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## Genetic approaches for the study of PTSD: Advances and challenges

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### Abstract

Post-traumatic stress disorder (PTSD) is a highly debilitating stress and anxiety-related disorder that occurs in response to specific trauma or abuse. Genetic risk factors may account for up to 30–40% of the heritability of PTSD. Understanding the gene pathways that are associated with PTSD, and how those genes interact with the fear and stress circuitry to mediate risk and resilience for PTSD will enable the development of targeted therapies to prevent the occurrence of or decrease the severity of this complex multi-gene disorder. This review will summarize recent research on genetic approaches to understanding PTSD risk and resilience in human populations, including candidate genes and their epigenetic modifications, genome-wide association studies and neural imaging genetics approaches. Despite challenges faced within this field of study such as inconsistent results and replications, genetic approaches still offer exciting opportunities for the identification and development of novel therapeutic targets and therapies in the future.

## II. Introduction

Post-traumatic Stress Disorder (PTSD) is a highly debilitating neuropsychiatric disorder in which fear-related memories of a traumatic event become overgeneralized and resistant to extinction (Figure 1). Symptoms include intrusive thoughts about the trauma accompanied with changes in physiology (increased heart rate and perspiration) as well as nightmares and flashbacks (1, 2).

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Although estimates suggest that 90% of individuals will be exposed to a significant traumatic event in their lifetime (3), only about 5–10% of the general population suffers from PTSD (4, 5).

These studies suggest that individual vulnerability and resilience are key factors to consider in the pathology of PTSD. Furthermore, twin studies have demonstrated that genetic risk factors may account for up to 30–40% of the heritability of PTSD (6). The recent discovery of the *Tac2* gene in mediating fear consolidation (7) is one example of how a gene discovery driven approach could shed light on the pathology and novel potential therapeutic targets in PTSD.

In addition to identifying genes that have been implicated in PTSD, we will discuss the epigenetic modifications of these risk genes. As such modifications are potentially reversible by drugs, behavioral therapy or environmental changes, this opens up new promising therapeutic avenues for PTSD. Beyond reviewing genetics studies, we also discuss the need for complementary approaches at multiple levels of biological complexity and emphasize the importance of combining and integrating findings across levels for a better understanding of biological pathways from gene to disease. These may include multi-modal imaging genetics studies, bioinformatic analyses, and functional analyses of cell and animal models.

### III. Candidate gene studies

Candidate gene studies for PTSD involve the identification of genetic risk variants using prior knowledge and literature. In this section, we will discuss current findings in monoaminergic neurotransmitters, the hypothalamic-pituitary-adrenal (HPA) axis, neurotrophin, neuropeptide and receptor genes. While we will only discuss a small number of examples of candidate gene studies for PTSD, many excellent reviews have been published to date and the authors direct the reader to a number of such publications (6, 8–14). Such targeted studies have been at times criticized for not being unbiased, as compared with genome-wide association studies, or subject to file-drawer effects and other potential biases. Nonetheless, a number of pathways have been replicated multiple times and have survived meta-analytic analyses suggesting some possibly important genetic signals, as outlined below.

#### A. Monoaminergic neurotransmitters

The serotonergic system has been studied extensively in the regulation of mood and the dysregulation of this system has been implicated in the pathophysiology of PTSD (15, 16). Several studies have found that a high risk of developing PTSD is associated with a specific polymorphism in the promoter region of the serotonin transporter gene *SLC6A4*. The *5-HTTLPR* polymorphism contains two predominant alleles, L (long) and S (short) representing different lengths of a polymorphic promoter region, with the S-allele associated with reduced serotonin transporter gene expression, leading to reduced serotonin reuptake. Studies have indicated that risk for PTSD development is associated with genotype (mainly S-allele carriers, also associated with depression) and high levels of trauma/stress (Figure 2A) (17–20). However, several studies have reported no association (21, 22) and ultimately association studies of functional polymorphisms of the serotonin transporter gene have been

inconclusive; in fact a meta-analysis of 12 studies did not find evidence of overall association, however homozygosity for the S allele was associated with PTSD in individuals with classified high trauma exposure (23). Other studies have demonstrated a correlation between methylation of *SLC6A4* and PTSD symptoms following traumatic events. Individuals with more traumatic events were found to be at increased risk for PTSD, but only when they had lower methylation levels at the *SLC6A4* locus. At higher methylation levels, individuals with more traumatic events were protected from developing PTSD (24, 25). Such findings are very interesting in their suggestion that methylation status of *SLC6A4* interacts with the number of traumatic events to mediate the risk of PTSD. Importantly, this study did not observe an effect of *SLC6A4* genotype on PTSD (26). Although these studies need replication in larger cohorts, they are consistent with a role for serotonergic regulation of emotional processing interacting with trauma and stress exposure to increase risk for (or resilience from) PTSD-related symptoms.

Another monoaminergic neurotransmitter that is likely involved in the pathophysiology of PTSD is dopamine. Attention, vigilance, arousal, and sleep are processes that are negatively impacted in PTSD, and dopamine is key for their regulation (27). A polymorphism in the gene encoding the dopamine transporter (*SLC6A3* also known as DAT or DAT1) has a 40-base pair repeat that is polymorphic in the population. Genetic variants in dopamine transporters have been associated with PTSD (28–30). For example, 9-repeat (9R) allele of *SLC6A3* is associated with PTSD symptoms. Interestingly, an increased risk for PTSD might be mediated by high methylation of the *SLC6A3* promoter locus (CpG site cg13202751) in 9R allele carriers. (Figure 2B) (31). However, there has been at least one published study reporting no association of the 9-repeat allele of *SLC6A3* with PTSD (32).

The dopamine receptor D2 (*DRD2*) contains rs1800497, a single nucleotide polymorphism (SNP) with T (A1) and C (A2) alleles. This allele is associated with PTSD in Caucasian war veterans (33) and excessive alcohol intake (34). The dopamine D3 receptor (*DRD3*) gene (involved in relevant processes such as executive functioning and emotional reactivity) has also been implicated in PTSD. In one study, 4 single nucleotide polymorphisms (SNPs), showed evidence of association with PTSD (35). However, two published studies in different cohorts have demonstrated no association between PTSD diagnosis or symptom severity with the A1 allele of *DRD2* (32, 36), although one of these studies did find a significant interaction effect between *DRD2* TaqIA and the *BDNF* Val66Met variants on score on the Davidson Trauma Scale (DTS)(36).

Two enzymes involved in monoamine metabolism are dopamine beta-hydroxylase (*DBH*) and catechol-O-methyltransferase (*COMT*). A polymorphism in *DBH* (-1021C/T; rs1611115) has been shown to account for 35–52% of the variation in plasma-DBH activity. War veterans with PTSD and a civilian sample of African Americans with PTSD who carried the CC genotype of the *DBH*-1021C/T variant had lower plasma DBH activity (37–39). *COMT* contains a functional polymorphism at codon 158 (rs4680) leading to a significant reduction in enzyme activity. The Met158 allele is also associated with a decreased ability to extinguish conditioned fear, a key feature of animal models of PTSD. Furthermore, a significant association between one or more copies of the Met158 allele and PTSD in addition to a gene–environment interaction between the Met158 allele and the

number of traumatic event types in predicting PTSD has been described. Individuals with a Met/Met genotype display decreased fear inhibition, potentially as a result of higher methylation in the COMT promoter region (Figure 2C)(40–42). Thus, regulation of COMT and DBH may be important factors in the regulation of fear related processes in PTSD patients.

## B. Hypothalamic-pituitary-adrenal axis candidate genes

A key feature of PTSD is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. A large body of work has shown that PTSD is often characterized by a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, such that the system is altered and hyper-responsive to cortisol feedback (43–45). These effects may be observed in PTSD patients, of which a large number display consistently lower cortisol responses in dexamethasone suppression tests indicating enhanced negative feedback in the HPA axis (44, 46). The glucocorticoid receptor (GR) mediates negative feedback of the HPA axis, thus the HPA axis effects in individuals with PTSD are thought to occur, in part, via enhanced sensitivity of GR-mediated feedback mechanism, which acts to suppress stress-related cortisol release. Several polymorphisms of the glucocorticoid receptor gene have been observed in individuals with PTSD (47, 48). The SNP Bcl-1 is associated with hypersensitivity and enhanced feedback to glucocorticoid levels correlating with lower cortisol levels. Carriers who are homozygous for the Bcl-1 SNP (G allele) were found to have more traumatic memories than heterozygous or non-carriers of the SNP, 6 months after intensive care unit care (49). In addition, individuals with lifetime PTSD showed lower morning cortisol release, higher GR expression, and lower overall methylation levels in the examined GR promoter regions. Consistent with these findings, GR promoter methylation levels are lower in veterans with PTSD compared to those without PTSD (50). As with the other candidate gene studies described above, differing results have found no significant association between GR polymorphisms (N363S and BclI) and PTSD diagnosis in a group of Vietnam veterans (51).

A different gene, steroid receptor chaperone FK506 binding protein 5, (*FKBP5*) is thought to be involved in the pathogenesis of stress-related disorders as it regulates the stress system by altering GR sensitivity (52, 53). SNPs in *FKBP5* result in enhanced glucocorticoid receptor sensitivity which lead to lower basal cortisol levels and increased risk for PTSD following a traumatic experience. Four SNPs in *FKBP5* (rs9296158, rs3800373, 1360780, rs9470080, that are in high linkage disequilibrium with each other) have been shown to interact with child abuse severity to predict adult PTSD in a primarily African American civilian cohort (54, 55). More recently, one of these polymorphisms in *FKBP5* (rs1360780), that increases the risk of developing stress-related psychiatric disorders in adulthood, was found to be dependent on changes in DNA methylation occurring as a consequence of childhood trauma-dependent stress (Figure 2D) (56). Other studies indicate that genetic variation in *FKBP5* influences the risk of anxiety and/or depressive disorders in early life and interact with childhood abuse to increase the risk of PTSD (57–59).

The neuropeptide, pituitary adenylate cyclase-activating polypeptide (PACAP), is involved in regulating corticotrophin-releasing hormone (CRH) a key mediator of the stress axis.

Recently, a genetic variant in the PAC1 receptor (*ADCYAP1R1*; rs2267735) that disrupts a putative estrogen response element, has been found to be associated with PTSD in a primarily African-American cohort of women (Figure 2E, left) (60–62). In addition, genetic variation at the *ADCYAP1R1* locus interacts with childhood maltreatment to influence the risk of developing PTSD later in life, specifically in women (63). Finally, PTSD patients display changes in peripheral blood DNA methylation and mRNA expression of the *ADCYAP1R1* transcript (Figure 2E, right) (62). In contrast, in two separate, presumably less traumatized patient cohorts, the above association with the *ADCYAP1R1* variant was not replicated (64). Together, these studies suggest that the PACAP/PAC1 pathway plays an important role in the abnormal stress responses associated with PTSD.

### C. Additional candidate genes

Brain-derived neurotrophic factor (BDNF), a key regulator of neuronal plasticity, is known to be associated with depression as well as the extinction of fear, a key process disrupted in PTSD (65). A SNP in the gene encoding human BDNF gives rise to a functional variant at codon 66 where the amino acid valine (Val) is substituted by methionine (Met), also referred to as the Val66Met polymorphism, and has been suggested to be relevant in PTSD (for a review, please see Andero and Ressler, 2012). In humans, the frequency of the Met/Met in BDNF gene although low in certain populations (<5%), (66) was higher in individuals with PTSD compared to controls and individuals with the BDNF polymorphism Val66Met; the allelic frequencies of the Met/Met genotype and Met carriers was 33.3% in individuals with PTSD compared to 17.5% in non-PTSD controls (67, 68).

Met carriers have been shown to have significantly higher levels of startle responsiveness, an intermediate phenotype for PTSD, when compared to Val/Val carriers. Additionally, subjects with PTSD show higher levels of BDNF in their peripheral blood plasma compared to traumatized controls without PTSD (Figure 2F, left). Such investigations into BDNF levels in the periphery, while promising, cannot be equated with brain function. Further evidence has shown that Met/Met carriers who experienced fewer than four stressful life events had significantly higher PTSD symptoms compared to Val/Val and Val/Met carriers (Figure 2F, right). Finally, PTSD patients with the Met-66 allele of BDNF displayed a poorer response to exposure therapy compared with patients with the Val/Val allele (69). With regard to epigenetic modification of the BDNF gene and PTSD risk, there is a modest association between increased methylation of one CpG site within the BDNF gene and PTSD status (70, 71). Additionally, the Val66Met SNP has been shown to cause decreased hippocampal volume, deficits in declarative memory and impaired fear extinction (72–74). Despite the above positive findings, a number of studies have found no association (29, 75–77), (although a significant interaction has been reported between the above described DRD2 Taq1A (rs1800497) and Val66Met (rs6265) in predicting severity of PTSD (36).

GABAergic systems are known to play a role in the pathophysiology of anxiety and depression, both of which are common in individuals suffering from PTSD. Three polymorphisms in the GABA<sub>A</sub> receptor subunit alpha 2 (*GABRA2*) were found to have significant interactions with childhood trauma to predict PTSD (78).

Apolipoprotein E (ApoE) regulates the binding of lipoproteins to the low-density lipoprotein receptor and regulates neuronal and glial responses to stress. The gene *APOE* is polymorphic and a significant association between the *ApoE2* allele and impaired memory, an increase in re-experiencing of traumatic memories and salivary cortisol levels, was reported in combat-exposed PTSD patients (78). Regulator of G-protein Signaling 2 (*RGS2*) has been implicated in learning and memory processes. An association with *RGS2* (rs4606) and PTSD after traumatic hurricane experience was found under conditions of high stress and low social support (79). A different study found a significant association between *RGS2* (rs4606) and post-traumatic growth thereby suggesting this gene may play a role in recovery from trauma (80).

Cholecystokinin (CCK) is a neuropeptide that has been implicated fear acquisition and extinction in rodents (81). A study in war veterans has demonstrated that a single nucleotide polymorphism in the promoter region of the CCK gene was associated with an increased prevalence of PTSD as well as with severity of PTSD symptoms (81).

Other studies have reported associations between PTSD and cannabinoid receptor (*CNR1*) gene variants. A polymorphism in the *CNR1* gene (rs1049353) interacts with childhood physical abuse to predict posttraumatic threat symptoms, specifically to increase severity of threat or fear (82). A different study examined the association between genetic variation in the nicotinic receptor gene family and the PTSD. A novel association between rs12898919 in the cholinergic receptor nicotinic alpha-5 (*CHRNA5*) gene and PTSD was observed in non-hispanic white patients suggesting that *CHRNA5* gene is associated with increased risk for PTSD (83).

Overall, candidate gene studies of PTSD, like those reviewed in the above section, have been underpowered, thus making many positive and negative results and findings difficult to interpret. In addition, mixed results have been observed across a subset of genes involved in serotonergic, dopaminergic, and neuroendocrine function. Furthermore, there are clearly limitations in study design and non-reproducibility of findings. Factors such as sex, race, trauma history are often not consistently addresses in study designs, thus causing difficulty in drawing conclusions across multiple different studies. Overall, although over-arching statements based on candidate gene approach studies are premature, genes identified through these avenues hold promise as potential biomarkers to undergo further investigation. For example, convincing evidence has been shown in the study of *FKBP5*, in which a gene by environment (G x E) effect between early adversity and variation in *FKBP5* has been reported. Subsequent work has demonstrated a mechanistic account of the influence of this particular genetic variation on alteration of the stress response via epigenetic alterations of gene expression and downstream glucocorticoid function(56).

Genome-wide association studies (GWAS) large-scale, collaborative approaches, which will briefly be described below, offer beginning steps towards a goal of well-powered, hypothesis-neutral studies. Such approaches are needed to identify more robust candidate genes, which will be essential in identifying targets for research in the treatment of PTSD.



#### IV. Genome-wide association studies

Genome-wide association studies (GWAS) involve an unbiased approach to identify disease-associated genetic variants, across the vast genome of 3 billion base pairs of DNA and approximately 20,000 protein-coding genes that may predict disease. Most GWAS arrays test ~1 Million SNP variants, providing the most robust methods to perform unbiased genetic discovery. At least six successful GWAS studies have been reported for PTSD to date as outlined below.

The first GWAS of PTSD identified a genome-wide significant association between PTSD and a SNP (rs8042149) in the retinoid-related orphan receptor gene (RORA) (84). Furthermore, certain variations in this gene may predispose individuals with a history of child abuse to PTSD(85). Changes in RORA levels may decrease the ability of neurons to respond to oxidative stress, steroid hormone changes as well as inflammation often induced by trauma(84). The association between the RORA SNP rs8042129 and PTSD was also reported in a cohort of Florida hurricane survivors (86). In other replication cohorts, other SNPs within RORA have been nominally associated with PTSD (84), however, another study has found that associations between RORA SNPs were not detected in two independent replication samples (87).

In another very recent study using an unbiased gene-based approach, the Neuroligin or *NLGN1* gene that encodes a synaptic adhesion molecule, was found to be associated with PTSD in two different civilian traumatized cohorts. In both cohorts, the *NLGN1* SNP with the strongest association was also associated with *NLGN1* expression in postmortem cerebellum or frontal cortex tissue, respectively. *NLGN1* plays a role in synaptogenesis and synaptic maintenance, specifically in mediating the formation and maturation of synapses within the mammalian brain, and has been shown to be a potent trigger for the de novo formation of synaptic connections in addition to being implicated in other psychiatric disorders such as Autism (88–90). Furthermore, mouse model studies have found that depletion of neuroligin-1 in the lateral amygdala results in a deficit in storage of associative fear memory, suggesting an important role in fear learning and memory.

Another gene that has been recently implicated in the development of PTSD risk is Tollid-Like 1 or *TLL-1*, a zinc dependent metalloprotease which plays an important role in remodeling of the extracellular matrix (91). After GWAS analyses in a sample of European Americans and African Americans, *TLL-1* was found to be a new susceptibility gene for PTSD(92).

In a different study, a GWAS design was used to identify genes associated with PTSD within a multi-racial sample largely composed of U.S. veterans. The authors identified SNPs within many candidate genes that were nominally significant. The most significant genes were *UNC13C* and *DSCAM* within the non-Hispanic black group whereas the most significant genes within the non-Hispanic white group were *TBC1D2*, *SDC2* and *PCDH7*. Many of these genes have been previously implicated in both development and disorders of the central nervous system (93–95).

In a study performed in military personnel, whole transcriptome analysis was performed to compare gene-expression profiles in individuals with PTSD and matched controls without PTSD. Analysis of expression profiles led to the discovery of 203 differentially expressed genes in PTSD, of which 72% were upregulated, many of which were associated with the innate immune, neuroendocrine, and NF- $\kappa$ B systems (96).

The largest genome-wide association study of PTSD to date, carried out in a US military sample, found a genome-wide significant association with *ANKRD55*, a gene involved in autoimmune and inflammatory disorders(97). Furthermore, a multi-ethnic/racial GWAS of PTSD provided evidence for the phosphoribosyl transferase domain containing 1 gene or *PRTFDC1*, encoding an enzyme in the purine metabolic enzyme family, to be involved in PTSD pathology(98); *PRTFDC1* has been shown to play a role as a possible tumor – suppressor gene (99), however, its role in the etiology of PTSD is unknown at present.

The recently formed Psychiatric Genomics Consortium-PTSD continues to encourage further discovery of genes involved in the pathology and susceptibility of or resilience to PTSD (100). A key challenge in GWAS approach is the replication of studies and findings from the different studies have not consistently implicated a primary set of PTSD risk loci. Several factors may play a role in non-replication, including false positives, heterogeneity across samples, as well as inflation of effect size estimates in moderately powered samples. Moving forward, progress in identifying the genetic factors underlying PTSD will hugely benefit from efforts such as the PGC's PTSD Workgroup whose goal is to bring together GWAS data sets. Currently, genotyping has been completed or is underway for approximately 20,000 cases and 50,000 controls (100).

## V. Neuroimaging genetics

Neuroimaging genetics provides another technique that has been used to identify genes relevant in PTSD and the neuroimaging intermediate phenotypes associated with PTSD. Individuals suffering from PTSD have been shown to exhibit specific patterns of information processing, such as attentional biases for trauma-related cues and impairments in sustained attention and memory that may be mediated by structural changes in the brain (101, 102).

Several genes appear to play a role in the pathophysiology of PTSD, while simultaneously exerting effects on specific brain structures and their corresponding functions. Studies of the serotonin transporter gene (*SLC6A4*) have focused on the SNP rs25531, present in a degenerate repeat in the promoter region known as *5-HTTLPR*. This SNP is associated with heightened amygdala activation in S-allele carriers of this gene, in response to threat related cues(103). Other neuroimaging studies have found that allelic variants of *FKBP5*, *COMT* and *NPY* associate differentially with behavioral and neural responses to threat-relevant facial expressions. For example, there is increased activation in the amygdala and hippocampus in response to threat cues in carriers of risk alleles of *FKBP5*. Increased amygdala responses to angry and fearful faces have also been observed in risk allele carriers for *COMT* (Val-allele carriers for SNP rs4680) and *NPY*.



Recent work has shown that a variant in the opioid receptor-like 1 gene (*OPRL1*) was associated with PTSD symptoms and fear-potentiated startle, along with amygdala-insult connectivity by fMRI (Andero et al., 2013). Additionally, the variant in *OPRL1* was also associated with PTSD symptoms and fear-potentiated startle. *OPRL1* encoded the amygdala nociception (NOP)/orphanin FQ receptor (NOP-R), and mouse studies have shown that administration of NOP-R agonist into the central amygdala impairs fear consolidation (104), thus suggesting a potential “drug-able target” for future investigation. Such an approach is supported by the finding that administration of morphine, an opioid agonist, following trauma exposure, reduced the incidence of PTSD later on (105).

As with the approaches described in the prior sections related to candidate gene studies and GWAS, genetic neuroimaging studies have also not been consistent. Such inconsistencies highlight the need for replication with larger sample sizes, as well as a greater effort to examine specific genetic effects in different demographic groups. Additionally, the majority of neuroimaging genetics studies have focused on the amygdala and hippocampus; a broader investigation of other regions known to play a role in PTSD and stress related disorders such as the prefrontal cortical regions, the anterior cingulate, dorsolateral prefrontal cortex, etc. will be important targets for future studies. Despite these challenges, the studies discussed in the above section highlight the importance of studying structural differences in the brains of individuals that possess specific SNPs in relevant genes which may cause changes in behavior along with dysregulation in physiological processes such as learning, memory and HPA axis activity, all of which influence the development of PTSD (6).

## VI. Conclusions

As detailed in the present review, both candidate gene approaches and GWAS studies have shed light on a number of novel genes which may play a role in the pathophysiology of PTSD. Despite these important steps forward, many candidate gene approaches and GWAS studies have been inconsistent with many non-replicated effects. As such, candidate gene study approaches will require greater sample sizes in addition to being combined with convergent molecular biological evidence and research using animal models, as has been shown so robustly in the case of *FKBP5*. Additionally, recent work investigating the fatty acid amide hydrolase (FAAH) gene has nicely used a cross-species approach by studying genetic knock-in mouse model in parallel with human variant allele carriers to investigate alterations in neural connectivity and circuitry, biochemistry and anxiety-like and fear learning behavior(106, 107). Such translational approaches are promising in their investigation of both phenotype and mechanisms across species.

With regards to GWAS studies, there is a great need for large-scale unbiased genome-wide approaches which have been proven successful in the study of other psychiatric disorders such as Autism Spectrum Disorders, Schizophrenia and Bipolar Disorder. The field as a whole will benefit tremendously from current efforts to bring together GWAS data sets, led by the PGC’s PTSD Workgroup. The next step in the discovery of novel gene targets will be to manipulate identified genetic targets in animal models in parallel to performing neuroimaging genetics in humans. Additionally, the identification of genetic targets with available agonists or antagonists, may be investigated in the context of animal models of fear

learning and memory to validate and provide preliminary evidence (blockade of consolidation or enhancement of extinction, etc.) for potential therapeutics for the treatment of PTSD. Such an approach may allow for the discovery of previously unknown genetic targets and novel therapies that may eventually decrease the risk and enhance the resilience of individuals towards developing PTSD.

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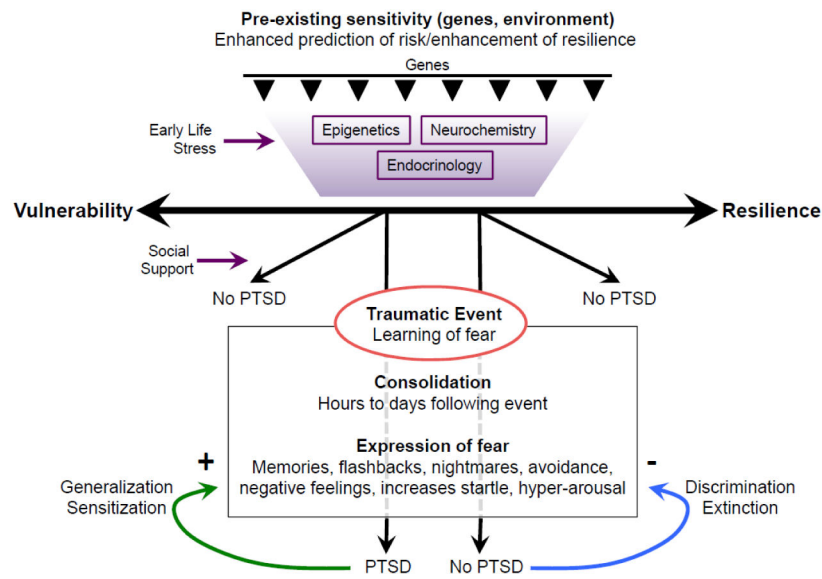
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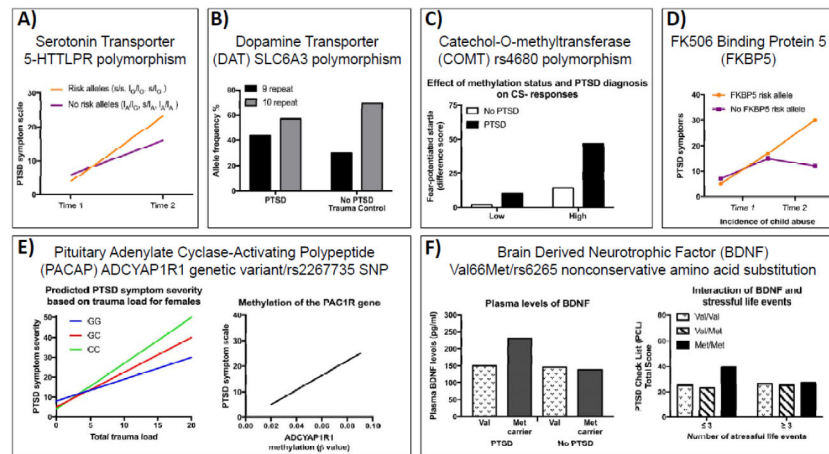


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**Figure 1. Schematic of the development of gene by environment (G x E) interactions, and the development of post-traumatic stress disorder (PTSD)**

Genetic heritability along with early life stress and childhood trauma comprise much of the risk for depression and anxiety related disorders such as PTSD. Following the traumatic event, the learned fear memory is consolidated to a more permanent state. The expression of the fear memory may manifest as the above described symptoms. Individuals that develop PTSD fail to discriminate and extinguish fear memories, and instead exhibit sensitization and generalization of the fear response. Enhancing the extinction and discrimination of learned fear memories are key behavioral responses that are targeted in the treatment of PTSD via psychotherapeutic approaches such as exposure based psychotherapy and pharmacological assisted psychotherapy.



**Figure 2. Examples of Genetic Variants associated with differential risk for Post traumatic Stress Symptoms**

A) The 5-HTTLPR multimarker genotype predicts posttraumatic stress disorder (PTSD) symptom scores and severity two to four weeks following trauma. The 5-HTTLPR risk alleles (orange line) result in increased PTSD symptoms compared to the non-risk alleles (purple line) (graph adapted from Mercer et al., 2012). B) The SLC6A3 polymorphism of the dopamine transporter 9 and 10 repeat (black and grey bars, respectively) allele and genotype frequencies in individuals with chronic PTSD and trauma control survivors without PTSD (Segman et al., 2002; Drury et al., 2009). C) Individuals with the Met/Met genotype in the COMT functional polymorphism at codon 158 (rs4680) demonstrate impaired fear inhibition as demonstrated by enhanced fear potentiated startle to the CS – (safety signal), which may be the result of increased methylation of the COMT promoter region (graph adapted from Norrholm et al., 2013). D) The FKBP5 risk allele (orange line) results in increases in adult PTSD symptoms following exposure to childhood trauma compared to the protective allele (purple line) (graph adapted from Klengel et al., 2013). E) Females (but not males) with high levels of plasma PACAP38 display increased PTSD symptoms. Rs2267735 is a SNP spanning the PAC1R gene and there is an interaction between total trauma load and the risk CC genotype in females (left) (graph adapted from Almi et al., 2013). Methylation at the PAC1R locus is significantly positively correlated with PTSD symptoms (right) (graph adapted from Ressler et al., 2011). F) A nonconservative amino acid substitution (Val66Met, rs6265) in the BDNF gene has been identified. Met carriers with PTSD have significantly higher plasma levels of BDNF (left). Met/Met homozygote carriers who experienced fewer than four stressful life events had significantly higher PTSD check list (PCL) scores compared to Val/Val and Val/Met carriers (right) (graphs adapted from Zhang et al., 2013).