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Commentary

FKBP5 Polymorphisms Modify the Effects of Childhood Trauma

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Childhood trauma is a well-established risk factor for mental and physical health problems over the life course (Anda *et al*, 2005). However, individuals vary widely in response to childhood trauma with some showing persistent adverse effects and other emerging apparently unimpaired. One goal of genotype–environment interaction (G × E) research has been to better understand the neurobiological mechanisms underlying this variation. Genes regulating the hypothalamic–pituitary–adrenal (HPA) axis are particularly good candidates for this research. Animal models and human correlational studies suggest that childhood trauma alters the development of the HPA axis and this may account for childhood trauma's manifold and persistent adverse effects (Lupien *et al*, 2009).

Emerging evidence suggests that genetic variation modifies HPA axis susceptibility to the effects of childhood trauma. SNPs in the *FKBP5* gene, a glucocorticoid receptor-regulator cochaperone of stress proteins, have been associated with peritraumatic dissociation among injured children (Koenen *et al*, 2005), recovery from psychosocial stress in normal controls (Ising *et al*, 2008), and modify the association between childhood abuse and posttraumatic stress disorder (PTSD; (Binder *et al*, 2008). In this issue, Roy *et al* (2010) and Xie *et al* (2010) examine the interaction of *FKBP5* and childhood trauma in the etiology of suicide attempts and PTSD, respectively. These studies highlight the promise and challenges of the G × E approach in understanding vulnerability and resilience to childhood trauma.

Roy and colleagues present evidence that variation in the *FKBP5* gene modifies the association between childhood trauma and suicide attempts in a largely male, African-American sample. The 2122 haplotype of *FKBP5*, which is compromised of four SNPs (rs3800373, rs9296158, rs1360780, rs9470080), increased risk of suicide attempts only among individuals reporting high levels of childhood trauma. The authors perform denser SNP coverage of the *FKBP5* gene than those carried out previously in order to better understand the observed associations. The results revealed significant gene by childhood trauma interactions for rs3800373, rs9296158, rs1360780 and a significant main effect for rs9470080, all of which have been implicated in stress-related outcomes in at least one prior study (Koenen *et al*, 2005; Binder *et al*, 2008; Ising *et al*, 2008). However, Roy *et al*'s (2010) findings are in the opposite direction of previous work; the putatively 'protective' alleles of these SNPs were associated with suicide attempts under high trauma conditions.

Xie and colleagues take advantage of a large sample of European and African-American individuals recruited for studies of the genetics of substance dependence to examine whether variation in four *FKBP5* SNPs (rs3800373, rs9296158, rs1360780, rs9470080) modify the association between childhood adversity and PTSD. Childhood adversity was measured using as part of a structured diagnostic interview. Consistent with previous work (Binder *et al*, 2008), the authors report a significant interaction for rs9470080, whereby African-American individuals with the TT genotype had the highest risk of PTSD when exposed to any childhood adversity but the lowest risk under no adversity. This interaction was not significant for European Americans—a population that had not been assessed previously for G × E interactions at this locus for PTSD.

Taken together and considered within the larger literature on *FKBP5*, Roy *et al* (2010) and Xie *et al* (2010) highlight four challenges for researchers attempting to make sense of the role of genotype in modifying the effects of childhood trauma. The first challenge is in the measurement of childhood trauma, which varies across studies in terms of age of exposure, type of event (eg, direct experience of abuse or witnessed violence) and analytic treatment as qualitative or quantitative. Neurobiological effects of childhood trauma vary with type and timing of exposure (Lupien *et al*, 2009). Detection of G × E has also been shown to vary by how childhood trauma is measured (Polanczyk *et al*, 2009). Differences in childhood trauma assessment may, therefore, produce discrepant findings.

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The second challenge is that childhood trauma is associated with psychiatric outcomes that appear to have different patterns of HPA axis dysregulation. As noted by Roy *et al*, PTSD has been associated with sensitization of the HPA axis due to stressful exposures (Heim and Nemeroff, 2009). In contrast, alcohol dependence has been associated with a blunted HPA axis response to stress (Richardson *et al*, 2008). Roy *et al* (2010) suggest that their discrepant genetic findings may reflect compromised HPA axis responsivity related to substance dependence among their study participants.

The third challenge is to consider how sampling may influence G × E findings. Both Roy *et al* (2010) and Xie *et al* (2010), similar to the vast majority of genetic studies, rely at least in part on clinical and convenience samples. Most individuals with psychiatric problems do not seek treatment and, therefore, clinical samples are not representative of individuals with the disorder in the general population. A substantial proportion of the samples in both studies were also substance dependent. Genetic and environmental influences on etiology may vary by comorbidity profile.

The fourth challenge is the intriguing possibility of race-specific G × E effects presented by Xie *et al* (2010). Earlier work by this same group showed race-specific G × E effects for childhood adversity at the serotonin transporter promoter (*5-HTTLPR*) locus, with significant results detected among European Americans, but not African Americans (Xie *et al*, 2010). These data suggest that G × E effects may vary with ancestry at neurobiologically relevant loci for psychiatric outcomes. Given racial and ethnic differences in social and individual level environmental exposures (Roberts *et al*, 2010) known to affect psychiatric outcomes, an important question for future G × E research is how environmental factors at multiple levels influence putative race-specific effects.

The work by Roy *et al* (2010) and Xie *et al* (2010) move the literature forward by offering, on the one hand, denser SNP characterization of the *FKBP5* locus in the context of a psychiatric outcome not previously associated with variation at this gene and, on the other hand, assessing *FKBP5* × childhood adversity effects for PTSD in the largest sample of European Americans and African Americans to date. The four challenges raised by these two studies should motivate more, and better quality, rather than less, research on how genotypes and a range of environmental factors jointly produce mental disorders, in order to improve our understanding of the neurobiological mechanisms underlying vulnerability and resilience in response to childhood trauma.

DISCLOSURE

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