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Further Support for an Association between the Memory-Related Gene *WWC1* and Posttraumatic Stress Disorder: Results from the Detroit Neighborhood Health Study

To the Editor:

Posttraumatic stress disorder (PTSD) is moderately heritable, with approximately 30% to 40% of the variance associated with the disorder attributable to genetic variance (1). However, relatively little is known about specific genetic loci implicated in PTSD (2). The development of pathological fear-related memories for a traumatic event is posited as a key factor in the etiology of PTSD, and there has been recent interest in examining whether genes involved in the molecular processes underlying long-term memory consolidation and stabilization are associated with risk for PTSD (3). One such gene is *WWC1*, which encodes the scaffolding protein KIBRA. KIBRA is thought to play a role in synaptic plasticity and long-term potentiation, and it is expressed primarily in memory-related brain areas (e.g., hippocampus) (4). There is now robust support for an association between a single nucleotide polymorphism (SNP) in *WWC1* (rs17070145) and human episodic memory performance (5).

In a recent report in *Biological Psychiatry*, Wilker *et al.* (6) described the first association between variation in the *WWC1* gene and lifetime PTSD. Using data from two independent samples of survivors from conflict zones in Africa, minor allele carriers of two SNPs in *WWC1* (rs10038727 and rs4576167) exhibited a decreased risk of lifetime PTSD, over and above the effects of lifetime traumatic load. We sought to replicate the association between variation in *WWC1* and lifetime PTSD using available genetic data from a sample of the Detroit Neighborhood Health Study (DNHS).

The DNHS is a longitudinal, epidemiologic study of factors associated with trauma exposure, PTSD, and other mental disorders in a representative sample of predominantly African American adults from the urban Detroit area [for more details, see (7)]. Participants completed a 40-minute interview assessing demographics, lifetime exposure to 20 different traumatic events, and psychopathology. The PTSD Checklist-Civilian Version (8) was used to assess PTSD symptoms in reference to the worst traumatic event identified by the participant, as well as to a randomly selected event from the remaining events endorsed. Diagnoses of lifetime PTSD were given if DSM-IV criteria A to F were met with respect to either the worst or the randomly selected event. Participants were also invited to provide whole blood or saliva samples for genotyping. The DNHS was approved by the Institutional Review Board at the University of Michigan, and all participants provided written, informed consent.

Of the three SNPs in *WWC1* that have been associated with memory and PTSD (rs17070145, rs10038727, and rs4576167), only one SNP—rs10038727—was genotyped in the DNHS. A total of 598 participants (57% female participants, 83% African American, mean age = 52.3 years, SD = 16.1 years, range = 18–95) provided information regarding trauma exposure and PTSD and had valid data for rs10038727. *WWC1* rs10038727 minor (A) allele frequency was .19, and genotype frequencies were as follows: A/A (n = 20, 3.3%), A/G (n = 186, 31.1%), and G/G (n = 392, 65.6%). Genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium, $p = .79$.

A logistic regression analysis predicting lifetime PTSD status was conducted, with sex, age, and lifetime traumatic load (calculated by summing the number of traumatic event types endorsed) entered as covariates. The first two principal components from a multidimensional scaling analysis of genome-wide data were also included as covariates to adjust for population stratification. Results revealed that the *WWC1* rs10038727 SNP (coded additively) significantly predicted lifetime PTSD status, with the minor (A) allele associated with a reduced risk of PTSD, odds ratio = .64 (95% confidence interval = .406–.997), $p = .049$. Greater traumatic load was additionally associated with a greater risk of lifetime PTSD, odds ratio = 1.23 (95% confidence interval = 1.155–1.304), $p < .0001$. Consistent with Wilker *et al.* (6), we did not find evidence of a significant interaction between rs10038727 genotype and lifetime traumatic load in predicting lifetime PTSD status, $p = .56$. Additionally, lifetime traumatic load and rs10038727 genotype were not correlated, $r = -.02$, $p = .68$.

Results of the current study provide independent replication of a relationship between rs10038727 in *WWC1* and reduced risk of lifetime PTSD. Whereas Wilker *et al.* (6) originally identified this association in African samples of survivors from conflict zones, our results extend this finding to a predominantly African American sample of individuals residing in neighborhoods with high rates of trauma exposure in urban Detroit. Although there is some indirect evidence suggesting that rs10038727 may play a regulatory role given its location in an intronic region with high transcription factor binding affinity (6), direct investigations of molecular processes that underlie the association between this SNP and PTSD are needed. KIBRA has been postulated to influence synaptic plasticity and long-term potentiation by interacting with different binding partners (e.g., protein kinase Mζ, dendrin) (9,10), and it is of interest for future research to examine whether rs10038727 may impact these processes. Further research should also investigate the additional SNPs in *WWC1* that have been associated with memory and PTSD, given that only rs10038727 was genotyped in the DNHS. Nevertheless, our current findings support the importance of memory-related genes in risk for PTSD. Additional research studying *WWC1* genotype, component aspects of memory (e.g., encoding, memory extinction), and functional neuroimaging of memory-related brain regions may be useful for elucidating how genetic variation in memory-related genes may contribute to PTSD risk in trauma survivors.

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This study was supported by National Institutes of Health Grants DA022720 (AEA) and DA022720-S1 (AEA).

Dr. Pietrzak is a scientific consultant to CogState Ltd. The remaining authors report no biomedical financial interests or potential conflicts of interest.

0006-3223/$36.00

Please also see associated correspondence, http://dx.doi.org/10.1016/j.biopsych.2014.05.003.

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http://dx.doi.org/10.1016/j.biopsych.2014.03.033