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Genetics of PTSD: Fear Conditioning as a Model for Future Research

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Abstract

In the last decade, the number of publications in psychiatric genetics has nearly tripled but little attention has been paid to the role of genetic factors in the etiology of posttraumatic stress disorder (PTSD). The present review summarizes the current state of genetic research on PTSD. First, we outline information regarding genetic influences provided by family investigations and by twin studies. Second, we propose the fear-conditioning model of PTSD as a framework for the nomination of candidate genes that may be related to the disorder. Third, we review lines of evidence from three neurobiological systems involved in fear conditioning, and we summarize published investigations of genetic variants studied in association with PTSD in these three systems. Finally, we review gene-by-environment interaction research, a promising novel approach to genetic research in PTSD.

Keywords

posttraumatic stress disorder; trauma; genetics; gene-by-environment interaction

Although epidemiological studies reveal that the majority of individuals have been exposed to at least one potentially-traumatic event (PTE) during their lifetime, a minority of trauma-exposed individuals develop posttraumatic stress disorder (PTSD) [1]. Genetic research has the potential to inform our understanding of why some individuals are vulnerable and others resilient to the effect of PTEs. The present paper provides an overview of genetic factors in the etiology of PTSD, with a focus on how our understanding of underlying neurobiologic alterations in patients with PTSD [2] should inform future research in this area.

PTSD is Heritable

If genetic factors play an etiological role in PTSD, family members of individuals with PTSD should have a higher prevalence of PTSD than similarly trauma-exposed family members who did not develop PTSD. This pattern has been shown in trauma-exposed adult children of Holocaust survivors; specifically, adult children of survivors with PTSD were more likely following trauma exposure to develop PTSD than were adult children of survivors without PTSD [3] This familial association has also been found in Cambodian refugees [4]. However, since family members frequently share important environmental experiences, family studies cannot

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tell us whether a disorder runs in families for genetic or environmental reasons. Twin studies have been used to distinguish between genetic and environmental contributions to risk for PTSD.

Twin studies have made three important contributions to our understanding of the genetic etiology of PTSD. First, and perhaps most notably, they indicate that genetic factors influence exposure to PTEs. This is referred to as gene-environment correlation, whereby selection of environment, and subsequently potential for exposure to trauma, is partly determined by genetic factors [5]. For example, twin studies have demonstrated that genetic factors influence exposure to PTEs. Lyons et al. [6] included members of the Vietnam Era Twin Registry (VET) and studied variables indicative of war-related trauma (e.g., volunteering for service in Southest Asia, service in Southeast Asia, combat exposure, being awarded a combat medal). Heritability estimates ranged from 35% for Southeast Asia service to 54% for being awarded a combat medal. Additionally, a civilian study found evidence for a gene-environment correlation for assaultive violence [7]. Second, twin studies suggest genetic influences explain a substantial proportion of vulnerability to PTSD even after accounting for genetic influences on PTE exposure. An early examination of the Vietnam Era Twin (VET) Registry reported that 30% of the variance in PTSD was accounted for by genetic factors, even after controlling for combat exposure [8]. Similarly, a twin study of male and female civilian volunteers identified similar heritability of PTSD, with further variance accounted for by non-shared environmental factors [7]. The findings from these two twin studies suggest that genetic factors play an important role in vulnerability to developing PTSD. Third, data from twin studies on PTSD indicate some degree of distinctness of genetic influences on PTSD, and some degree of overlap in genetic contributions with other mental disorders. For example, genetic influences on major depression account for the majority of the genetic variance in PTSD [9, 10]. Genetic influences common to generalized anxiety disorder and panic disorder symptoms account for approximately 60% of the genetic variance in PTSD [11] and those common to alcohol and drug dependence [12] and nicotine dependence [13] account for over 40% of the variance associated with PTSD. Thus, the majority of genes that affect risk for PTSD also influence risk for other psychiatric disorders and vice versa.

The twin studies cannot tell us which genes are important in PTSD etiology. Molecular genetic studies that seek to identify specific genes implicated PTSD are needed to achieve that goal.

Translational Research and Molecular Studies of PTSD

Molecular genetic investigations seek to identify specific genes that may confer increased risk or resilience for a phenotype. Identification of such genes can inform our understanding of neurobiologic factors that may influence the development, maintenance, or treatment of a disorder. It should be noted that although molecular genetic research has the potential to inform knowledge of disorder etiology, this methodology is not without its drawbacks (e.g., difficulties in interpretation of findings, determination of functional variants). Nonetheless, one promising approach to molecular genetic research, the candidate-gene association methodology, uses knowledge of the underlying biology of a disorder to inform selection of potential candidate genes. We propose that the fear conditioning model of PTSD offers a promising framework for selecting candidate genes for association studies, thereby nominating candidate genes for PTSD, beyond those that have been previously studied.

Fear Conditioning Model of PTSD

Given the critical role of PTE exposure in subsequent development of PTSD, the acute stress response to PTE exposure provides a helpful framework for understanding the pathogenesis of PTSD. Typically, exposure to an acute stressor triggers the “fight-or-flight” response, initiating activity in the hypothalamic-pituitary-adrenal (HPA) axis, the locus coreruleus and

noradrenergic systems, and the neuro-circuitry of fear system. From an evolutionary perspective, activation of this stress response in potentially dangerous circumstances may allow an individual to identify danger, mobilize resources for escape or defense [14] and may also permit encoding of information to promote rapid identification of similar danger in the future [15]. However, this adaptive response has also been implicated in fear conditioning models of PTSD etiology. Pitman [16] hypothesized that elevations in catecholamines during and immediately following PTE exposure may serve as a mechanism through which memories can be "over-consolidated," resulting in the intrusive recollections and re-experiencing symptoms of PTSD. Subsequent repetitive reliving and re-encoding of the traumatic event following the PTE exposure may reinforce aberrant memory formation [17]. Furthermore, individuals with PTSD show difficulties with extinction; initial fear conditioned responses are particularly intractable [18]. Since the neurobiologic processes underlying the fear-conditioning in animal models and human correlational studies of PTSD are well-characterized, the fear-conditioning model provides a promising guide for the selection of candidate genes; however, it should be noted that these circuits potentially involve thousands of genes that may or may not be implicated in the disorder. Further, PTSD is a complex disorder, meaning it likely is developed and maintained by many genetic and environmental factors. Below, we review the lines of evidence for the three neurobiologic systems implicated in the fear-conditioning model (i.e., HPA axis, locus coeruleus and noradrenergic system, limbic-frontal neuro-circuitry of fear), suggesting a partial list of candidate genes for future molecular genetic PTSD studies (see Table 1). We include a review of all published molecular genetic studies of PTSD within each section (see Table 2).

HPA Axis

The HPA axis regulates the release of stress hormones and is activated by corticotrophin-releasing hormone (CRH) which in turn activates the noradrenergic system [19]. Variation in CRH system genes and binding proteins (CRH-BP) are hypothesized to mediate a highly stress reactive temperament which may be particularly vulnerable to HPA axis dysregulation when faced with a PTE. Lines of evidence from transgenic [20], primate [21], and human studies [22] support this notion. Therefore, it is likely that variants in the CRH and its receptors (CRH-R1, CRH-R2), and CRH-BP may be associated with risk of PTSD.

Modulation of CRH response to threat relies on a complex feedback system involving the glucocorticoid receptors (GCCR, GCR2) and regulating genes (e.g., FKBP5). Increased sensitivity of glucocorticoid receptors have been posited to mediate HPA axis dysregulation in PTSD [23], and genetic variation in this feedback system is also thought to contribute to HPA axis dysregulation [24]. This increased glucocorticoid sensitivity has been found to be negatively correlated with age at first PTE exposure, suggesting early adversity may magnify the effect of GCCR genetic variation [25]. Given evidence that PTSD patients hypersuppress cortisol in response to low-dose dexamethasone treatment [26], fear conditioning models have been expanded to incorporate altered posttrauma cortisol response. Yehuda and colleagues proposed that exaggerated catecholamine increases during traumatic stress without the regulatory influence of accompanying cortisol increases could lead to inappropriate memory formation (either over-salient or fragmented memories) and result in the intrusion symptoms that characterize PTSD [27]. Low peritrauma cortisol levels may fail to contain the noradrenergic stress response, leading to consequent prolonged increases in levels in norepinephrine in the brain [28], and altered consolidation and retrieval of traumatic memories [29]. Research has also implicated glucocorticoids in modulation of extinction of fear memories [30]. Nonetheless, the only published investigation of glucocorticoid genes in PTSD reported no association between two glucocorticoid receptor polymorphisms (N363S and BclI) and PTSD [31].

One key regulating gene of this system is *FKPB5*. A recent study revealed that polymorphisms in *FKBP5* moderate PTSD given exposure to childhood sexual abuse [32]. Further, dexamethasone suppression test data also demonstrated a GxE interaction between *FKBP5* polymorphisms and PTSD status, suggesting that these polymorphisms have functional consequences on glucocorticoid response system sensitivity. Polymorphisms in FKBP5 were also found to be associated with peri-traumatic dissociation [33] which predicts the development of PTSD [34]. Thus, variation in the glucocorticoid receptor genes (GCCR, GCR2[GRLL1]) and glucocorticoid regulating genes (e.g., FKBP5) may be related to increased risk of PTSD.

Yet another system that may play a key role in regulation of the HPA axis is the endocannabinoid system [35]. Endocannabinoids, endogenous ligands for cannabinoid type 1 receptors, appear to constrain corticosterone release [35, 36] and play a key homeostatic role in HPA axis activity. A recent family-based sample of trios (youth and biological parents recruited for youth ADHD diagnosis), examined associations between the cannabinoid receptor gene (CNR1) and numerous psychiatric diagnoses in both youth and parents [37]. Two variants (C-A and C-G) were associated with PTSD in a sample of Caucasian parents recruited from Los Angeles, California with a similar but nonsignificant trend observed in a Finnish sample. However, no differences were observed in the Los Angeles trios, though comorbid PTSD was uncommon (n = 6) in the youth. Beyond the potential effects of endocannabinoids on HPA axis function, endocannabinoid signaling has also been implicated in learning and memory processes, including extinction of fear memory [38].

Locus coeruleus/noradrenergic system

Noradrenergic hyperactivity in the basolateral amygdala is hypothesized to mediate the overconsoliation of fear memory in PTSD [34]. Emotional arousal is associated with enhanced norepinephrine (NE) release in limbic areas [39]. Several genes are involved in synaptic availability of NE including the NE transporter gene (SLC6A2, also called NET1), the dopamine beta hydroxylase gene (DBH), and the catechol O-methytransferase gene (COMT). The only genetic study of these NE-related genes investigated polymorphisms within DBH in a study of combat-related PTSD, and reported no difference in genotype frequency for the -1021C/T polymorphism of the DBH gene and PTSD, but did find that PTSD cases with the 'CC' genotype had lower DBH activity than non-PTSD cases with the same genotype [40]. Variation in the alpha2C adrenergic receptor (ADRA2C), a terminal autoreceptor for NE, may also be associated with the altered NE feedback implicated in PTSD, as ADRA2C agonists (e.g., opioids), administered shortly after traumatic exposure reduce risk of developing PTSD [41]. Beta-1 (ADRB1) and beta-2 (ADRB2) adrenergic receptors also appear to mediate memory overconsolidation [17], and administration of beta-adrenergic antagonists (e.g., propranolol), in the acute aftermath of PTE exposure reduces risk of developing PTSD [42]; following, ADRB1 is implicated, as polymorphisms in ADRB1 influence responsiveness to beta-blockers [43]. Neuropeptide Y (NPY) is co-localized with norepinephrine, and released in association with burst firing of noradrenergic neurons, and has been found to be lower in those with PTSD [44]. Through its receptors (NPY1R, NPY2R), NPY may attenuate the release of norepinephrine and acetylcholine in the hypothalamus, medulla, and sympathetic nervous system and moderate the fight-flight response [2]. Leu7Pro SNP in the NPY gene may influence circulating levels of NPY; however, in the one association study of this loci, no significant association was found [45]. Variation in noradrenergic system genes, such as SLC6A2 (NET1), DBH, COMT, ADRA2C, ADRB1, ADRB2, NPY, NPY1R, and NPY2R may therefore be associated with risk for PTSD.

Neuro-circuitry of Fear

Neuro-circuitry models of PTSD implicate exaggerated amygdala responsiveness, deficient frontal cortical function, and deficient hippocampal function in the pathogenesis of the disorder

[46]. Both the GRP gene, which encodes gastrin-releasing peptide, and stathmin, which inhibits microtubule formation, are highly expressed in the amygdala's lateral nucleus. The GRP and stathmin genes appear to be required for the regulation of fear conditioning in mice [47]. Examination of the homologous genes in humans, GRP and STMN1, with PTSD may be warranted.

Dopamine (DA) [48], serotonin [49], and opioid neurotransmitter systems [50] are involved in modulation of traumatic memories. Animal models have demonstrated stress-related responsivity of DA enervation in the amygdala, with findings suggesting that response to stress may be modulated by genetically-determined DA receptors [51]. DA system genes have received the most attention in molecular genetic studies of PTSD; five out of the six gene association studies of DA system genes studied the association between marker alleles at the D2 DA receptor gene (DRD2) and PTSD. Whereas initial investigations found a positive association with the DRD2A1 allele [52, 53], a subsequent investigation found no association with the DRD2A1 allele or with any combination of alleles for the DRD2 locus. [54] However, it is important to note that Gelernter and colleagues did not assess for trauma exposure in the control group, and following, it is possible that, following trauma exposure, the control participants might have developed PTSD, thereby limiting the utility of this comparison group. A recent investigation of three polymorphisms of the DRD2 region revealed a significant association between the 957C>T polymorphism ('C' risk allele) and PTSD in war veterans; the two other polymorphisms (TaqIA, -141delC) were not associated with PTSD [55]. An additional study found a positive association between DRD2A1 and PTSD only in the subset of PTSD cases who engaged in harmful drinking [56]. The final study examined a slightly different facet of DA transmission in patients with chronic PTSD and PTE-exposed healthy controls, reporting a positive association between of the DA transporter SLC6A3 (DAT1) 3'polymorphism and chronic PTSD [57].

Serotonin (5-HT) has also been tied inhibition of amygdala-modulated development of fear memories [49]. Surprisingly few studies have examined serotonergic system genes and PTSD. One investigation examined an insertion/deletion polymorphism in the promoter region of the serotonin transporter (SLC6A4, locus 5-HTTLPR), with the short (s) variant less transcriptionally efficient than the long (l) allele [58]. Of note, given evidence for extinction deficits in individuals with PTSD [18], individuals with the s allele show decoupling of the amygdala-frontal brain feedback circuit responsible for extinction of fear conditioning [59]. A candidate gene investigation study of 5-HTTLPR reported an excess of s/s genotypes in Korean PTSD patients compared with normal controls [60]. The serotonin 2A receptor gene polymorphism has also been studied in related to PTSD in a case-control design [61]. A trend was found for higher frequency of 'G/G' genotype in PTSD cases, and this association was significant among female participants. Of note, although the control group did not meet criteria for "major psychiatric problems," it was not reported if these individuals were assessed for trauma history.

Brain imaging studies in PTSD also support a role for the hippocampus, with PTSD reported to be associated with reduced hippocampal volume and function [62]. A twin study suggested that differences in hippocampal volume represent familial vulnerability to developing PTSD [63]. A polymorphism in the coding region (V66M) that reduces trafficking and release of brain-derived neurotrophic factor (BDNF) has been associated with hippocampal deficits and reduced hippocampal volume [64]. However, both published molecular genetic studies of BDNF and PTSD failed to identify and association between PTSD and BDNF variants. [65, 66]. The effects of the V66M polymorphism in BDNF on vulnerability to PTSD may be mediated by its roles in hippocampal neurogenesis in adulthood and in moderating downstream events in monaminergic signal transduction and cAMP response element binding protein 1 (CREB1) gene expression [67], and CREB1 gene expression in the acute aftermath of PTE exposure has

been associated with risk of developing PTSD [68]. Therefore it is possible that genes implicated in the neuro-circuitry of fear (e.g, GRP, STMN1, SLC6A3 (DAT1), DRD2, SLC6A4 (5HTTLPR), OPRM1, BDNF, CREB1) will be associated with PTSD.

GxE in PTSD: Environment in PTSD

A number of psychosocial risk factors for PTSD (e.g., low social support, female gender) have been demonstrated [69]. Further, aspects of the PTE (e.g., PTE severity, duration, interpersonal victimization) have been related to increased risk for the disorder [69]. However, similar to the genetics literature, the psychosocial literature has yet to account for the majority of variance in PTSD, thereby underscoring the need for novel methodological approaches. As reviewed above, most extant genetic research is guided by a "main effects" model that examines effects of either genotype or environment upon manifestation of psychiatric phenotypes; in fact, out of the 17 case-control candidate gene studies conducted to date on PTSD, all but three have used this model, with mixed success [70]. Stated wisely by Moffitt and colleagues " … it seems reasonable to suggest that whenever there is variation among human's psychological reactions to a major environmental pathogen for mental disorder, [gene-environment interactions] must be expected to some degree (p.473) [71]." The GxE model proposes that the effects of environmental stressors on psychiatric disorder phenotypes are moderated by genotype. In contrast to the "main effect" model, the interaction model proposed by Moffitt and colleagues [71] provides a new paradigm for the study of phenotypic expression that is highly fitting for PTSD research, given that the key criteria of the disorder is exposure to an environmental stressor.

Two GxE studies of PTSD have been published and one is in press. A recent examination of adults recruited from an inner-city mental health clinic found polymorphisms in FKBP5 moderated the association between PTSD symptoms and childhood abuse [32]. Notably, this interaction remained significant even after controlling for depression severity, age, sex, levels of non-child abuse PTE exposure, and genetic ancestry. Studying adults exposed to the 2004 Florida hurricanes, Kilpatrick and colleagues' [72] found that the 's/s' genotype of the 5-HTTLPR polymorphism was associated with increased risk of PTSD, but only under conditions of high environmental stress exposure (i.e., high hurricane exposure and low social support). Also using data from the 2004 Hurricane study, Amstadter and colleagues [73] found the 'C' allele of rs4606 in *RGS2* to be associated with increased risk of both lifetime and post-hurricane PTSD under high stress conditions (low social support and prior PTE exposure for lifetime PTSD; low social support and high hurricane exposure for post-hurricane PTSD). These studies suggest GxE studies of PTSD may be a fruitful area of future research.

Concluding Statements

PTSD is a chronic and debilitating condition that often leads to the accumulation of disabilities and various physiological and psychological disturbances. Compared to the body of genetically-informed literature on other psychiatric phenotypes, the literature on PTSD is in its infancy and there is a significant need for the expansion and development of this area of science. Identification of risk genes for PTSD has clear public health significance with respect to a) primary prevention of disorder among at risk populations, b) secondary prevention of disorder development among exposed individuals, and c) the allocation of limited treatment resources to those who are most likely to be affected. Once the risk or protective gene variants are confirmed, individuals with the risk variants who are PTE exposed may be targeted for early intervention and treatment strategies, such as pharmaceutical interventions designed to mimic the more protective profile. This area of research, if focused not only on risk models, but also on resilience factors may provide further understanding of the discrepancy in the prevalence of those exposed to a PTE versus those who develop PTSD. The identification of

modifiable environmental factors (e.g., social support) that buffer the effects of environmental pathogens and genetic vulnerability to stress will have important clinical implications. We refer readers to other publications for more detailed recommendations for genetic research in PTSD [74] and for gene-environment interaction in PTSD [70].

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Table 1

Candidate Genes Suggested by Fear-Conditioning Model of Posttraumatic Stress Disorder

HPA axis	Locus coeruleus/noradrenergic system	Limbic-frontal neuro-circuitry of fear
CRH	SLC6A2 (NET1)	GRP
CRH-R1	DBH	STMN1
CRH-R2	COMT	SLC6A3 (DAT1)
CRH-BP	ADRA2C	DRD2
GCCR	ADRB1	SLC6A4 (5HTTLPR)
GCR2 (GRLL1)	ADRB2	OPRM1
FKBP5	NPY	BDNF
	NPY1R, NPY2R	CREB1

Table 2

Review of published case-control candidate gene associations studies of PTSD by neurobiological system

First author	Year	Trauma Exposed Controls?	Trauma Type	Gene Name (Symbol)	Finding
			HPA Axis		
Bachman	2005	yes	Combat	Glucocorticoid Receptor (GCCR)	No significant association between GCCR polymorphisms and PTSD
Binder*	2008	Yes	Various	FKBP5	4 SNPs in *FKBP5* significantly interacted with severity of child abuse in prediction of adult PTSD symptoms ps<.0004
Lu	2008	No	Not specified	Cannabinoid Receptor Gene (CNR1)	Excess C-A and C-G variants in Caucasian parents of youth with ADHD who report PTSD
			Locus Coeruleus/Noradrenergic System		
Lappalainen	2002	No	Combat	Neuropeptide Y (NPY)	No significant association between Leu7Pro polymorphism and PTSD
Mustapic	2007	Yes	Combat	Dopamine Beta-Hydroxylase (DBH)	No association of -1021C/T variant with PTSD; PTSD CC genotype cases had lower DBH activity than non-PTSD CC cases p<.001
			Limbic-frontal Neuro-circuitry of Fear		
Comings	1991	No	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele in PTSD cases p=.007
Comings	1996	Yes	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele in PTSD cases p=.041
	1996	Yes	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele in PTSD cases p=.002
Gelernter	1999	No	Combat	Dopamine Receptor D2 (DRD2)	No significant association between D2A1 allele/DRD2 haplotypes and PTSD
Young	2002	No	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele only in PTSD cases with harmful drinking p<.001
Voisey	2008	Yes	Combat	Dopamine Receptor D2 (DRD2)	Excess C allele in 957C>T in PTSD; no differences in Taq1A or -141delC
Segman	2002	Yes	Various	Dopamine Transporter (DAT1)	Excess 9-repeat allele in PTSD cases p=.012

First author	Year	Trauma Exposed Controls?	Trauma Type	Gene Name (Symbol)	Finding
Lee	2005	No	Various	Serotonin Transporter (SLC6A4)	Excess s allele in PTSD cases p = .04
Lee	2007	Yes	Not specified	Serotonin 2A receptor (5-HTR2A)	Excess GG genotype in female PTSD p = .04
Zhang	2006	Not specified	Not specified	Brain Derived Neurotrophic Factor (BDNF)	No significant association between three BDNF variants and PTSD
Lee	2006	Yes	Not specified	Brain derived Neurotrophic Factor (BDNF)	No significant association between BDNF Val66Met and PTSD
Kilpatrick*	2007	Yes	Hurricane	Serotonin Transporter (SLC6A4)	Significant association between s/s genotype and PTSD in adults with high hurricane exposure and low social support
Amstadter*	2009	Yes	Hurricane; Various	Regulator of G-Protein Signaling 2 (RGS2)	Significant association between CC genotype and post-hurricane PTSD in adults with high hurricane exposure and low social support; significant association between CC genotype and lifetime PTSD in adults with prior trauma exposure and low social support

*= GxE study; PTSD = posttraumatic stress disorder; SNPs = single nucleotide polymorphisms; D2DA1 = Al one allele of DRD2 gene; s allele = short version (versus long) of the serotonin transporter promoter polymorphism.