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Support for association of *RORA* variant and post traumatic stress symptoms in a population-based study of hurricane exposed adults

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Post-traumatic stress disorder (PTSD) is moderately heritable, with estimates ranging from 30 to 70%.[1] However, most of the genetic variation accounting for this heritability has yet to be identified, and the majority of molecular studies to date on PTSD have been candidate gene designs.[2] Only one genome wide association study of PTSD has been published. In a sample of white non-Hispanic trauma-exposed veterans and their spouses/partners with and without PTSD, Logue and colleagues[3] found that one single nucleotide polymorphism (SNP; rs8042149) in the retinoid-related orphan receptor alpha gene (*RORA*) reached genome-wide significance. *RORA* has been implicated, in part, in protecting brain cells from the damaging effects of injury, stress and disease,[3] and it is possible that individuals with the variation in *RORA* may be at increased risk for developing PTSD due to deficits in initiating neuroprotective processes after trauma. We sought to provide supporting evidence for the genetic association between *RORA**rs8042149 and PTSD using data from the 2004 Florida hurricanes study.

The 2004 Florida hurricanes study is based on a stressor-exposed epidemiologic sample of adults who were living in Florida counties that were declared disaster areas following Hurricanes: Charley, Francis, Ivan or Jeanne. Participants were selected via random digit-dial procedures, and they were interviewed via telephone about hurricane exposure, social support and posthurricane PTSD symptoms. Participants also were asked to provide saliva samples for genotyping (for details on response rate and associations of participation in the study, see[4,5]). In this sample, we tested the most significant variant in *RORA* reported by Logue *et al.*[3] by examining the association between rs8042129 and posthurricane *DSM-IV* PTSD symptom count (range 0–17, $M = 1.6$, *s.d.* = 2.6). We chose the symptom count as our

CONFLICT OF INTEREST

The authors declare no conflict of interest.

outcome given the low prevalence of full diagnostic PTSD (2.7%). To reduce potential bias of population stratification, the sample for this report consisted of the self-identified European-American subsample of adults exposed to the 2004 Florida hurricanes who returned a DNA sample that yielded valid data for rs8042129 (n = 551; 65% female). *RORA* rs8042129 genotype frequencies were in Harvey–Weinberg equilibrium, and genotype frequencies were as follows: G/G (n = 159, 28.9%), G/T (n = 280, 50.8%) and T/T (n = 112, 20.3%). A linear regression analysis predicting posthurricane PTSD symptoms was conducted, controlling for covariates that emerged as significant predictors of PTSD in previous analyses (sex, age, hurricane exposure, social support; for example, Amstadter *et al.*).[6] The overall model was significant, $F(5,538) = 9.75$, $P<0.001$. Furthermore, the *RORA* rs8042149 SNP accounted for significant variance in PTSD symptom severity, $\beta = -0.09$, $t = -2.20$, $P = 0.028$. Specifically, the G allele was associated with higher PTSD symptoms after the hurricane.

In summary, we were able to support the association between rs8042149 and PTSD symptom count in a sample of adults who were exposed to an acute stressor. As demonstrated by Logue *et al.*,[3] we found a main effect of rs8042149 on post-trauma distress, with the G allele being associated with higher PTSD symptom levels. Similar to Logue *et al.*,[3] we found this association in a European-American sample. However, whereas Logue *et al.*[3] observed this relation in a sample of veterans and their spouses/ partners with a diverse history of traumatic experiences, we extended this finding to a sample of individuals exposed to a recent natural disaster. A major strength of replicating this finding with a disaster-exposed epidemiologic sample is that the possible effects of a gene-environment correlation were reduced because exposure to non-assaultive trauma (for example, natural disasters) has been found to have lower heritability estimates than exposure to assaultive traumas.[1] One notable limitation of the present study is the low prevalence of PTSD, and low overall average PTSD symptom count, suggesting the need for replication in more severely affected samples.

This study adds to a growing body of research that suggests that polymorphisms of the *RORA* gene are associated with risk for various forms of psychopathology, including PTSD, autism, ADHD, bipolar disorder and depression.[7–10] Further research is needed to understand better how *RORA* polymorphisms may contribute to the development of psychopathology. *RORA* is a member of the NR1 subfamily of nuclear hormone receptors, and the protein encoded by the gene is implicated in a number of processes, including brain development, neuroprotection and the regulation of circadian rhythms and steroid hormones.[3] Although understanding of *RORA*'s role in PTSD in particular is limited, it is possible that deficits in these functions may exacerbate the deleterious effects of trauma on the brain. Future research should examine how genetic variation in *RORA* may translate into differential functional and structural outcomes that may put individuals at risk for PTSD.

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