PERSPECTIVE

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Incorporating the social environment in genotype environment interaction studies of mental disorders

That both genetic (nature) and environmental (nurture) factors contribute to the aetiology of depression and other common mental disorders is well recognised. However, the study of gene-environment interaction (G × E) in mental disorders has recently incited a great deal of controversy. We have suggested (1) that what is needed is more, and better quality, rather than less, research on how genotypes and a range of environmental factors jointly produce mental disorders. In particular, we believe that the non-replication of genetic main effects and G × E in mental disorders may be explained at least in part by the lack of consideration of relevant social environmental contexts.

The controversy

In 2003, Caspi et al. (2) published a groundbreaking article which found that a common variable number of tandem repeats polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*), designated as *5-HTTLPR*, moderated the relation between stressful life events and depression. Specifically, individuals possessing one or two copies of the short (s) *5-HTTLPR* allele that is less transcriptionally efficient than the long (l) allele (3), had higher levels of depression and suicidality in the context of recent life stressors. This article was lauded in the scientific [Behavioural Genetics. Getting the short end of the allele (4)] and popular press [Tapping the Mood Gene (5)]. The study offered the hope that consideration of environmental factors would improve our ability to identify genes that increase the risk for depression, and for mental disorders more broadly. At the same time, the results suggested that certain genetic factors increased risk of mental disorders only in the context of an adverse environment thus providing encouragement to researchers whose primary focus was the role of the environment and who felt bruised and neglected in the much proclaimed 'Genomic Era.(6–8)' Caspi et al. (2) has been cited 1669 times at this writing and hundreds of empirical G × E studies (42 examining the interaction between the 5-HTTLPR locus and adverse environments in risk of depression) have been published, concerned with a wide range of behavioural phenotypes from depression and antisocial behaviour to substance abuse and smoking.

Enthusiasm for G × E studies of mental disorders was recently brought into question by Risch et al.'s (9) meta-analysis that found no evidence for significant interaction(s) between *5-HTTLPR* genotype and stressful life events in risk for depression. Based on their analysis, Risch et al. (9) critiqued the G × E approach stating 'Despite the lack of valid confirmation of the Caspi et al. results, the approach to implicate candidate genes that had failed previous direct association studies through inclusion of an environmental exposure has been rapidly embraced, and substantial resources have been devoted to subsequent research'. They concluded that the study of G × E interactions in psychiatric disorders should await the identification of 'robust marginal gene associations'. Like the original Caspi et al. (2) report, the Risch et al. (9) article received widespread attention in the scientific [Much Touted 'Depression Risk Gene' May Not Add to Risk After All (10) and popular press Report on Gene for Depression Is Now Faulted (11)]. The result has been much confusion amongst lay persons and debate amongst scientists as to how best to study the role of both genetic and environmental factors in the aetiology of depression.

The social environment modifies genetic effects on common mental disorders

Unfortunately, the framing of this controversy in both the scientific and lay media has fueled the growing polarisation between two groups of scientists who share the common goal of disentangling the aetiology of common mental disorders but are focused on different research questions. The first are the geneticists who aim to discover new gene-disorder associations and use agnostic genome-wide association study (GWAS) methods to do so. The second are the researchers (typically developmental psychopathologists and psychiatric epidemiologists) who aim to understand how variation in candidate genes explains differential vulnerability to environmental risk factors. Although both groups bring important insight to the study of factors that contribute to commonly occurring mental disorders, missing from both approaches is a consideration of how the social environment may modify genetic effects on mental illness.

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The social environment and mental disorders

The social environment refers to characteristics of individuals' local environment that may be determinants of mental disorders and are independent of individual characteristics. Social environmental characteristics may be compositional aggregates of individual-level characteristics (e.g. poverty rate) or contextual factors that have no individual-level analogue (e.g. residential segregation, income distribution, amount of green space in urban contexts).

Nearly a century of research has documented the relation between features of the social environment (SE) and mental health and disorders (12,13). With respect to depression, specific social environmental factors known to contribute to the disorder include quality of the built environment (14,15), neighbourhood socioeconomic status (16) and urbanicity (17). G × E studies of depression, however, have thus far focused predominantly on characteristics acting at the individual or family level. Emerging evidence suggests that features of the social environment can also modify the effects of genetic factors on mental disorders including depression.

Three strands of evidence suggest that nested multilevel environmental influences may combine with genetic factors to shape the risk of mental disorders. First, genotype-phenotype associations have been very consistently demonstrated in animal models, including the serotonin transporter gene and depression and anxiety-like behaviour (18–20). Recent work by Kalin et al. is particularly relevant (21). Their findings indicate that rhesus monkey carriers of the s-allele in the promoter region of the serotonin transporter gene, rh-SLC6A4 showed increased amygdala activity in the context of stressful situations – relocation and threat – as compared with monkeys with the l/l genotype. No increased amygdala activation was observed when rhesus monkeys were in their home cages. The authors conclude, 'These findings demonstrate context-dependent intermediate phenotypes in s carriers that provide a framework for understanding the mechanisms underlying the vulnerabilities of s-allele carriers exposed to different types of stressors' (p. 1021).

Second, twin studies have demonstrated that the heritability (or the proportion of phenotypical variation in a population that is attributable to genetic variation amongst individuals) of many phenotypes is modified by environmental characteristics (22). For example, genetic influences on variation in intelligence and antisocial behaviour are larger amongst individuals from higher as compared with lower childhood socioeconomic status backgrounds (23,24). Genetic factors explain significant variation in cortisol reactivity to unfamiliar situations amongst young children from backgrounds characterised by low adversity; under conditions of high adversity genetic factors were not significant (25). The heritability of daily smoking has also been shown to vary by social context being highest in schools where the most popular students (26) are smokers and lowest in states with strong tobacco-control policies (27). Twin studies have also demonstrated social environmental modification of genetic effects, with heritability of antisocial behaviour reported to be higher amongst adolescent boys residing in socioeconomically advantaged neighbourhoods and, similarly, genetic effects on antisocial behaviour reported to be higher amongst adolescent girls residing in neighbourhoods with low levels of ethnic diversity (24).

Third, emerging evidence suggests that measured genotype-phenotype associations may also be modified by features of social environments. We have shown that specific features of county of residence (e.g. unemployment rate and crime rate) modify the association between *5-HTTLPR* and post-traumatic stress disorder (PTSD) amongst adults exposed to the 2004 Florida hurricanes (28). Specifically, the 's' allele of the *5-HTTLPR* polymorphism was associated with decreased risk of PTSD (as well as major depression and generalised anxiety disorder) in the low-risk environments (e.g. low unemployment rates) but increased risk of PTSD in the high-risk environments. We have found similar results for generalised anxiety disorder (Figure 1). In multivariable models taking into account potential individual-level confounders, the interaction between the *5-HTTLPR* genotype and unemployment rate was significantly ($p < 0.05$) associated with risk of GAD: the s/s genotype was associated with greater risk of GAD in high unemployment counties and with lower risk of GAD in low unemployment counties compared with other genotypes. Social environmental modification of genetic effects at the 5-HTTLPR locus have also be reported for housing type (public vs. private) and depressive symptoms amongst adolescent boys (29).

Conclusions

This area of research is novel and we can only offer early conjecture about the mechanisms through which the social environment may influence the risk of mental disorders. Clearly, much work is needed to either replicate, or refute, our work and that of others cited above and to help understand the

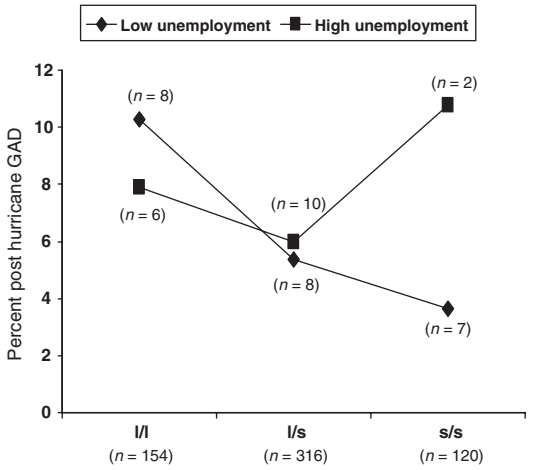

Figure 1 Prevalence of generalised anxiety disorder diagnosis(GAD) by-*5HTTLPR* genotype and county-level unemployment rate dichotomized as high vs. low. Logistic regression models using generalised estimating equations are adjusted for gender, age, ancestral proportion, individual-level unemployment, low social support, high hurricane exposure, other potentially-traumatic events, as well as the main effects of *5-HTTLPR* and county-level unemployment. Interaction effect for *5-HTTLPR* × county-level unemployment is OR = 2.04 (95% CI: 1.01, 4.16)

mechanisms that may explain these observations. However, as pointed out by Risch et al. (9), we would expect to observe the type of 'cross-over' interaction documented in our data and that of others (30) under conditions of a significant G × E in the absence of a genetic main effect. In addition, if it is true that features of the social environment influence genotype-phenotype associations, unmeasured environmental context could well be confounding G × E findings which limit the measurement of 'E' to life events or other individual-level exposures.

In conclusion, these data argue for extending gene-environment interaction studies to include features of the social environment in future research. The magnitude of relative risk of disease conferred by the social environment is likely to be far less than that conferred by individual-level risk factors. However, the ubiquity of exposure to social environmental variables suggests these factors will play a substantial role in determining the population distribution of depression and other common mental disorders.

Author contributions

KCK initiated the study and wrote the first draft of this article and all authors contributed to the planning and subsequent revisions of the article.

Disclosures

We declare no competing interests.

K. C. Koenen,[1] M. Uddin,[2] A. B. Amstadter,[3] S. Galea[4]
[1]Departments of Society, Human Development, and Health and Epidemiology, Harvard School of Public Health, Boston, MA, USA
[2]School of Public Health, University of Michigan, Ann Arbor, MI, USA
[3]Medical University of South Carolina, Charleston, SC, USA
[4]Gelman Professor and Chair of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

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