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The First Steps on the Path toward Genomic Predictors of Behavioral Therapy for PTSD

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COMMENTARY

Not everyone who has personally experienced, or has been exposed to, severe trauma develops posttraumatic stress disorder (PTSD). The risk – resilience equation is complex and, as we are becoming increasingly aware, includes both genetic predictors and environmental stressors, starting in early childhood. For example, as Binder and colleagues (1) first showed, *FKBP5*, a gene influencing activity of the hypothalamic-pituitary-adrenal axis, together with exposure to childhood trauma but not adult stressors, predicted the development of PTSD in a low income, urban African American sample. There is much to be understood about the etiology of PTSD and equally there is much to be learnt about developing new treatment options and improving rates of response to the current first line treatment for PTSD: cognitive behavioral therapy (CBT).

PTSD is thought to result from impaired fear extinction learning i.e. the inability to suppress frightening or disturbing memories of a traumatic event (2). A key player in the formation of fear-related memories via the hippocampus, amygdala and prefrontal cortex is brain-derived neurotrophic factor (BDNF) that, together with its receptor tyrosine kinase receptor B (TrkB) is an important regulator of neuronal development, function, survival and synaptic plasticity (2, 3). Stress results in BDNF over-expression in the hippocampus, most likely a compensatory mechanism that appears to enhance fear extinction (2). However some individuals have a compromised BDNF protective response to stress since they are Met allele carriers of the *BDNF* gene polymorphism Val66Met (rs6265) and have reduced secretion and neuroplastic effects of the BDNF protein (3). Even apparently healthy Met allele carriers have lower hippocampal volumes relative to Val/Val homozygotes (3). Notably, the Met allele has been associated with slower suppression of the learned fear response in mice and humans (4).

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It is clearly important to understand predictors for the disease for preventive purposes but also to determine treatment options. Are individuals who are more likely to develop PTSD more or less likely to respond to treatment? Can we tailor treatment options to PTSD subgroups based on genotype? We are beginning to make progress in delineating individualized responses to pharmacotherapies for behavioral disorders. For example, *FKBP5* gene variation predicts speed of response to antidepressants (5) and the 5-HTTLPR high activity variant in *SLC6A4*, the gene encoding the serotonin transporter predicts greater responsiveness of PTSD symptoms to sertraline (6). Eventually, successful treatment of most behavioral disorders is likely to result from a combination of behavioral, psychosocial as well as pharmacological therapies. However, at this time CBT is still the first choice of treatment for PTSD but many patients unfortunately do not respond. One approach to this problem is to determine whether there are genetic variants that might identify groups of high and low responders to particular forms of behavioral therapy. The results of one of the first studies to take this approach are reported in this issue of *Biological Psychiatry*. Felmingham and colleagues (7) investigated whether the *BDNF* Val66Met polymorphism would predict response to an 8-week exposure-based CBT program in a study of 55 Caucasian patients with PTSD. Exposure therapy is designed to facilitate extinction learning by having the patient confront and learn to deal with cues to their traumatic events, thereby eventually reducing fear and anxiety connected with these reminders and also reducing avoidant behavior. Although the Val/Val homozygotes and Met allele carriers started with the same score on the Clinician Administered PTSD Scale (CAPS), after exposure-based CBT Val/Val homozygotes showed a 62% reduction in the CAPS score compared with a 40% reduction in Met allele carriers. Although considered preliminary because of small sample size, this is an important study that is the first step on the path toward genomic predictors of behavioral therapy. Moreover, this study should be put into the context of ethnicity: it has greatest relevance in Asians in whom the Met allele is abundant, moderate relevance in Caucasians amongst whom the Met allele frequency is less than 20% and least relevance in individuals of African ancestry in whom the Met allele frequency is close to zero.

Other genes and gene pathways are known to influence fear extinction, such as *COMT* and genes within the GABAergic and serotonergic systems. It would be worthwhile investigating these candidate genes, and particularly common functional polymorphisms, as predictors for response to exposure therapy. For example, carriers of the low activity variant of the *SLC6A4* 5-HTTLPR polymorphism experience greater amygdala activation in response to fearful stimuli and have impaired neuronal feedback circuitry that is responsible for the extinction of negative affect (8). Several studies have demonstrated that the low activity variant predicts PTSD, particularly in the context of childhood trauma (8). Indeed, before their *BDNF* study (7), the aforementioned group had performed a preliminary study within a subset of the same dataset and found that the low activity 5-HTTLPR variant was associated with fewer treatment gains to exposure-based CBT relative to other genotypes (8). However, when 5-HTTLPR genotypes were included with *BDNF* genotypes in the hierarchical multiple regression analysis (7), the effect of 5-HTTLPR dropped out, although this could be a feature of small sample size. Interestingly, a newly noted common functional SNP rs3813034 in the 3' untranslated region of *SLC6A4* has been associated with impaired retention of fear extinction memory with possible relevance for exposure-based CBT (9).

Another relevant, common functional polymorphism is *COMT* Val158Met (rs4860) that has been shown to influence fear extinction (10). The low activity Met allele has been associated with rumination and diminished stress resilience together with anxiety disorders in women only (10). In a study of Rwandan refugees who had experienced horrendous atrocities in the genocide attacks, Met/Met homozygotes exhibited a high risk for PTSD independent of the severity of traumatic load (10). Since the Met allele is common in all ethnicities, *COMT* Val158Met might well influence response to exposure-based CBT across a broad range of individuals, perhaps with a sexually dimorphic effect.

In the few studies that have emerged thus far, it seems that genetic variants that predict increased vulnerability to PTSD also predict a poorer response to exposure-based CBT and also a poorer response to SSRI antidepressants. The question then arises as to how we are to improve treatment for this most disadvantaged subset of patients with PTSD. As alluded to at the start of this commentary, G x E interactions are increasingly being recognized such that ‘two strikes’: genetic vulnerability and exposure to childhood trauma, can be pre-requisites for development of psychopathology, including PTSD (1). It is conceivable that recognition and treatment of the lasting effects of underlying childhood trauma may improve behavioral treatment outcomes for adult psychopathology.

The current literature is small but the results are tantalizing. The first steps have been taken. However it must be borne in mind that the influence of one gene on a behavioral outcome is likely to have only a modest clinical impact. It should be noted that there are likely to be numerous genetic variants with small effects that contribute to the response to behavioral therapy. Indeed, Felmingham and colleagues (7) showed that the improvement in PTSD symptoms after exposure therapy was a modest 1.6 times greater in *BDNF* Val/Val homozygotes relative to Met allele carriers (although improvement relative to the rare Met/Met homozygotes was likely to be much greater) and *BDNF* genotype contributed to only 14% of the variance in treatment response after controlling for other predictors. Adequately powered clinical trials are necessary to determine whether genotype effects are sufficiently large to potentially inform the selection of patients for particular treatments. However this is of itself challenging, for example since clinical trials rarely deal with ethnic stratification effects and clinical trial samples may reflect selection biases.

Optimistically looking to the future, it is clear that large studies need to be performed, preferably longitudinally, initially to explore candidate gene effects including gene – gene interactions, for example of *BDNF* Val66Met and 5-HTTLPR. It would be important to perform large genome-wide association studies (GWAS) for behavioral treatment outcomes in order to find new variants that might better identify treatment subgroups. With the advent of next-generation sequencing, it is possible that eventually personalized panels of common and rare variants might be stronger, clinically relevant predictors of the success of various treatment options. Finally, although not the topic of this commentary, we should be cognizant of the emerging literature on epigenetic influences on PTSD (2) and other behavioral disorders.

References

1. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*. 2008; 299:1291–1305. [PubMed: 18349090]
2. Andero R, Ressler KJ. Fear extinction and BDNF: translating animal models of PTSD to the clinic. *Genes Brain Behav*. 2012; 11:503–512. [PubMed: 22530815]
3. Lipsky RH, Marini AM. Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. *Ann N Y Acad Sci*. 2007; 1122:130–143. [PubMed: 18077569]
4. Frielingsdorf H, Bath KG, Soliman F, Difede J, Casey BJ, Lee FS. Variant brain-derived neurotrophic factor Val66Met endophenotypes: implications for posttraumatic stress disorder. *Ann N Y Acad Sci*. 2010; 1208:150–157. [PubMed: 20955337]
5. Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Pütz B, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet*. 2004; 36:1319–1325. [PubMed: 15565110]
6. Mushtaq D, Ali A, Margoob MA, Murtaza I, Andrade C. Association between serotonin transporter gene promoter-region polymorphism and 4- and 12-week treatment response to sertraline in posttraumatic stress disorder. *J Affect Disord*. 2012; 136:955–962. [PubMed: 21962566]
7. Felmingham KL, Dobson-Stone C, Schofield PR, Quirk GJ, Bryant RA. The Brain-Derived Neurotrophic Factor Val66Met Polymorphism Predicts Response to Exposure Therapy in Posttraumatic Stress Disorder. *Biol Psychiatry*. 2013 Jan 8. [Epub ahead of print]. 10.1016/j.biopsych.2012.10.033
8. Bryant RA, Felmingham KL, Falconer EM, Pe Benito L, Dobson-Stone C, Pierce KD, et al. Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. *Biol Psychiatry*. 2010; 67:1217–1219. [PubMed: 20434135]
9. Hartley CA, McKenna MC, Salman R, Holmes A, Casey BJ, Phelps EA, Glatt CE. Serotonin transporter polyadenylation polymorphism modulates the retention of fear extinction memory. *Proc Natl Acad Sci USA*. 2012; 109:5493–5498. [PubMed: 22431634]
10. Kolassa IT, Kolassa S, Ertl V, Papassotiropoulos A, De Quervain DJ. The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-o-methyltransferase Val(158)Met polymorphism. *Biol Psychiatry*. 2010; 67:304–308. [PubMed: 19944409]