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Review

Progress towards understanding the genetics of posttraumatic stress disorder

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a complex syndrome that occurs following exposure to a potentially life threatening traumatic event. This review summarises the literature on the genetics of PTSD including gene–environment interactions (GxE), epigenetics and genetics of treatment response. Numerous genes have been shown to be associated with PTSD using candidate gene approaches. Genome-wide association studies have been limited due to the large sample size required to reach statistical power. Studies have shown that GxE interactions are important for PTSD susceptibility. Epigenetics plays an important role in PTSD susceptibility and some of the most promising studies show stress and child abuse trigger epigenetic changes. Much of the molecular genetics of PTSD remains to be elucidated. However, it is clear that identifying genetic markers and environmental triggers has the potential to advance early PTSD diagnosis and therapeutic interventions and ultimately ease the personal and financial burden of this debilitating disorder.

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1. Introduction

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*)(American Psychiatric Association, 2013) posttraumatic stress disorder (PTSD) is no longer classified as an anxiety disorder but is categorised in disorders relating to traumatic and stressful events (Friedman, 2013). Some of the symptoms of PTSD are characteristic but there are some that overlap with other psychiatric disorders (Schnurr, 2013). The trauma can cause significant changes in the hypothalamic pituitary adrenal axis (HPA) (Yehuda, 2001) determining future responses to stress. PTSD can lead to profound social dysfunction as memories from the traumatic event can result in fear responses that mimic the original exposure. Those with PTSD can experience sleep difficulties, are easily frightened and have concentration and memory problems (Brunello et al., 2001). As a result sufferers may experience relationship challenges, substance misuse and experience feelings of isolation, hopelessness and anger. PTSD can result from a variety of traumatic events including military combat, violet assaults, physical and sexual abuse, terrorist encounters, natural disasters and serious accidents. Females are twice as likely to develop PTSD compared to males (Breslau, 2009; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). However, most individuals that are exposed to a life threatening experience will not develop PTSD (Breslau, 2009) and this is largely thought to be determined by genetics. This review will focus on epigenetics and the genetic

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and environmental risk factors of PTSD as well as the genetics of treatment response.

2. Heritability of PTSD

Twin studies of Vietnam veterans have confirmed that genetic vulnerability is associated with PTSD (Koenen et al., 2002; Lyons et al., 1993; True et al., 1993). Approximately 30% of the variance in liability for PTSD symptoms (including re-experiencing, avoidance and hyper-arousal) was found to be genetic after analysing phenotypes of monozygotic and dizygotic twins (Koenen et al., 2002; Lyons et al., 1993; True et al., 1993). A recent twin study suggests that heritable influences account for 46% of the variance in PTSD (Sartor et al., 2012) but this could be as high as 71% in females (Sartor et al., 2011).

Full pedigrees for PTSD have not been collected as genetic vulnerability to PTSD can only be assessed if a traumatic experience has occurred. However, some studies of family history have shed light on familial susceptibility to PTSD. One of the first was a study of World War One veterans with "psycho-neurosis" who were compared with controls that had a physical injury as a result of war. None of the controls reported a family history of "psychoneurosis" compared to 75% of the cases (Wolfsohn, 1918).

3. Genetic risk and signalling pathways

There have been numerous genetic association studies examining the role of various genes in PTSD and these are summarised in Table 1. The table lists 68 candidate gene studies covering 31 genes that examined association between PTSD or a PTSD-related phenotype and numerous polymorphisms. It also lists six genome wide association studies (GWAS) that identified four genes associated with PTSD. Table 1 list studies that detected association as well as those that failed to detect association, although it is likely that many negative studies have not been published. The earliest study in 1991 (Comings et al., 1991) examined the rs1800497 single nucleotide polymorphism (SNP), also known as *Taq*IA. This SNP was originally considered to be in the dopamine D2 receptor (*DRD2*) gene as it is only 10 kilobases downstream but it was later discovered that it lies in a tyrosine kinase gene known as the ankyrin repeat and kinase domain containing 1 gene *ANKK1* (Dubertret et al., 2004). However, it has been postulated that the involvement of *Taq*IA in psychiatric disorders is due to its proximity to, and regulatory effect on the *DRD2* gene (Swagell et al., 2012). Between 1991 and 2004 there was a total of six PTSD association studies, four of which involved the *Taq*IA or other *DRD2* SNPs (Table 1). Since that time there has been increased activity in this area, particularly in the last few years.

There have been a total of eight studies examining *DRD2*/*Taq*IA SNPs (Table 1). Because of the role of dopamine in stress biology, it is not surprising that dopamine-regulating genes including *DRD2* have been found to be associated with PTSD (Comings, Muhleman, & Gysin, 1996; Lawford et al., 2003; Voisey et al., 2009) although the case for *Taq*IA is less convincing. A pair of polymorphisms in the promoter of the serotonin transporter gene (*SLC6A4*) have also been implicated in PTSD risk and produce a low expression allele (Lee et al., 2005). This involved a *SCL6A4* variable number of tandem repeats polymorphism (VNTR) in the promoter region (referred to in Table 1 as 5′-VNTR) with short (14 repeats) and long (16 repeats) alleles and a modifying *SCL6A4* A/G polymorphism (rs25531). Only the long repeat allele that also contains the rs25531 A allele results in high levels of *SCL6A4* expression while all short alleles and long alleles combined with the rs25531 G allele result in low levels of *SCL6A4* expression. Table 1 lists 17 association studies of the *SLC6A4* promoter polymorphisms, some of which only examined the 5′-VNTR polymorphism. The majority of these studies detected association with the *SLC6A4* polymorphisms (14 studies detected association and three did not). Despite this, a recent meta analysis of 13 studies showed that there is no support for a direct effect of *SLC6A4* polymorphisms in PTSD (Navarro-Mateu, Escamez, Koenen, Alonso, & Sanchez-Meca, 2013). More recently, a non-synonymous polymorphism in brain–derived neurotrophic factor (*BDNF*) was found associated with psychotic symptoms in PTSD (Pivac et al., 2012) and fear conditioning (Felmingham, Dobson-Stone, Schofield, Quirk, & Bryant, 2013; Soliman et al., 2010).

Identifying genes that modulate the actions of glucocorticoids including stress and cognition may identify novel SNPs associated with PTSD. The *NOS1AP* gene encodes nitric oxide synthase 1 adaptor protein that binds to the signalling molecule, neuronal nitric oxide synthase (nNOS). Nitric oxide (NO) is produced from its precursor L-arginine by the enzyme NO synthase (NOS) which includes at least three distinct isoforms—neuronal (nNOS), endothelial, and inducible NOS. Studies have found that NO release is involved in the activation of glutamate *N*-methyl-D-aspartate (NMDA) receptors (Southam & Garthwaite, 1993). NOS1AP competes with postsynaptic density protein-95 (PSD-95) for nNOS binding and is thought to reduce NMDA receptor signalling via PSD-95 and nNOS. An earlier study that identified NOS1AP found that overexpression of NOS1AP results in a loss of PSD95/nNOS complexes in transfected cells (Jaffrey, Snowman, Eliasson, Cohen, & Snyder, 1998). The NO cascade has also been shown to be responsible for hippocampal shrinkage. Cognitive defects evident from PTSD are thought to be the result of hippocampal degeneration (Elzinga & Bremner, 2002). During stress, glutamate is released via increased sensitivity of hippocampal glucocorticoid receptors which in turn increase the risk of hippocampus atrophy (Sapolsky, 2001). Rat studies have found stress mediated glucocorticoid release activated NOS activity which subsequently down-regulated hippocampal NMDA receptors and total gamma-aminobutyric acid (GABA) levels (Harvey, Oosthuizen, Brand, Wegener, & Stein, 2004). A partial agonist of the NMDA receptor, D-cycloserine, has proved successful in the treatment of PTSD (Heresco-Levy et al., 2002).

A SNP, rs386261, in *NOS1AP* has recently been found associated with PTSD in Vietnam War veterans (Lawford et al., 2013). The study also found that the GG genotype was associated with increased severity of depression in patients with PTSD which may increase suicide risk and indicate a comorbid phenotype. This study and many of the studies listed in Table 1 should be viewed with caution until they have been replicated, as they are the first reports of association in the genes studied. Although PTSD is seen as an anxiety disorder, it is frequently comorbid with depression and studies have identified genes common to both (Koenen et al., 2008; Lawford, Young, Noble, Kann, & Ritchie, 2006). As much as 58% of the genetic variance in PTSD could be attributed to heritable influences shared with major depressive disorder (Koenen et al., 2008). A study of Vietnam veterans also found that PTSD risk was higher in individuals that had a family history of depression (True et al., 1993) suggesting that PTSD and depression share common genetic liability.

Table 1 highlights some of the difficulties faced when conducting genetic association studies in PTSD. Generally speaking the size of the cohorts of PTSD cases and controls is quite small and the type of trauma to which many of the PTSD cases were exposed was either poorly defined or of a varied nature. It is well recognised that there is more power to detect genetic association when the phenotype of the cases is more severe and more uniform. It is therefore recommended that future studies concentrate on PTSD patients who present with profound impairments following exposure to a relatively uniform trauma such as a specific natural disaster or a particular military conflict.

Genome-wide association studies (GWAS) are commonly used to identify genetic associations in case/control studies of disease.