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No association between *RORA* polymorphisms and PTSD in two independent samples

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Logue *et al.*[1] reported genome-wide significant association between a polymorphism (rs8042149) in the *RORA* gene, encoding the retinoic acid orphan receptor A, and posttraumatic stress disorder (PTSD) in a cohort of trauma-exposed white non-Hispanic US veterans and their partners. The genome-wide association study yielded evidence of association for three additional SNPs at the 10^{-6} threshold in the same cohort (rs8041061, rs8024133, rs11071561). Amstadter *et al.*[2] reported a significant association between rs8042149 and PTSD symptoms in the 2004 Florida Hurricane Study. The *RORA* gene encodes a nuclear hormone receptor that regulates the transcription activity of nearby genes. It is widely expressed in the brain, where it protects cortical neurons against oxidative stress-induced apoptosis by increasing the expression of antioxidant proteins.[1] Logue *et al.*[1] proposed that genetic variations in *RORA* may alter its expression, reducing the capacity of neurons to respond to biochemical stressors induced by traumatic stress.

We set out to replicate the association of variations in the *RORA* gene with lifetime risk of PTSD and to test whether *RORA* genotypes modified the association between cumulative trauma exposure and PTSD in two independent data sets.

The first data set was primarily European American—a PTSD subsample ($N = 2616$ trauma-exposed women) from the Nurses Health Study II (NHSII).[3] The ascertainment of this data set and assessment of PTSD have been described.[4] PTSD diagnosis was defined according to DSM-IV criteria ($n = 849$ cases, $n = 1767$ trauma-exposed controls). PTSD symptom severity was defined as the sum of the symptom ratings (1: 'not at all' to '5: extremely') across the 17 questions (mean = 32.73, s.d. = 13.08). PTSD symptom count was defined as the number of PTSD symptoms endorsed (mean = 7.15, s.d. = 4.57). A measure of cumulative trauma exposure was created by summing the number of different traumatic event types experienced. Four polymorphisms mapping to *RORA* were genotyped for each sample using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA), in 384-well format or using the TaqMan OpenArrayTM SNP Genotyping Platform (Applied Biosystems) according to the manufacturer's instructions. All markers were in Hardy–Weinberg equilibrium. To reduce concern about population stratification, we restricted analysis to 2616 self-reported European-American women. Analyses were conducted in PLINK.[5]

SNPs rs8042149, the original genome-wide significant marker, rs11071561, rs8041061 and rs8024133 were not associated with lifetime PTSD under the additive, recessive or dominant models (Table 1).

SNPs rs8041061, rs8042149 and rs8024133 showed no evidence of association with either symptom severity or symptom count (*P*-values ranged from 0.06 to 0.54). SNP rs11071561 was associated with PTSD symptom severity ($P = 0.02$) in the same direction as in Logue *et al.*,[1] but was not associated with symptom count ($P = 0.07$). However, the association with symptom severity did not reach the threshold for significance after correcting for multiple testing ($P = 0.0125$). We further tested whether SNPs in the *RORA* gene modified the relation between cumulative trauma exposure and PTSD for diagnosis, symptom severity and symptom count. There was also no evidence of genotype–environment interaction for any PTSD phenotype (*P*-values ranged from 0.29 to 0.97).

The second data set was composed of more than 2000 Iraq and Afghanistan-era US Veterans (PTSD cases and trauma-exposed controls) collected through the Mental Illness Research, Education and Clinical Center (MIRECC) housed in the Veterans Integrated Service Network 6 of the Department of Veteran Affairs. The data set included 880 European Americans (447 lifetime PTSD cases, 433 controls; 16% female) and 1157 African Americans (586 cases, 571 controls; 32% female). PTSD status was evaluated by the Davidson Trauma Scale[6,7] and trauma exposure was measured by the Traumatic Life Events Questionnaire.[8] DNA extracted from blood was genotyped by Taqman assays (Applied Biosystems) for nine SNPs in RORA (rs16942660, rs8041061, rs8042149, rs8024133, rs11071561, rs341401, rs11071587, rs11071588, rs893290). Statistical analysis was conducted using PLINK[5] independently in the self-reported European-American and African-American subjects. Under additive, recessive and dominant genetic models, controlling for the effects of gender and trauma, two SNPs were nominally associated with PTSD among African Americans under the recessive model (rs16942660, $P = 0.04$; rs8041061, $P = 0.03$), although the associations did not reach the threshold for significance after correcting for multiple testing ($P = 0.005$; Table 1). Sex-stratified analyses under the dominant model identified rs341401 ($P = 0.004$) as being significantly associated with PTSD among African-American females only and rs11071587 ($P = 0.008$) as being significantly associated with PTSD among Caucasian females only. However, once this model was adjusted for the effects of resilience,[9] the association was no longer significant ($P = 0.037$) after correcting for multiple testing ($P = 0.005$).

We were unable to replicate findings by Logue *et al.*[1] or Amstadter *et al.*[2] of an association between variations in the *RORA* gene and PTSD. Our samples had high power (>99%) to detect the effect size reported by Logue *et al.*[1] with odds ratios between 1.8 and 2.1 under an additive model with the same risk alleles. We also found no evidence that *RORA* polymorphisms

Table 1. Main results of genetic association analysis

Chr	SNP	Study	Group	Minor allele	Minor allele frequency	Additive model P-value	Dominant model P-value	Recessive model P-value
15	rs8041061	*NHS2*	*EA*	C	0.47	0.79	0.57	0.35
		MIRECC	*EA*	C	0.48	0.68	0.86	0.62
		MIRECC	AA	A	0.14	0.62	0.84	0.03
15	rs8042149	*NHS2*	*EA*	A	0.47	0.56	0.21	0.82
		MIRECC	*EA*	A	0.43	0.23	0.29	0.38
		MIRECC	AA	C	0.25	0.61	0.40	0.63
15	rs8024133	*NHS2*	*EA*	G	0.45	0.63	0.25	0.08
		MIRECC	*EA*	G	0.44	0.94	0.82	0.68
		MIRECC	AA	A	0.17	0.34	0.46	0.32
15	rs11071561	*NHS2*	*EA*	A	0.43	0.31	0.81	0.09
		MIRECC	*EA*	A	0.40	0.73	0.69	0.89
		MIRECC	AA	T	0.33	0.82	0.52	0.62

Abbreviations: AA, African American; EA, European American; SNP, single-nucleotide polymorphism.

modified the relation of trauma exposure with PTSD. As it has been shown with other psychiatric disorders,[10] PTSD may be highly polygenic and very large sample sizes may be needed to detect robust genotype–PTSD associations. Our findings do not, however, exclude the possibility that RORA has a role in the etiopathogenesis of PTSD. Our replication samples differ principally from Logue *et al.*[1] sample on three grounds: ethnicity, type and severity of trauma exposure, gender distribution. Further research is needed to understand how these factors influence the role of RORA in PTSD.

CONFLICT OF INTEREST

These authors declare no conflict of interest.

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Increased expression of *MARCKS* in post-mortem brain of violent suicide completers is related to transcription of a long, noncoding, antisense RNA

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A recent study by Le-Niculescu *et al.*[1] implicated several blood biomarkers for predicting and tracking suicidal ideation (SI) in a population at high risk for suicide (diagnosed with bipolar and