Adverse childhood experiences and developmental psychopathology: why should we consider gene-environment interaction for prevention and intervention strategies?

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Both internalising (anxiety and depression) and externalising (impulsivity, aggression, attention deficit) problems are common in children and adolescents.[1] These problems can be serious and, if left unattended, they often continue into adulthood and are associated with other health problems and psychosocial difficulties, such as poor academic performance and impaired social relationships.[2–5] Therefore, research aiming at increasing our understanding of the risk factors, pathways and mechanisms of developmental psychopathology is crucial in aiding the development of effective prevention and intervention strategies.

The influence of early life circumstances on lifelong development, function and physical and mental health has been the subject of repeated inquiry.[6] A growing body of evidence has emerged for the associations between a wide range of adverse childhood experiences (ACEs) and developmental psychopathology.[7] ACEs are childhood events that often occur within the child's family or social setting, can vary in severity, and can disrupt the child's physical or psychological health and development.[8,9] Family-related childhood adversities, such as divorce,[10,11] childhood maltreatment,[12–14] parental loss and separation,[15,16] and parental psychopathology,[17] have been extensively examined in this context. The role of socio-economic adversities in both family and social settings (e.g., family and neighbourhood poverty) in the development of psychopathology has also been examined. Specifically, parental education, parental occupation, and financial hardship have been found to be associated with both internalising and externalising problems.[18] Moreover, as ACEs have been found to co-occur,[19] researcher have also begun to explore the impact of multiple or cumulative ACEs. For example, one study found that the influence of childhood poverty on externalising symptoms of 17 year olds is mediated by an accumulation of other risk factors,

including subsequent separation from family and substandard housing.[20] Notably, the effects of ACEs may vary with age[21], gender[22], and the developmental stage of the child[17] and different mechanisms may be involved in their persistence over time. Some effects of childhood adversities have been found to be dependent on the occurrence of subsequent stressors where as others may be confined to individuals with pre-existing vulnerabilities. Further to this it has been widely acknowledged that many children exposed to environmental risk factors may also be at increased biological (genetic) risk[23]. Accordingly, researchers across different social and biological disciplines, including education, psychology, epidemiology, neuroscience and genetics, have been focusing on the interplay between environmental and genetic risk factors involved in the development and onset of psychopathology.

Gene-environment interaction (G×E) refers to a phenomenon of gene-environment interplay when genetic effects on a trait or disorder depends on the environment, or when environmental effects depends on genetic factors.[24,25] There are different types of G×E interactions. For example, genetic factors can influence a child's response to adverse experiences. This G×E type is implied in a diathesis-stress model: genetic factors serve as vulnerability factors for children who experience one or more adversities (e.g., poverty, maltreatment), so that children with genetic risk are more susceptible to the development of psychopathology, whereas children without genetic risk are resilient to the development of psychopathology. For example, research has suggested that the effect of childhood maltreatment on antisocial behaviour might be stronger in people with a less active form of the monoamine oxidase A (*MAOA*) gene, and this effect is found to be stronger for males than females.[26,27] Research has also demonstrated that the serotonin transporter gene (*5-HTT*) interacts with stressful life events in the development of depression: a less active form of the *5-HTT* gene (S-allele) increases the risk of depression in response to stressful life events more than two-fold.[28] When the interaction between the *5-HTT* gene and stressful life events was studied using longitudinal cohort data, it was found that individuals with two short *5-HTTLPR* alleles and childhood maltreatment had elevated risk of persistent but not single-episode depression.[29]

Another G×E type refers to the situation when genetic factors amplify a child's sensitivity to both positive and negative environments. This G×E type is implicated in a differential susceptibility model: children genetically more susceptible to negative influences (e.g., poverty, maltreatment) could also be more susceptible to positive influences (e.g., educational provision, social support).[30] For example, in a study of the dopamine D4 receptor (*DRD4*) gene, maternal sensitivity, and behavioural problems in children, it was shown that low maternal sensitivity was associated with behavioural problems, but only in children with the 7R allele of the *DRD4* gene. Children with the same gene variant and mother with high sensitivity displayed the lowest level of behavioural problems. For children without the 7R allele of the *DRD4* gene, differences in maternal sensitivity had no effect on behavioural problems.[31] Another study provides evidence for an interaction between family SES and the *5-HTT* gene in relation to juvenile delinquency: a long (more active) form of the *5-HTT* gene (L-allele) show the highest plasticity in boys because of the curvilinear associations between family SES and delinquency. The same pattern was found among girls with a short (less active) form of the gene (S-allele), who also showed curvilinear associations between family SES and delinquency.[32] This suggests that the association between SES and delinquency may partly depend on individual genetic differences in sensitivity to environmental influence. Therefore, identification of this type of G×Es would be useful in identifying children with adverse experiences who could also benefit the most from interventions.

Moreover, it has been shown that specific genetic factors can 'suit' some environments better than others.[33,34] For example, it has been found that S-allele of the serotonin transporter gene (*5-HTT*) is more likely to increases the risk for depression in individualistic rather than in collectivistic cultures.[34] This and other findings suggest that cultural values may co-act with genetic factors during the evolution. Therefore, children from different populations or cultures can differ in their risk for psychopathology, and may benefit for different, population-specific, intervention and prevention strategies.

Recently, a new line of research has started to uncover molecular mechanism of co-action between genetic and environmental influences. An increasing number of studies have demonstrated that various environmental factors (e.g., stress, parenting) can affect gene expression and, subsequently, child psychological development.[35,36]

To summarise, genetic variation underlies individual differences in response to various environmental exposures. These differences are stable over time and can help to identify individuals who are at particular risk for developing psychopathology and/or can benefit more from interventions. However, to date, only a few genes have been reliably implicated in the modulation of environmental effects on psychopathology. In future, complex combinations of multiple genetic variants across the whole genome (i.e., polygenic risk scores), and their interactions with multiple adverse experiences, need to be considered in order to gain a better understanding of the role of G×E interaction in risk and resilience pathways. This knowledge will guide the development of evidence-based, more focused (e.g., family- or person-oriented) prevention and intervention programmes for decreasing the risks of developmental psychopathology on the basis of individual genetic (or gene–environment) screening.

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