Causes and consequences of childhood maltreatment: Insights from genomics

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Childhood maltreatment remains a global problem despite extensive efforts to eradicate it.[1] It is associated with adverse outcomes. One reason current prevention and treatment approaches show poor effectiveness is the scarce knowledge on victim-level risk factors (we use "victim" in this Comment as the appropriate term used by medical and legal professionals).[2] By studying childhood maltreatment as a phenotype of the victim, researchers have revealed that genes account for as much as 60% of the variation in individual differences in childhood maltreatment.[3] This finding might seem paradoxical as childhood maltreatment is an environmental exposure involving actions inflicted upon the child by another person. However, environmental exposures might be mediated through genetically influenced characteristics of the individual (in this case, the child), a phenomenon known as gene–environment correlation.[4] Therefore, genes that influence the child's characteristics might indirectly confer risk for childhood maltreatment, although this possibility does not imply biological determinism or culpability of the child; these genes might account for some of the heritability of experienced negative parenting.[5] Genetically informed investigations of childhood maltreatment can show how childhood maltreatment originates and clarify whether relationships between childhood maltreatment and

putative outcomes are causal or explained by common susceptibilities.

In *The Lancet Psychiatry*, Varun Warrier and colleagues[6] make substantial progress in this line of enquiry. The authors did a meta-analysis of genome-wide association studies (GWAS; N=185414) identifying 14 genetic regions associated with childhood maltreatment. Additive genetic effects explained a modest proportion of individual differences in childhood maltreatment (single nucleotide polymorphism heritability 0·079 [SE 0·0042]) with notable genetic overlap across childhood maltreatment types and operationalisations (genetic correlations 0·24–1·00). Using polygenic score analyses, Warrier and colleagues showed that most genetic effects (58%) reflected children's traits that might evoke (reactive gene-environment correlation) or predispose to (active gene-environment correlation) abusive or neglectful behaviour in a parent or caregiver. The authors further examined causal relationships between childhood maltreatment and associated adult outcomes using Mendelian randomisation. The results supported unidirectional causal effects of childhood maltreatment on depression and bidirectional effects on ADHD and schizophrenia, but did not find causal links with coronary artery disease, type 2 diabetes, and the inflammatory marker C-reactive protein.

The identification of genes associated with childhood maltreatment provides strong evidence that genetically influenced phenotypes can increase risk for childhood maltreatment. This finding prompts further research to identify risk-associated phenotypes, which could inform prevention efforts. One approach is to estimate the genetic overlap between childhood maltreatment and hypothesised phenotypes. Warrier and colleagues6 identified shared genetic regions between childhood maltreatment and health conditions, risky behaviour, and educational attainment, suggesting several possible risk-associated phenotypes that require further investigation.

Genome-wide investigations also offer ways to disentangle child-specific from family-specific aetiological processes. The results presented by Warrier and colleagues[6] suggest that different gene–environment mechanisms could arise in different individuals. They found stronger genetic transmission of childhood maltreatment in children whose traits are likely to influence parental behaviour (eg, autism relative to typical development),

supporting child-specific effects and indicating promising prevention targets. Although passive gene–environment correlation was not excluded, several parental risk factors did not substantially reduce the variance in childhood maltreatment explained by genes. Further research, especially prospective longitudinal work, is needed to disentangle these processes.

Knowing which genomic regions are associated with childhood maltreatment allows further testing for causality. Evidence of causal effects on depression substantiates correlational data,[7] but bidirectional relationships with other mental health outcomes require further examination. For instance, when childhood maltreatment is reported retrospectively, causal analyses of child and adult phenotypes should be separated. Otherwise, it remains unclear whether causal effects of adult disorders reflect early markers of such disorders triggering childhood maltreatment or recall bias.[8] Nevertheless, the genetic overlap estimated across prospective and retrospective accounts suggests that child phenotypes were at play beyond interpretation effects. Challenging previous evidence,[9] there were no causal effects of childhood maltreatment on several physical health outcomes in the study by Warrier and colleagues. Additional genetically informed studies are warranted to elucidate pathways underlying the observed associations. One approach could be to examine expression profiles of genes agnostically identified from GWAS. For example, most genes found by Warrier and colleagues[6] influence brain function. If childhood maltreatment mediates the relationship between genetic risk and adult disease via effects on brain development, preventing childhood maltreatment might also avert modifiable disease outcomes.

The study by Warrier and colleagues[6] highlights the potential of molecular genetics to guide innovation in childhood maltreatment prevention and treatment through the identification of predisposing phenotypes, gene–environment correlation processes, and causal relationships. Although prevention programmes for reducing the effect of parental risk factors exist, genetic effects on childhood maltreatment underscore the importance of also considering the child's risk profile. These findings call for genetically informed intervention trials with objective measures of treatment outcome to establish which developmental processes are affected by childhood maltreatment and, crucially, how to restore them.

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