Commentary

Biological Psychiatry: GOS

Genetic Contributions to Reported Childhood Maltreatment: What It Means and How It Could Mean More

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That there is a "heritable" component to experiencing and recalling trauma, including childhood maltreatment, has been documented in twin studies that also suggest shared genetic components with psychopathology [e.g., (1)]. In the current issue of *Biological Psychiatry: Global Open Science*, ter Kuile *et al.* (2) examine contributions of common genetic variants influencing health and behavioral traits and psychiatric disorders to the heritability of reported childhood maltreatment. Using genomic structural equation modeling of genome-wide association study (GWAS) summary statistics, selected, in part, based on genetic correlations (r_g) with reported childhood maltreatment (|single nucleotide polymorphism [SNP]$-r_g$| $>$ 0.25), the authors identify relevant traits (general risk tolerance and subjective well-being) and disorders (autism spectrum disorder and posttraumatic stress disorder) that collectively explain 58% of the SNP-based heritability (h^2_{SNP}) of reported childhood maltreatment. These findings provoke readers to consider the varied mechanisms by which childhood maltreatment might interface and interfere with psychiatric health and well-being. In this commentary, we consider the implications of studying childhood maltreatment in large genotyped cohorts and discuss the prospect of using family-based designs to extend the hypotheses generated by ter Kuile *et al.*

ter Kuile *et al.* (2) use a GWAS meta-analysis (3) of indices of reported childhood maltreatment. They do not find differences between childhood maltreatment and combined lifetime retrospectively reported adult and childhood trauma, suggesting that genetic mechanisms linking traumas to these indices may be invariant to timing of exposure, a finding that is somewhat in contrast to studies that suggest the primacy of early life trauma [e.g., (4)]. An alternative explanation is that trauma begets trauma (i.e., chronicity) or that third variables, such as resource scarcity, or as the authors note, genetic liability (e.g., psychopathology that influences subjective interpretation of trauma across the lifespan), induce lifetime co-occurrence.

The childhood maltreatment construct used by ter Kuile *et al.* (2) is a composite of emotional and physical abuse and neglect and sexual abuse. In one of the samples in the meta-analysis, Warrier *et al.* (3) demonstrate that while genetic correlations between emotional abuse and neglect and with the overall maltreatment construct (SNP$-r_g > 0.82$) are high, genetic correlations between emotional and physical abuse and neglect and sexual abuse are less prominent (SNP$-r_g$ = 0.24–0.71). This raises the question of whether constructs that rely on the commonality underlying forms of childhood trauma are more likely to favor the identification of genetic mechanisms (e.g., gene–environment correlations). Important distinctions may exist among subtypes of childhood maltreatment that implicate qualitatively or quantitatively differential associations between risk biomarkers and psychopathology or differ with respect to their influence on heightened vigilance and threat processing as well as neglect- and deprivation-induced cognitive deficits (5).

Other factors, including population characteristics, respondent type, and maltreatment assessment format, may also have influenced these findings. The examined childhood maltreatment GWAS meta-analysis included multiple samples varying in respondents (e.g., self-report vs. parent or caregiver report), timing of report or recall (i.e., retrospective vs. prospective), and assessment format, including measures and definitions of maltreatment. Warrier *et al.* (3) concluded that at least some of these potential sources of heterogeneity may not have substantively impacted their collective findings and consequently, those presented in ter Kuile *et al.* (2). For instance, despite meta-analyses suggesting weak correspondence (k = 0.19) (6), Warrier *et al.* found that the genetic correlation between prospective and retrospective reports was high (SNP$-r_g$ = 0.72). To address the potential confounding or influential effects of socioeconomic disadvantage, and partially account for selection bias, Warrier *et al.* examined the effect of including a material deprivation index as a covariate in their UK Biobank GWAS, and found that the h^2_{SNP} of reported childhood maltreatment was not attenuated. Yet the qualitative types of childhood maltreatment that are evident or reported in population versus high-risk cohorts, the role of volunteer/selection bias (e.g., lower recruitment and participation, and higher attrition of individuals due to maltreatment sequelae), biased caregiver reports (e.g., where the caregiver is the perpetrator of maltreatment or feels implicated or stigmatized by the questions), and recall bias may have influenced findings. While these caveats are not a critique of either the current publication (2) or the original GWAS meta-analysis (3), they are notable considerations when extrapolating these findings to other samples, and especially for future studies that may pursue individual bivariate genetic associations arising from this publication.

Beyond the psychometric constraints of previous assessments, a related and notable problem in psychiatric genetics more broadly that also affects ter Kuile *et al.* (2) is the reliance on data from individuals of predominantly European ancestry.

SEE CORRESPONDING ARTICLE ON PAGE 716

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The problem with not being able to study individuals from global populations is manifold. Besides the obvious equity gap, extant measures of childhood maltreatment are likely Eurocentric and require cultural norming and consideration of other group-specific risk factors [e.g., systemic and institutional discrimination (7)]. There are also well-known inconsistencies in whether and why the prevalence of childhood maltreatment may be elevated in certain populations with several lines of evidence implicating biased reporting by medical, social, or judicial services as contributors [e.g., (8)]. The reason that the Warrier *et al.* and ter Kuile *et al.* studies were restricted to individuals of European ancestry is because large-scale GWAS data on childhood maltreatment are not available for other population groups, despite the burden that they impose on child well-being in these very populations. Well-powered genetic studies that represent the experiences of local and global communities are necessary.

The findings of this study re-emphasize classical questions regarding the interpretation of shared genetic variance between health and behavioral traits, psychiatric disorders, and reported childhood maltreatment and raise intriguing possibilities for further study. As the authors note, "... influences on retrospectively reported trauma are complex and difficult to disentangle" (2). Accordingly, ter Kuile *et al.* highlight plausible mechanisms by which observed genetic associations may reflect both heightened vulnerability to trauma exposure (e.g., difficulty processing social cues may increase risk for maltreatment in children with autism spectrum disorder) as well as the subjective experience, interpretation, and report of trauma (e.g., greater risk tolerance may increase likelihood of reporting maltreatment, the disclosure of which may be perceived as "risky"). The authors are thoughtful in their consideration that the current study serves as a depot of statistical insight rather than a test of specific hypothesized mechanisms, which likely require additional types of data, such as family-based study designs. Studies of the intergenerational transmission of childhood maltreatment have long provided insights into its enduring impact [e.g., (9)]. Further, the ability to study within-person change while controlling for between-person genetic differences via relative-as-control designs serve as a powerful framework for causal inferences, especially when genetic and early life environmental contributors are intertwined.

Beyond putting the various hypothesized gene–environment interplay mechanisms posited by ter Kuile *et al.* (2) to the test, family-based study designs that include longitudinal data on identical and fraternal twins or even nontwin siblings allow for opportunities to interrogate the effects of childhood trauma on emergent psychopathology, setting aside (to the extent possible) the confounding role of genetic liability, even in the absence of genomic data. For instance, within pairs of twins discordant for childhood sexual abuse, one study found elevated rates of psychopathology in the twin-pair member who did not report abuse, suggesting correlated genetic and familial environmental pathways (10). However, the likelihood of psychopathology in the twin-pair member who reported abuse was considerably higher, underscoring mechanisms beyond genetic commonality. One might speculate that twin pair discordance in childhood trauma may itself represent recall bias or third variable confounding, but the opportunities to study the sequelae of childhood trauma while matching for genetic background can be achieved within such study designs by adopting a life course perspective. Figure 1 represents an illustration of the potential of these designs. For example, in the case of twins discordant for childhood trauma and concordant for later life trauma or psychopathology, shared genetic factors nonspecific to childhood trauma may be implicated. Within the more typically identified twin pairs where members are concordant for childhood trauma, longitudinal data could reveal the risk and, importantly,

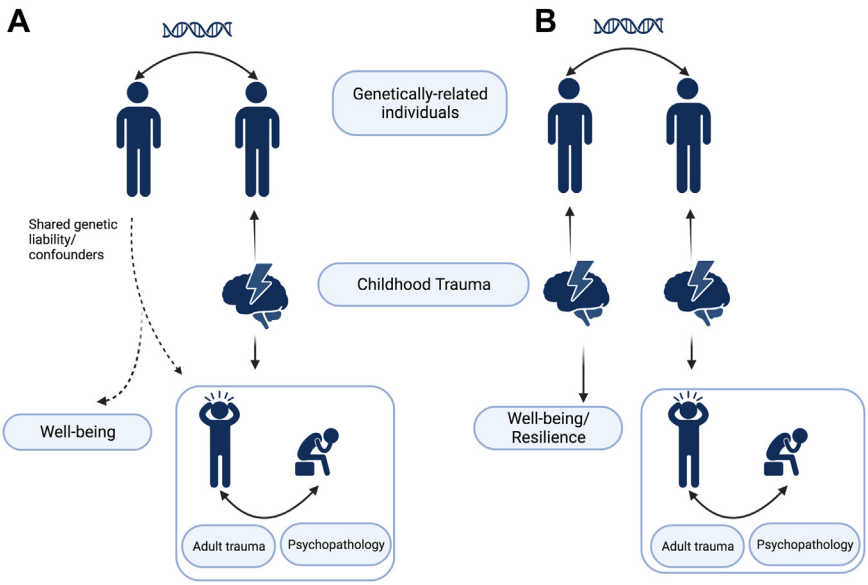

Figure 1. The utility of family-based study designs in genetic and causal hypothesis testing. Twin pairs represent a specific family design where inherited genetic similarities within pairs are either 100% (identical) or 50% (fraternal). **(A)** A pair of twins discordant for childhood trauma. As the twins share genetic liability, any downstream effects of trauma exposure would reflect nongenetic (i.e., not due to inherited genetic factors) mechanisms of childhood trauma (or a confounder) on later-life trauma and psychopathology (depicted as interrelated). If the twin member unexposed to childhood trauma develops psychopathology, then genetic factors shared with their exposed twin may be implicated. **(B)** Another approach of longitudinally characterizing twin pairs concordant for childhood trauma. Despite experiencing childhood trauma, if one genetically related individual does not develop psychopathology or experience later trauma, then such studies provide opportunities to identify these noninherited resilience factors that disrupt the transmission of trauma toxicity and can be used to inform future interventions to deter the deleterious cascade set in motion by childhood trauma. Figure created using BioRender.com.

resilience mechanisms that exacerbate or mitigate onset of and emerging discordance in subsequent psychopathology. These designs could also be extended to accommodate the study of both parents and offspring to examine genetic and environmental factors influencing the intergenerational transmission of trauma.

Pointing to a heritability estimate that is far below unity, ter Kuile *et al.* (2) note that "h^2_{SNP} of reported trauma does not mean that some individuals are genetically determined to experience trauma." As a reminder, heritability is not a person-specific metric. While genetic risk scores are increasingly being evaluated in disease stratification, the nature-nurture entanglement masquerading as genetic contributions in ter Kuile *et al.* make these genetic findings far more nuanced. Rather, studies investigating the heritable component to childhood maltreatment should be viewed, in our opinion, as the starting point for the development of study designs that evaluate how we might disrupt the toxicity imposed by childhood trauma despite genetic contributions.

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Article Information

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