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Association of FKBP5, COMT and CHRNA5 polymorphisms with PTSD among outpatients at risk for PTSD

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To the Editor:

Several genetic components for posttraumatic stress disorder (PTSD) have been identified, including biologic pathways involving the hypothalamic–pituitary–adrenocortical, locus coeruleus/noradrenergic, and the limbic systems (Broekman, et al., 2007; Koenen, 2007; Rauch and Drevets, 2009). In our IRB-approved study, lifetime PTSD was assessed among adult outpatients with chronic, non-malignant pain, a condition commonly associated with PTSD (McFarlane, 2010). We assessed PTSD with an instrument widely used in previous epidemiologic studies (Boscarino et al., 2010). We examined genetic markers using a multivariate design that assessed single nucleotide polymorphisms (SNPs) located within the FK506 binding protein-5 (FKBP5), catechol-O-methyltransferase (COMT), and cholinergic receptor nicotinic alpha3/alpha-5 (CHRNA3/CHRNA5) gene clusters. SNPs were selected using agnostic LD tagging with consideration of prior evidence and functional annotation (Erlich, et al., 2010). The COMT gene is associated with anxiety disorders, psychosis, depression, and other conditions involving catecholamine pathway regulation (Craddock, et al., 2006; Montag et al., 2008). This gene is also associated with PTSD (Kolassa et al., 2010). The FKBP5 gene regulates glucocorticoid receptor sensitivity, is functionally involved in HPA stress axis activity, and is associated with PTSD (Binder, 2009; Gillespie, et al., 2009). The CHRNA3/5 gene cluster, which encodes components of the nicotinic acetylcholine receptor, is associated with nicotine dependence, smoking, and other substance misuse (Erlich, et al., 2010). PTSD is also associated with cigarette smoking and substance use (Boscarino et al., 2006; Fu et al., 2007).

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Using trained interviewers and following informed consent, we completed diagnostic interviews with 502 subjects and collected DNA to determine if FKBP5, COMT, and CHRNA3/5 SNPs were associated with PTSD (mean age = 55, S.D. = 13.4; PTSD = 15%, 95% CI = 11.7–18.1%). Non-Caucasian patients were excluded from this analysis. Genotyping was performed on an Applied BioSystems 7500 real-time PCR platform, using TaqMan kits. Using multivariate logistic regressions that included demographic (age, gender, income, education, and marital status) and environmental (trauma exposure, childhood adversity, and neuroticism) variables, 3 of 9 SNPs examined were associated with PTSD ($p<0.05$), including one within each of the FKBP5 (rs9470080), COMT (rs4680), and CHRNA5 (rs16969968) genes. A count of risk alleles in these 3 loci was also associated with PTSD (OR = 1.65, 95% CI = 1.25–2.16, $p = 0.000426$), suggesting that those with 4 or more PTSD risk alleles had ~ 7 times greater risk of PTSD, compared to those with no risk alleles ($1.65 \times 4 = 6.6$). We also included opioid dependence, reported pain, number of pain prescriptions, and ancestry (Northern European, Eastern European, and Sothern European/Other) in the model as a final analysis step, but this did not alter the results. Examination of risk-allele counts by PTSD status suggested that the “AA” genotype of the rs16969968 (CHRNA5) and rs4680 (COMT), and the “TT” genotype of rs9470080 (FKBP5) are more common among PTSD cases. Since our logistic regression detected a complex interaction between allele count × trauma exposure × childhood adversity × neuroticism ($p = 0.029$), we used Answer Tree Chi-square Automatic Interaction Detection to examine these effects (SPSS, Chicago, IL). This confirmed interactions with risk-allele count, indicating that those with higher risk-allele counts and exposure to higher trauma, higher childhood adversity, and higher neuroticism, were at much greater risk for PTSD. Conversely, those with no risk alleles appeared highly resilient to PTSD, regardless of environmental exposures.

This is the first study to report that SNP markers rs16969968, rs9470080, and rs4680, were each individually associated with PTSD and that a cumulative allele model using these SNPs was associated with higher PTSD risk. FKBP5 polymorphisms are known to regulate the cortisol-binding affinity and nuclear translocation of the glucocorticoid receptor and polymorphisms at this locus have been associated with PTSD. COMT polymorphisms have been found to affect fear extinction and are thought to play a role in anxiety disorders and PTSD. The CHRNA gene has been associated with nicotine dependence and PTSD is associated with cigarette smoking and other substance misuse. Additional research is recommended to confirm these findings. The involvement of the CHRNA gene in PTSD, fear circuitry, and stress regulation is biologically plausible and worthy of further investigation.

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