The Role of Memory-related Gene *WWC1* (*KIBRA*) in Lifetime Posttraumatic Stress Disorder: Evidence from Two Independent Samples from African Conflict Regions

Sarah Wilker, Stephan Kolassa, Christian Vogler, Birke Lingenfelder, Thomas Elbert, Andreas Papassotiropoulos, Dominique J.-F. de Quervain, and Iris-Tatjana Kolassa

Background: Posttraumatic stress disorder (PTSD) results from the formation of a strong memory for the sensory-perceptual and affective representations of traumatic experiences, which is detached from the corresponding autobiographical context information. Because *WWC1*, the gene encoding protein KIBRA, is associated with long-term memory performance, we hypothesized that common *WWC1* alleles influence the risk for a lifetime diagnosis of PTSD.

Methods: Traumatic load and diagnosis of current and lifetime PTSD were assessed in two independent African samples of survivors from conflict zones who had faced severe trauma ($n = 392$, Rwanda, and $n = 399$, Northern Uganda, respectively). Array-based single nucleotide polymorphism (SNP) genotyping was performed. The influence of *WWC1* tagging SNPs and traumatic load on lifetime PTSD was estimated by means of logistic regression models with correction for multiple comparisons in the Rwandan sample. Replication analysis was performed in the independent Ugandan sample.

Results: An association of two neighboring SNPs in almost complete linkage disequilibrium, rs10038727 and rs4576167, with lifetime PTSD was discovered in the Rwandan sample. Although each traumatic event added to the probability of lifetime PTSD in a dose-dependent manner in both genotype groups, carriers of the minor allele of both SNPs displayed a diminished risk ($p = .007$, odds ratio = .29 [95% confidence interval = .15–.54]). This effect was confirmed in the independent Ugandan sample.

Conclusions: This study reveals an association between two *WWC1* SNPs and the likelihood of PTSD development, indicating that this memory-related gene might be involved in processes that occur in response to traumatic stress and influence the strengthening of fear memories.

Key Words: Genetics, *KIBRA*, memory, posttraumatic stress disorder, risk, trauma, *WWC1*

Posttraumatic stress disorder (PTSD) affects the psychological health of a significant fraction of people victimized by war and conflict (1) and is associated with low functioning, high rates of suicidality (2), and adverse physical health outcomes (3). The number of traumatic stressors experienced (traumatic load) increases PTSD vulnerability in a dose-dependent manner (4,5). However, there exists a remarkable interindividual variability in PTSD susceptibility subsequent to trauma, of which some 30–40% can be explained by genetic factors (6,7).

The most prominent clinical feature of PTSD are intrusive recollections of the traumatic experiences that comprise reliving the trauma in forms of nightmares, thoughts, pictures, sensations, or flashbacks. Vivid intrusive memories are frequently accompanied by an inability to adequately remember the context and chronology of the traumatic events (8). Because these symptoms have been observed relatively invariant all over the globe, it was deduced that they share a common psychophysiological origin, that is, the structure of memories (8). Prominent theories of PTSD development distinguish between low-level, sensation-based representations, which can be easily triggered by sensory cues and abstract, context-bound representations of autobiographical experiences (9–14). The latter are essential for the allocation of events in time and space and are mainly mediated by the hippocampus and surrounding medial temporal lobe structures (10). Whereas these two forms of representation are generally well integrated, they are dissociated in PTSD. Likewise, a trauma reminder can activate the sensation-based representations of the trauma without activating the respective contextual information, resulting in the typical intrusive symptoms (9–14).

The consequent conceptualization of PTSD as a disorder of memory disturbance is supported by numerous studies reporting PTSD-related impairments in memory and cognition (15–17). Furthermore, cumulative evidence showed smaller hippocampal volume in patients with PTSD (18,19), which might represent either a consequence of traumatic stress or a preexisting vulnerability (20). Co-twin studies support that these observations can be partly explained by genetic factors, because smaller hippocampal volumes (21) and lower cognitive functioning (22) have been observed not only in Vietnam veterans with PTSD but also in their stay-at-home identical twins. Despite the importance of genetic factors as well as memory processes in PTSD etiology, few association studies explored genes involved in the molecular cascades of long-term memory formation.

The ubiquitously expressed protein KIBRA consists of 1113 amino acids and contains the following main structures (listed from N to C terminus): two WW-domains, responsible for the interaction with different proteins; a C2-like domain, implying

From the Clinical and Biological Psychology (SW, I-TK), Institute for Psychology and Education, University of Ulm, Ulm, Germany; SAP Switzerland AG (SK), Tägerwilen, Switzerland; the Division of Molecular Neuroscience (CV, AP), University of Basel, Basel, Switzerland; Clinical Psychology and Neuropsychology (BL, TE, I-TK), University of Konstanz, Konstanz, Germany; and the Division of Cognitive Neuroscience (DJ-FdQ), University of Basel, Basel, Switzerland.

Address correspondence to Sarah Wilker, M.A., Clinical and Biological Psychology, Institute for Psychology and Education, University of Ulm, Albert-Einstein Allee 47, 89069 Ulm, Germany; E-mail: sarah.wilker@uni-ulm.de.

Received Nov 15, 2012; revised Feb 13, 2013; accepted Feb 28, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.02.022

that KIBRA is a calcium binding protein; and a glutaminergic stretch (23). The intronic single nucleotide polymorphism (SNP) rs17070145 located within *WWC1*, the gene encoding KIBRA, has been associated with episodic memory performance in a genome-wide scan (24). The reported association of rs17070145 minor (T-allele) and enhanced episodic memory performance was confirmed by the majority of replication studies (25–32), but nonreplications were also reported (33–37). A recent meta-analytic investigation summarized data from 17 samples and revealed a significant association of rs17070145 and episodic memory, which remained significant when including data from unpublished studies to counteract publication bias (38).

Furthermore, KIBRA is expressed in memory-related brain areas (i.e., hippocampus and cortex) (39) and is supposed to be involved in neuroplastic processes through interaction with its binding partners (40,41). For example, KIBRA interacts with protein kinase Mζ, a brain-specific, constitutively active variant of protein kinase Cζ (42,43), which was found to be necessary for long-term potentiation maintenance (44). Further interactions of KIBRA involve dendrin (23), as well as synaptopodin (45), involved in the organization of the cytoskeleton and synaptic plasticity. Moreover, it was shown in vitro and in vivo that KIBRA is part of an α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR) complex. Adult KIBRA knockout mice showed large impairments in hippocampal long-term potentiation and fear memory, indicating that KIBRA regulates memory processes by regulating AMPAR trafficking (46). In summary, the initial reports of a genetic association of the *WWC1* rs17070145 and human memory were extended by subsequent studies showing potential underlying cellular mechanisms (42,43,46).

We report the results of the first study investigating the association of common *WWC1* alleles on the risk for PTSD development in two independent samples from conflict zones. In contrast to the majority of previous association studies on PTSD, we investigated a large number of dense tag SNPs covering *WWC1* (±100 kbp). We hypothesized that common *WWC1* alleles—by influencing memory strength—are associated with the risk for PTSD development subsequent to traumatic stress. Because the samples were investigated several years after the end of the respective conflicts, and spontaneous remission was likely to occur in the interim, our main hypothesis was to find an association with lifetime PTSD.

Methods and Materials

Samples

Rwandan Sample. A total number of 466 survivors of the Rwandan genocide were interviewed in the refugee settlement Nakivale, Uganda, in 2006–2007 (47–50). However, after accounting for missing data (exclusion of $n = 20$) and genotyping errors (exclusion of $n = 54$), analyses were based on a sample of $n = 392$ (194 women, mean age = 34.62, SD = 5.89). All procedures were approved by the Ethics Committee of the University of Konstanz, Germany, and the University of Mbarara, Uganda.

Ugandan Sample. A sample of 454 survivors of the conflict with the Lord's Resistance Army (LRA), including a large proportion of forcefully recruited (child) soldiers, were interviewed in the former Internally Displaced Persons Camp Anaka. After genotypic quality control (exclusion of $n = 49$) and accounting for missing data (exclusion of $n = 16$), $n = 399$ (213 women, mean age = 32.27, SD = 11.83) study participants entered statistical analysis. All procedures were approved by the Ethics Committee of the German Psychological Society and the Ugandan National Council for Science and Technology.

In both samples, only one family member (defined as one member of a household) was allowed to participate in the study to avoid population substructure caused by kinship of participants. The trained interviewers approached the families in their homes, gave a detailed explanation of all study procedures, and asked for one family member (above the age of 18 years) who was significantly affected by the conflict to volunteer to participate. If more than one family member volunteered to participate, the most affected person was chosen. Before study participation, subjects gave written informed consent. All procedures followed the *Declaration of Helsinki*.

Behavioral Data

Similar diagnostic instruments were used in both samples. Current and lifetime PTSD cases were diagnosed in a structured interview on the basis of the Posttraumatic Diagnostic Scale (PDS) (51). Traumatic load was estimated by assessing the number of traumatic event types experienced (i.e., combat experiences, injuries by weapon, rape) by means of a 36-item event checklist, which has been used in previous studies (47–50). This event list, which was initially applied to the Rwandan sample, was extended by 26 items to include several atrocities specific to the LRA (e.g., forced to eat human flesh). Depressive symptoms were ascertained with the depression section of the Hopkins Symptom Checklist (HSCL-D) (52).

Trained local interviewers and expert psychologists in the field of trauma from the Universities of Ulm and Konstanz conducted the diagnostic interviews. Local interviewers attended 6-week training on the concepts of PTSD, depression, and quantitative data assessment before data collection. All diagnostic instruments were translated into the local languages, Kinyarwanda (Rwandan sample) and Luo (Ugandan sample), respectively, followed by blind back-translations and subsequent corrections by independent translators. The psychometric qualities of the translated instruments were ensured by assessing retest reliability and consistency with expert ratings (53,54).

In the sample of 392 Rwandan survivors, 172 (44.87%) fulfilled DSM IV-TR criteria of current PTSD, and 277 (70.66%) reported a lifetime history of PTSD. On average, study subjects reported almost 12 different traumatic event types (mean = 11.98, SD = 5.26, range = 0–25), and only two subjects reported no trauma exposure at all. Besides, the mean HSCL-D score in the sample was 1.76 (SD = .59), indicating a high prevalence of depressive symptoms.

Prevalence of PTSD symptoms was smaller in the Ugandan sample, in which $n = 40$ (10%) fulfilled diagnosis of current and $n = 223$ (55.8%) of lifetime PTSD. The mean traumatic load score was 24.09 (SD = 8.48, range = 3–59). This relatively high value, compared with the Rwandan sample, can be understood as a consequence of the aforementioned extension and precision of the event list. The mean HSCL-D-score was 1.58 (SD = .56).

Genotyping

Saliva samples were collected with Oragene Self Collection Kits (DNA Genothek, Ottawa, Ontario, Canada), and DNA was isolated by use of standard protocols. Genotyping was performed as described in the *Genome-Wide Human SNP Nsp/Sty 6.0 User Guide* (Affymetrix Inc., Santa Clara, California). All tag SNPs investigated within *WWC1* were ascertained by use of the USCS human genome browser hg 19 release (55), and the analysis window was enlarged for 100 kbp flanking the 5′ and 3′ regions, respectively, to ensure inclusion of most regulating regions of