assess, for example, the extent of co-localization between GWAS loci and eQTLS [81–83], or mQTLs [84], and have been successfully applied to elucidate genetic architecture of schizophrenia [78, 80•, 83, 85]. However, these methods make a number of necessary simplifying assumptions regarding allelic heterogeneity and linkage disequilibrium (LD) structure, as well as assuming only a single causal variant or eQTL. Addressing these assumptions can produce additional useful information about disease risk; for example, investigating multiple eQTLs rather than a single "maximum" eQTL improves fine-mapping of schizophrenia GWAS loci [78]. For example, eQTL associations for the "candidate" PTSD risk SNP rs363276 (affecting expression of solute carrier family 18 member 2 (SLC18A2) and PDZ domain containing 8 (PDZD8)) have been recently reported, using amygdala and dorsolateral prefrontal cortex postmortem gene expression data [86].

A natural extension to these eQTL-based approaches is to consider simultaneously the effect of all local variants on gene expression. Transcriptomic imputation (TI) approaches [87, 88] use large, well-curated eQTL reference panels [85, 89••, 90] to codify relationships between all variants within the *cis*-region and expression of a given gene; these relationships may

then be used to predict genetically regulated gene expression from genotypes, and test for association with case-control status [87, 88, 91]. As well as the obvious benefit of biologically interpretable results, this approach allows researchers to study for the first time genes with only modest effect sizes, which likely constitute a large proportion of the risk for psychiatric disorders [85, 92]. Further, gene expression levels may be probed in traditionally inaccessible tissues, circumventing many of the confounders present in RNA-seq or other transcriptomic analyses. Finally, the use of genetically regulated gene expression means that directions of effect are easy to interpret.

Unlike traditional transcriptome studies, in which gene expression may be affected by disease-related behaviors and environmental factors, and at specific developmental times when tissue is collected, TI-determined genetically regulated gene expression changes is less influenced by these factors [87]. For instance, many of the genes identified with this method for schizophrenia are expressed specifically pre-natally or post-natally, well before disease onset [93]. Such findings suggest that genetic regulation of differential gene expression during brain development may set up neural circuits that have differential risk for disease development later in life. Such approaches to TI have been successfully applied to identify associated genes in a number of psychiatric disorders including schizophrenia, bipolar disorder, anorexia nervosa [91, 94–96], and studies of the imputed transcriptome in PTSD are underway [97].

Electronic Health Records for Phenome-Wide Association Studies Electronic health records (EHRs) present an exciting opportunity for researchers to study psychiatric disease risk. These records are often linked to genotypes through population- or hospital-based biobanks, and, importantly, tend to be demographically representative of the general population [98, 99]. The deep phenotyping available through EHRs enable researchers to consider the impact of a gene or variant on all recorded traits, phenotypes, endophenotypes, and behaviors, rather than on a specific disease or trait, using a phenome-wide association study (PheWAS) [100–103, 104•]. A number of elegant algorithms and software packages exist to run these analyses [105, 106], and PheWAS catalogs are openly available [107]. Testing PTSD-associated variants and genes using this approach may substantiate epidemiological observations about comorbid phenotypes (for example, an increased risk of cardiovascular disease [70, 108, 109]), and clarify whether these comorbidities are due to shared genetic etiology, some shared effect of exposure to trauma, PTSD treatment, or some other factor. The longitudinal aspect of EHRs will also allow researchers to track whether comorbid conditions precede PTSD onset or trauma exposure, as well as whether symptoms persist after treatment for PTSD. Such a longitudinal assessment recently showed that there was no relationship with sleep-disordered breathing on cognition in a sample of Vietnam veterans with PTSD [110].

Conclusions

In this brief review, we have examined the current evidence for heritability of PTSD, as well as large-scale, unbiased genome-wide association studies searching for new genomic variants associated with the syndrome. We also examined more modest epigenome-wide studies that have been performed to-date, in an effort to identify differential mDNA patterns associated with PTSD risk. Most psychiatric disorders, and certainly PTSD, are a result of both environmental risk (e.g., trauma exposure) and biological risk. Increasing evidence suggests that one mechanism for gene × environment interactions that differentiate risk vs. resilience is via epigenetic processes. Future work in this area provides promising opportunities for a more detailed mechanistic understanding of how environmental exposure interacts with the genome in neural systems. Finally, we discussed new approaches that may lead to identifying intermediate phenotypes more closely aligned with the biology of disease. The intersection of current large-scale studies with improving causal approaches provide a hopeful future for understanding the biology, which provide promise for future novel interventional approaches routed in mechanism.

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Compliance with Ethical Standards

Conflict of Interest Nikolaos P. Daskalakis, Chuda M. Rijal, Christopher King, and Laura M. Huckins declare no conflict of interest.

Kerry J. Ressler is on the Scientific Advisory Boards for Resilience Therapeutics, Sheppard Pratt-Lieber Research Institute, Laureate Institute for Brain Research, The Army STARRS Project, UCSD VA Center of Excellence for Stress and Mental Health—CESAMH, and the Anxiety and Depression Association of America. He provides fee-for-service consultation for Biogen and Resilience Therapeutics. He holds patents for use of D-cycloserine and psychotherapy, targeting PAC1 receptor for extinction, targeting tachykinin 2 for prevention of fear, targeting angiotensin to improve extinction of fear. Dr. Ressler is also founding member of Extinction Pharmaceuticals to develop d-Cycloserine to augment the effectiveness of psychotherapy, for which he has received no equity or income within the last 3 years. He receives or has received research funding from NIMH, HHMI, NARSAD, and the Burroughs Wellcome Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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