Commentary

Biological Psychiatry

Insights From Dimensional Phenotypic Definitions of Posttraumatic Stress Disorder and Trauma in Genome-wide Association Studies

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Large-scale genome-wide association studies (GWASs) have catalyzed genetic discovery in psychiatry. To date, hundreds of replicable molecular markers have been identified, providing translatable insights into downstream biological processes and the genetic architecture of psychiatric conditions. Posttraumatic stress disorder (PTSD) is the latest psychiatric target of molecular genetic inquiry that has undergone remarkable growth in recent years.

Two collaborative scientific consortia are at the forefront of genetic discovery in PTSD. In 2019, the Psychiatric Genomics Consortium (PGC)-PTSD Working Group reported a Freeze 2.0 GWAS of approximately 30,000 cases and 170,000 control subjects that found 6 independent genome-wide significant loci (1). In 2021, the Million Veterans Program (MVP) reported its largest PTSD GWAS of more than 250,000 military veterans, including more than 36,000 cases of PTSD (2). Both efforts are notable in the field of psychiatric genetics for their inclusion and analysis of participants of diverse ancestries, power limitations notwithstanding. This makes PTSD genetics well positioned to contribute to future discoveries of novel markers that are invariant in European populations.

The MVP GWAS discovered 3 significant loci in European ancestry case-control analyses, but the findings increased to 15 loci when dimensional PTSD phenotypes were used (2). Moreover, the MVP study reported higher heritability, a stronger polygenic signal, and higher genetic correlations with health-related traits for the dimensional PTSD measure than for the case-control classification. Likewise, in their study in the current issue of *Biological Psychiatry* based on the PGC-PTSD Freeze 2.0 dataset, Maihofer *et al.* (3) used a dimensional PTSD phenotype to enhance GWAS discovery power. The study consistently identified novel, replicable risk loci associated with PTSD symptom severity in participants of European ancestry.

While the well-powered case-control designs have been crucial to genetic discovery, the utility of integrating dimensional phenotypes into GWASs has previously been demonstrated in studies of psychiatric conditions such as depression and alcohol use (4). This quantitative approach is consistent with the common-trait common-variant framework, positing that polygenic influences operate across the full spectrum of severity, from nonclinical traits in the general population (e.g., avoidance of unpleasant thoughts about negative experiences or nightmares) to corresponding clinical diagnoses (e.g., PTSD) (5). Consistently, in both PTSD GWASs, genetic correlations between dimensional and case-control phenotypic definitions were close to +1, supporting the comparability of assessment of the same construct via different measurement methods (2,3).

Dimensional phenotypes are favored by power analyses under many realistic GWAS conditions (6,7). One such condition is a high prevalence rate, which for PTSD is estimated at around 10% in the general population and up to 30% in high-risk groups such as veterans and first responders. Moreover, in the leading PTSD GWASs (2,3), PTSD symptoms were generally assessed using extensively validated dimensional instruments, such as the Clinician-Administered PTSD Scale and the PTSD Checklist. Such measures reliably capture full information about symptom severity, including phenotypic variation among control subjects, which increases discovery power. Relatedly, dimensional assessments evade the power limitations associated with misclassifications of cases and controls—for example, in participants with subthreshold presentation or when the diagnostic criteria changed over time. Beyond potential statistical advantages, dimensional measures can be scalable and feasible to administer remotely in large population-based cohorts and biobanks.

Nonetheless, one potential unintended consequence of nondiagnostic phenotypes in GWAS is a lower specificity of discovered loci to a target condition (4). In particular, the use of "minimal phenotyping," i.e., assessments containing a small number of items or a single yes/no question, has been shown to capture a somewhat distinct qualitative construct than clinician-administered assessments. As a result, some of the additional markers discovered in GWASs with dimensional phenotypes might prove to be more broadly associated with vulnerability to additional manifestations of psychopathology. Arguably, PTSD measures such as the PTSD Checklist are multifaceted, align quite well with diagnoses, and are used to screen for probable PTSD in research and clinical practice, and therefore do not constitute minimal phenotyping. Nonetheless, the specificity of loci identified by Maihofer *et al.* (3) remain to be explicated.

The varying precision of discovered genomic markers is consistent with a genetic architecture of psychopathology that encompasses loci that transcend diagnostic boundaries by influencing shared liability to mental illness alongside loci that are specific to narrow constructs (8). Major dimensional frameworks, such as the Research Domain Criteria and the Hierarchical Taxonomy of Psychopathology, provide an opportunity to elucidate the precision of genetic findings for complex and heterogeneous disorders. Such frameworks

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propose psychiatric phenotypes that can be systematically aggregated (i.e., "lumped") into larger constructs, or "split" into biologically meaningful, discrete units of analysis. For example, the dimensional assessment of several phenotypes, such as PTSD, depression, and anxiety, allows researchers to identify a potentially larger number of loci associated with an internalizing spectrum alongside loci associated specifically with PTSD. Analytically, this approach consists of fitting statistical models to phenotypic data prior to conducting a traditional GWAS or its multivariate extensions (e.g., multi-trait analysis of GWAS). Genomic structural equation modeling is an alternative, post-GWAS method that can be used to disentangle genetic loci that are specific to PTSD from those that influence a broader psychological construct such as internalizing problems.

Maihofer *et al.* (3) leveraged multi-trait analysis of GWAS to pursue a similar multivariate strategy, but instead of the co-occurring psychopathology, the study incorporated a dimensional count of lifetime exposures to trauma. Trauma exposure is a highly relevant phenotype in this context because it is necessary for PTSD diagnosis. Capitalizing on the high genetic correlation between trauma and PTSD, joint analyses of these phenotypes increased the number of discovered PTSD loci from 5 to 9, consistent with the evidence that extended phenotypic information enhances genetic discovery. It is possible that some of the uncovered loci are not specific to PTSD and instead are involved in a broader phenotype of traumatic stress. Conversely, a GWAS of a narrower PTSD definition adjusted for trauma indicated that there remains a significant genetic vulnerability to PTSD independent of lifetime trauma.

Trauma exposure constitutes a clinically relevant GWAS target in its own right. Other than PTSD, the psychiatric sequelae of trauma can include major depressive disorder, substance use, and eating disorders. The rate of traumatic events far outweighs the prevalence of resulting psychopathology, with more than 70% of individuals in the general population reporting at least one trauma in their life. Given this high prevalence, dimensional measures that capture cumulative trauma exposure, as well as the type and severity of these events, are particularly informative for genetic studies. For example, inclusion of such measures would allow researchers to interrogate potential thresholds and dose-response effects in the genetic associations between trauma and PTSD. Moreover, screening for traumatic and other environmental exposures in all biobank participants, irrespective of their psychopathology outcomes, has yielded large samples that allow GWASs of specific trauma phenotypes, such as childhood maltreatment. In the context of PTSD research, universal screeners allow for the identification of trauma-exposed control subjects.

One translational opportunity of genetic discoveries in PTSD involves polygenic risk scores (PRSs) that capture part of an individual's genetic susceptibility to PTSD. To date, PTSD PRSs based on the discoveries in the PGC-PTSD and MVP cohorts significantly predicted PTSD symptom severity, heterogeneous symptom profiles, diagnostic status, and illness trajectories following trauma in several independent, deeply phenotyped samples (9,10). Moreover, PTSD PRSs are associated with other psychiatric disorders, including depression, likely by capturing transdiagnostic genetic risk (9). Nonetheless, the observed PRS effect sizes are small, and most of this research remains limited to participants of European ancestry.

Given that the quality of phenotype assessment in the GWAS contributes to the power and precision of the resulting PRS, it is anticipated that genetic instruments based on summary statistics from Maihofer *et al.* (3) will further enhance prediction. It is also plausible that the combined PTSD and trauma analyses from the multi-trait analysis of GWAS will produce a PRS that better accounts for environmental effects. At present, PTSD PRSs offer prediction that is independent from the measured trauma severity (9,10). Beyond an additive model, where PRS and environment contribute independently to disease risk, correlations and interactions between these factors can be explored.

Finally, the translation of results from the trauma GWAS can advance our understanding of the etiology and the outcomes of traumatic life events. For example, mediation models can directly test whether hypothesized personality and behavioral traits, such as risk taking, explain the path from identified risk loci to trauma exposure. Mechanistic insights would inform potential prevention targets beyond simply identifying individuals who are at risk. Moreover, a trauma PRS could be used as a covariate in studies that are focused on environmental effects on PTSD and other psychiatric outcomes, addressing potential confounding of results by genetic differences. Common genetic factors do not preclude a causal association between trauma and PTSD, which has been empirically demonstrated in studies using a co-twin control design.

In sum, beyond increasing discovery sample sizes, PTSD genetics has benefited from embracing dimensional phenotypic definitions and incorporating environmental exposures. The emerging architecture implicates risk loci at different levels of specificity, many of which are transdiagnostic, and with genetic influences partially shared between trauma exposure and subsequent risk for developing PTSD, and partially distinct to each phenotype. Downstream mechanisms and resulting genetics instruments such as PRSs will likely reflect this multitiered architecture.

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Article Information

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