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Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: A genome-wide association study across multiple ancestries implicates *PRTFDC1* as a potential PTSD gene

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Summary
Background: Research on the etiology of post-traumatic stress disorder (PTSD) has rapidly matured, moving from candidate gene studies to interrogation of the entire human genome in genome-wide association studies (GWAS). Here we present the results of a GWAS performed on samples from combat-exposed U.S. Marines and Sailors from the Marine Resiliency Study (MRS) scheduled for deployment to Iraq and/or Afghanistan. The MRS is a large,

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Trauma;
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prospective study with longitudinal follow-up designed to identify risk and resiliency factors for combat-induced stress-related symptoms. Previously implicated PTSD risk loci from the literature and polygenic risk scores across psychiatric disorders were also evaluated in the MRS cohort.

Methods: Participants ($N = 3494$) were assessed using the Clinician-Administered PTSD Scale and diagnosed using the *DSM-IV* diagnostic criterion. Subjects with partial and/or full PTSD diagnosis were called cases, all other subjects were designated controls, and study-wide maximum CAPS scores were used for longitudinal assessments. Genomic DNA was genotyped on the Illumina HumanOmniExpressExome array. Individual genetic ancestry was determined by supervised cluster analysis for subjects of European, African, Hispanic/Native American, and other descent. To test for association of SNPs with PTSD, logistic regressions were performed within each ancestry group and results were combined in meta-analyses. Measures of childhood and adult trauma were included to test for gene-by-environment (GxE) interactions. Polygenic risk scores from the Psychiatric Genomic Consortium were used for major depressive disorder (MDD), bipolar disorder (BPD), and schizophrenia (SCZ).

Results: The array produced >800 K directly genotyped and >21 M imputed markers in 3494 unrelated, trauma-exposed males, of which 940 were diagnosed with partial or full PTSD. The GWAS meta-analysis identified the phosphoribosyl transferase domain containing 1 gene (*PRTFDC1*) as a genome-wide significant PTSD locus (rs6482463; OR = 1.47, SE = 0.06, $p = 2.04 \times 10^{-9}$), with a similar effect across ancestry groups. Association of *PRTFDC1* with PTSD in an independent military cohort showed some evidence for replication. Loci with suggestive evidence of association ($n = 25$ genes, $p < 5 \times 10^{-6}$) further implicated genes related to immune response and the ubiquitin system, but these findings remain to be replicated in larger GWASs. A replication analysis of 25 putative PTSD genes from the literature found nominally significant SNPs for the majority of these genes, but associations did not remain significant after correction for multiple comparison. A cross-disorder analysis of polygenic risk scores from GWASs of BPD, MDD, and SCZ found that PTSD diagnosis was associated with risk sores of BPD, but not with MDD or SCZ.

Conclusions: This first multi-ethnic/racial GWAS of PTSD highlights the potential to increase power through meta-analyses across ancestry groups. We found evidence for *PRTFDC1* as a potential novel PTSD gene, a finding that awaits further replication. Our findings indicate that the genetic architecture of PTSD may be determined by many SNPs with small effects, and overlap with other neuropsychiatric disorders, consistent with current findings from large GWAS of other psychiatric disorders.

1. Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder and unique in that exposure to an environmental event (Criterion-A traumatic event; APA, 2000) is a necessary condition for diagnosis. Lifetime prevalence is ~8% in adult Americans (Kessler et al., 1995; Kilpatrick et al., 2013) and is especially high among those exposed to combat, with values ranging from 6% to 31% as reported in a recent review of studies on US combat veterans (Richardson et al., 2010). A large number of demographic and environmental factors and their interactions contribute to PTSD susceptibility, including female gender, age, existence of previous mental health issues, early life stress, as well as severity, duration and number of traumatic incidents, and other factors such as lack of social support (Zoladz and Diamond, 2013). Notably, there are race/ethnic differences in traumatic event exposure, in type of event, age at exposure, as well as the development of PTSD given a specific trauma, with African Americans having somewhat higher risks than whites and Asians (Roberts et al., 2010).

In addition, individual differences in heritable factors affect the risk to develop PTSD. Twin studies indicate that PTSD is moderately heritable, with genetic factors explaining a substantial proportion (30–46%) of vulnerability to PTSD (reviewed e.g. in Wolf et al., 2013). Remaining variance is attributable to the non-shared environment, including trauma encountered during war zone deployments. For some, combat exposure acts as a catalyst that augments the impact of hereditary and environmental contributions to PTSD (Wolf et al., 2013).

A large proportion of the genetic liability for PTSD is also shared with other mental disorders such as anxiety and panic disorder (Goenjian et al., 2008), major depressive disorder (MDD) (Fu et al., 2007; Sartor et al., 2012), and substance use (Xian et al., 2000), hence genes that confer risk for PTSD may also influence risk for other psychiatric disorders and vice versa (Nugent et al., 2008). Such pleiotropic effects have been demonstrated across several psychiatric disorders (Solovieff et al., 2013). For example, a recent study that examined schizophrenia (SCZ), bipolar disorder (BPD), MDD, and attention-deficit/hyperactivity disorder (ADHD) found that SNP-based heritability ranged from 17 to 29% within disorders. Genetic correlations between disorders were also observed with highest associations between SCZ and BPD, and moderate correlations between SCZ and MDD, BPD and MDD, and ADHD and MDD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Cross-Disorder Group of the Psychiatric Genomics Consortium and Genetic Risk Outcome of Psychosis Consortium, 2013).

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