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SCIENTIFIC CORRESPONDENCE

Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children

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SIR—Recently, Binder *et al*[1] reported association between two polymorphisms (rs3800373, rs1360780) in the FKBP5 gene, a glucocorticoid receptor-regulating cochaperone of stress proteins, and greater recurrence of depressive episodes and rapid response to antidepressant treatment in two independent samples. The authors cite the role of FKBP5 in hypothalamic–pituitary–adrenal (HPA) axis regulation, positing that these polymorphisms may result in 'more rapid onset of stress hormone hyperactivity after stressful life events' (p 1323). Animal models support genetically influenced individual differences in HPA axis regulation that produce variation in acute behavioral responses to stress.[2] One characteristic behavioral response to life-threatening stress is immobilization or freezing. This behavioral response to threat is thought to be evolutionarily conserved, and present in humans as peritraumatic dissociation. Behaviorally, peritraumatic dissociation is characterized by insensitivity to pain, losing time, feeling that the experience is unreal, or feeling as if something is happening in slow motion. Genetic influences on peritraumatic dissociation have not been examined previously. Here we report evidence for an association between the same polymorphisms in the FKBP5 gene studied by Binder *et al*[1] and peritraumatic dissociation in a sample of injured children.

Children ($n=46$) were enrolled following their admission to the hospital for an acute medical injury. They were: 24 African-Americans, 22 Whites; 34 boys, 12 girls; mean age = 14, SD = 3.1; range 7–18. Over 54% ($n=25$) of the injuries involved motor vehicle accidents, 24% ($n=11$) involved physical assaults including stabbings or gunshot wounds, 13% ($n=6$) involved falls, and the remaining four involved other types of injuries. Children were interviewed in the hospital by a master's level psychologist about dissociation during the injury using the Peritraumatic Dissociative Experiences Questionnaire (PDEQ)[3] and dissociation since the injury using the dissociation questions of the PTSD Reaction Index (PTSD-RI).[4] The distribution for both measures approximated normality. Injury severity score[5] was based on the surgeon's rating ($M=9.23$, SD = 7.01, range 1–34). Buccal DNA samples were obtained from each subject via mouthwash. DNA was isolated using the Gentra DNA isolation kit (Gentra Systems, Minneapolis, MN, USA). Two SNPS in the FKBP5 gene (rs3800373, rs1360780) were typed in each subject using real-time PCR technology (Applied Biosystems, Foster City, CA, USA). Both markers were in Hardy–Weinberg equilibrium (rs3800373 AA $n=14$ (32.6%); CA $n=24$ (55.8%); CC $n=5$ (11.6%); rs1360780 CC $n=14$ (31.1%); CT $n=26$ (57.8%); TT $n=5$ (11.1%)). Self-reported ethnicity was unrelated to either genotype distribution (rs3800373 $\chi^2(2)=0.77$, $P=0.68$; rs1360780 $\chi^2(2)=1.30$, $P=0.52$) or to either measure of dissociation (PDEQ $b=1.79$, SE = 2.54, $P=0.49$; PTSD-RI $b=-2.54$, SE = 1.30, $P=0.10$).

Table 1 presents the results of regression analyses using robust variance estimates. Both SNPs were significantly associated with dissociation during the injury and since the injury, after controlling for race, sex, age, and injury severity. For rs3800373, each C allele was associated with a half standard deviation increase in dissociation during the accident and a 0.70 standard deviation increase in dissociation since the accident. For rs1360780, each T allele was associated with an increase in dissociation. The R^2 change gives the proportion of the variance in dissociation accounted for by the SNP, over and above that accounted for by self-reported ethnicity, gender, age, and injury severity. Thus, marker rs3800373 uniquely explained 14% of the variance in dissociation.

Peritraumatic dissociation is highly correlated with other aspects of acute stress response such as hyperarousal. Although our findings are consistent with FKBP5 contributing to individual differences in peritraumatic dissociation, they are also consistent with an association between FKBP5 and other correlated aspects of acute stress response. Future research is needed to determine whether FKBP5 contributes specifically to peritraumatic dissociation or more generally to acute stress response following trauma.

Peritraumatic dissociation is a well-established risk factor for the development of post-traumatic stress disorder in adults (PTSD).[6] PTSD is a common psychiatric disorder that occurs following exposure to a traumatic event and has a lifetime prevalence of approximately 8% in the general population.[7] Peritraumatic dissociation has recently been shown to prospectively predict the development of PTSD in children who were sexually abused[8] and in children hospitalized for burns.[9] PTSD is known to have adverse consequences for children's long-term emotional, cognitive, and social development.[10] HPA axis sensitization and alterations in glucocorticoid receptor regulation are thought to underlie the development of PTSD.[11] FKBP5 is involved in HPA axis through its influence on glucocorticoid receptor

Table 1 Association between FKBP5 SNP genotypes with dissociation in medically injured children ($n = 46$) controlling for race, sex, age, and injury severity

Measure	*SNP*	*Coef.*	*Robust SE*	*Beta*	T	P-*value*	R^2 *change*	*Total* R^2
Dissociation during the accident	rs3800373	0.52	0.26	0.34	2.02	<0.05	0.0814	0.1389
	rs1360780	0.55	0.27	0.35	2.08	<0.05	0.1296	0.1871
Dissociation since the accident	rs3800373	0.69	0.18	0.42	3.86	<0.001	0.1395	0.2749
	rs1360780	0.47	0.21	0.28	2.24	<0.03	0.0695	0.2049

Robust variances were used to give nonbiased parameter estimates. Outcomes were standardized for this analysis. Therefore, coefficients can be interpreted in terms of proportion of a standard deviation unit change in outcome for each C allele in rs3800373 and T allele in rs1360780. R^2 change indicated the proportion of the variance in outcome explained by the SNP after controlling for self-reported ethnicity, gender, age, and injury severity. Total R^2 is the total variance explained when both the SNP and covariates are included in the model.

activity. Segman *et al*[12] recently reported an association between gene expression signatures following trauma and the development of PTSD. Thus, although our findings are preliminary, we believe they are of potential interest for researchers interested in understanding the neurobiological mechanisms that influence psychological responses to extreme stress and the development of PTSD.

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