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

Posttraumatic stress disorder (PTSD) is characterized by pathologic, intrusive memories of the experienced traumata. The risk to develop PTSD depends on the cumulative exposure to traumatic experience (traumatic load), on the extent of childhood adversities, and on genetic factors. The latter account for about one third of interindividual variability (1). Despite this pronounced genetic influence, little is known about the underlying genetic factors and molecular processes. Considering the strong role of fear memory development in PTSD, we recently argued for the investigation of memory-related genes in PTSD (2,3). Candidate gene association studies allow for such theory-driven analyses; however, they require replication to identify reliable associations between molecular genetic factors and PTSD.

The gene encoding the protein KIBRA (*WWC1*) is reliably associated with human episodic memory (4,5) and accumulating evidence from three independent samples now suggests a role of this gene in PTSD etiology. We discovered that *WWC1* genotype influenced PTSD risk in a sample of Rwandan genocide survivors and replicated this finding in a second study with survivors of the rebel war in Northern Uganda (6). Minor-allele carrier status of two *WWC1* single nucleotide polymorphisms (SNPs) (rs10038727 and rs4576167) was associated with decreased risk for lifetime PTSD development, an effect that held true for all levels of traumatic load. Our results on rs10038727 were replicated by Sumner *et al.* (7), who examined a large, predominantly African American sample from the Detroit Neighborhood Health Study. The authors also included a measure of lifetime trauma exposure and found a strong main effect of trauma. However, neither in this study nor in our study was a gene × environment (traumatic load) interaction effect observed.

The accumulating evidence for the relevance of *WWC1* genotype for both human memory and memory-related psychopathology brings up several research questions.

What Are the Underlying Molecular Mechanisms Relating *WWC1* SNPs to Human Memory and Trauma-Related Psychopathology?

KIBRA is a relatively large protein with several binding sites for its diverse interaction partners, including two WW domains, a calcium sensitive C2 domain, and an interaction site for the atypical protein kinase M ζ (PKMζ) implied in long-term potentiation maintenance. Vogt-Eisele *et al.* (8) replicated the co-expression of KIBRA and PKMζ and showed that KIBRA is necessary to prevent PKMζ degradation. KIBRA ablation was associated with reduced hippocampal PKMζ levels and diminished memory performance. Additionally, KIBRA may influence memory performance by regulating alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor trafficking (9). Recently, two novel exonic *WWC1* variants, which affect both human cognitive performance and the lipid binding specificity of the C2 domain, were discovered (10). The authors hypothesized that genotype-dependent differences in C2 domain lipid binding specificity might impact KIBRA's regulating influence on AMPA receptor turnover. Being in strong linkage disequilibrium with rs17070145, the SNP repeatedly found to be associated with episodic memory (4), the identified exonic variants may represent a causal mechanism of the observed associations between rs17070145 and human memory. By contrast, rs10038727, the SNP found to be associated with PTSD (6,7), is located much closer to the regions encoding the PKMζ interaction site. Zhang *et al.* (11) highlighted the existence of an exonic mutation at this site, which most likely influences PKMζ binding affinity (11) and only maps approximately 1000 base pairs from rs10038727. On the other hand, rs10038727, despite being an intronic variant, could be functional itself by altering transcription factor binding sensitivity (6). The exact molecular mechanisms underlying the relationship of *WWC1* polymorphisms with memory performance and PTSD hence remain elusive, with alterations of PKMζ binding affinity and AMPA receptor trafficking being promising candidates for further investigations.

Which Endophenotypes Mediate the Relationship between *WWC1* rs10038727 Genotype and PTSD?

While there is sound data on the relationship of *WWC1* rs17070145 and human memory performance, similar behavioral investigations for rs10038727 do not yet exist but would provide much needed information on the underlying mechanisms of this association. Interesting memory mechanisms for PTSD include associative learning (e.g., fear conditioning, extinction learning) and episodic memory for different emotionally charged information (2). Furthermore, *WWC1* rs17070145 genotype has been related to differential hippocampal activity during memory tasks (5,12) and seems to moderate age-dependent decline in hippocampal activity (13). Moreover, carriers of the memory-enhancing rs17070145 T-allele were found to have larger hippocampal volumes (14). Considering the fact that structural and functional alterations in the hippocampus have been also observed in PTSD (15,16), it would be interesting to investigate whether these alterations can be partly accounted for by *WWC1* genotype.

How Does *WWC1* Genotype Interact with Childhood Trauma to Predict PTSD?

The two studies investigating the effect of *WWC1* genotype on PTSD risk (6,7) assessed adult trauma and did not find a genotype × traumatic load interaction effect. However, interaction effects between early childhood adversity and genetic risk factors for PTSD have to be assumed (17). For instance, Klengel *et al.* (18) illustrated a molecular mechanism for gene × early environment interaction at the *FKBP5* locus: while risk allele carriers responded with demethylation near and at functional glucocorticoid response elements, noncarriers remained relatively unaffected by childhood abuse.

Is There a Role for *WWC1* in Other Psychiatric Disorders?

The connection between memory disturbance and PTSD is straightforward, as intrusive memories represent a core feature of PTSD. Yet, memory disturbances and intrusions are not limited to PTSD but also occur in other mental health disorders, like depression (19). If we acknowledge that personality development is a process fundamentally shaped by learning and memory of important experiences (20), memory-related genes such as *WWC1* might play a role in many psychiatric disorders beyond PTSD.

Correspondingly, meta-analyses of genetic data from the Psychiatric Genomics Consortium revealed shared genetic etiological factors for schizophrenia, depression, bipolar disorder, attention-deficit/hyperactivity disorder, and autism (21). A deeper look at genetic factors involved in the molecular processes of learning and memory could be fruitful in discovering shared and distinct genetic factors involved in the etiology of psychiatric disorders and might promote the formation of biologically informed diagnostic categories for mental health disorders (22), which are expected to ultimately improve clinical outcomes (23).

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