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Genotype–environment correlations: implications for determining the relationship between environmental exposures and psychiatric illness

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Abstract

Psychosocial risk factors for psychiatric illness are moderately heritable. This has two implications: first, that individuals actively shape their environments through heritable behaviour; second, that the relationship between environmental exposure and psychopathology may be confounded by genotype. We define three types of genotype–environment correlation (passive, evocative, and active), describe the evidence from quantitative and molecular genetic studies for their existence, and discuss the implications of genotype–environment correlations for the prevention and treatment of psychiatric disorder. Research designs are needed that can test which exposures have truly causal effects on mental illness and which are confounded by genotype, so that clinicians can make informed decisions about when modifying exposures will be likely to result in reductions in mental illness. By considering bi-directional and reciprocal relations between risk exposures and patients' behaviour, clinicians may develop a fuller picture of the causes of disorder and develop more effective treatment methods.

Keywords

Behavioural genetics; gene-environment correlation; gene-environment interplay; genetic epidemiology; twin studies

Definitions

Genotype–environment correlations refer to genetic differences in exposure to particular environments.[1] Psychologists and psychiatrists commonly refer to three types of genotype–environment correlation.

Passive genotype–environment correlation refers to the association between the genotype a child inherits from his or her parents and the environment in which the child is raised. For example, because parents who have histories of antisocial behaviour (which is moderately heritable) are at increased risk of abusing their children, maltreatment may be a marker for

genetic risk that parents transmit to children rather than a causal risk factor for children's conduct problems.[2]

Evocative (or reactive) genotype–environment correlation refers to the association between an individual's genetically influenced behaviour and others' reactions to that behaviour. For example, although arguing with a spouse may result in someone becoming depressed, it is equally plausible that individuals who are prone to depression tend to provoke arguments with significant others, calling into question the direction of the effect.

Active (or selective) genotype–environment correlation refers to the association between an individual's genetic propensities and the environmental niches that individual selects. For example, individuals who are characteristically extroverted may seek out very different social environments than those who are shy and withdrawn. These forms of genotype–environment correlation differ from gene–environment interaction (GxE), which refers to genetic differences in sensitivity to particular environmental effects.1 Genotype–environment correlations explain why individuals who have a genetic propensity to engage in sensation-seeking behaviours affiliate with drug-abusing peers.3 GxE explains why heavy drug use is most likely to lead to psychosis only among individuals with a particular genotype.4)

Evidence from the quantitative genetic literature

Twin and adoption studies have provided much of the evidence for genotype–environment correlations by demonstrating that putative environmental measures are heritable.[5,6] As reviewed by Kendler and Baker,[6] these include many environments that are associated with psychiatric illness, including marital quality, social support, parental discipline and warmth, family environment, and peer relationships. These also include desirable and undesirable life events, including divorce and exposure to trauma (Table 1). The weighted heritability of these environments ranges from 6% to 39%, with most ranging from 15% to 35%.[6]

How one interprets genotype–environment correlations depends on the type of sample included in quantitative genetic studies. When studies involve child twins reporting on their experiences (for example of parental discipline), genetic influences on the putative environment reflect the extent to which the child's genetic propensities elicit or evoke that experience.7–9 For example, Jaffee and colleagues8 found that a common genetic factor accounted for most of the observed relationship between children's antisocial behaviour and their experiences of corporal punishment. This suggests that genetic factors are correlated with spanking and smacking because they give rise to oppositional and antisocial behaviours that evoke those behaviours in parents. In contrast, when studies involve samples of adult twins reporting on their experiences (for example of administering discipline to children), genetic influences on the putative environment reflect the extent to which the adult's genetic propensities modify or create that experience.10

Environments are heritable because genotype influences the behaviours that evoke, select, and modify features of the environment. Thus, environments less amenable to behavioural modification tend to be less heritable. For example, negative life events that are beyond the control of the individual, such as the death of a loved one or losing one's home in a natural disaster, have lower heritability than negative life events that may be dependent on an individual's behaviour, such as getting a divorce or being fired from a job.[6] Similarly, personal life events (those that occur directly to an individual) are more highly heritable than network life events (those that occur to someone within an individual's social network, thus affecting the individual indirectly).[11]

Evidence from the molecular genetic literature

In contrast to quantitative genetic studies, which infer genetic influences from familial correlations, molecular genetic studies measure genotype directly. Significant genotype–environment associations have been reported between the γ-aminobutyric acid A α_2 receptor and marital status,[12] the serotonin transporter receptor 2A (*5HT2A*) gene and popularity,[13] the catechol-*O*-methyltransferase gene and daily hassles,[14] brain-derived neurotrophic factor and childhood adversity,[15] and the dopamine D_2 receptor gene and both parenting behaviour[16] and marital status.[17] Although the significant associations we describe require confirmation, these results suggest that it may be possible to identify specific genotypes that correlate with environmental variables.

At least one of these studies has demonstrated behavioural mediation of the genotype–environment correlation: men who were heterozygous or homozygous for the G allele of the G1438A *5HT2A* polymorphism were liked better by their peers than men who were homozygous for the A allele because they engaged in higher levels of rule-breaking behaviour.[13] However, significant genotype–environment correlations are relatively uncommon in molecular genetic studies. Because the genetic associations with behaviour that mediate genotype–environment correlations are likely to be small in magnitude, most molecular genetic studies are likely to have low power to detect genotype–environment associations.[18]

Implications for disease prevention

The existence of genotype–environment correlation raises two possibilities with implications for the prevention and treatment of psychiatric illness. The first possibility is that the relationship between psychosocial risk factors and psychiatric outcomes is not causal but confounded by genotype. In this case, modifying the putative risk environment will have little effect on psychiatric illness. For example, D'Onofrio et al.[19] used the Children of Twins design to test whether the relationship between parental divorce and offspring alcohol and emotional problems was accounted for by passive genotype–environment correlation. They found that the offspring of monozygotic (MZ) twin sisters who were discordant for divorce had equally high levels of emotional problems, suggesting that genetic factors that made twin siblings divorce-prone also increased their children's risk for depression and anxiety because MZ twins are genetically identical [VC3]. This finding suggests that preventing the parents' divorce would have had little impact on offspring risk for emotional problems (although the findings for alcohol problems were consistent with a causal role for divorce).

The second possibility is that the relationship between psychosocial risk factors and psychiatric outcomes is causal. In this case, modifying exposure to the risk environment should reduce levels of psychiatric illness. For example, Caspi and colleagues[20] asked mothers of monozygotic twins to speak about each of their children and then coded mothers' narratives for expressed negativity toward each child. The twin about whom mothers expressed more negativity tended to have significantly more conduct problems compared with his or her co-twin, even controlling for levels of twins' conduct problems measured 2 years earlier. This finding suggests that the effect of maternal negativity on the twins' behaviour was truly environmentally mediated, as monozygotic twins shared whatever genetic propensity would elicit negativity from their mother. In this case, modifying mothers' negativity would be expected to lead to reductions in children's emotional and behavioural problems.

In some cases, a causal link between psychosocial risk factors and psychiatric outcomes can be established, even if exposure to the risk environment is under genetic influence. For example, genetic differences among people partly explain why some smoke and others do not.[21] Yet, there is a strong body of evidence in support of a causal relationship between smoking during pregnancy and offspring birth weight[22,23] resulting from the deleterious effects of nicotine, carbon monoxide, and the other constituents of tobacco smoke on placental function and fetal cells. Similarly, there is evidence for a causal relationship between smoking during pregnancy and offspring attention deficit hyperactivity disorder, although this association is smaller in magnitude and may be accounted for partially by passive genotype–environment correlation.[24,25] The crucial point is that the origins of a risk factor and the mechanism by which its effects are exerted are separable and may be distinct.[26]

Complicating this account is the fact that there are often reciprocal relationships between psychosocial risk factors and psychiatric outcomes. For example, aggressive, difficult-to-manage children elicit more negative interactions with adults,[27] including harsh physical discipline,[8] but longitudinal studies show that harsh physical discipline is associated with growth in children's antisocial behaviour.[28] This implies that, for many disorders, successful treatment will need to be targeted at multiple levels, such as training patients to avoid situations that jeopardize their psychological well-being and modifying behaviours that elicit negative reactions from others, as well as training parents and partners to modify how they respond to provocations from patients.

Testing whether the relationship between exposure and outcome is genetically mediated

Research designs to test whether the relationship between exposures and psychiatric outcomes is consistent with a causal link include experimental and quasi-experimental designs29 (e.g. randomized controlled trials (RCTs), instrumental variable approaches, and regression discontinuity designs), genetically informative designs (e.g. adoption, Children of Twins, discordant monozygotic twin, and mendelian randomization[30] designs), and natural experiments in which an entire population experiences some exposure (e.g. World War II Dutch famine).31

These designs have different assumptions and purposes. For example, Children of Twins and adoption studies can test whether the relationship between family environment and offspring outcome is confounded by parental genotype due to passive genotype–environment correlation. Alternatively, methods such as RCTs or whole population exposures can eliminate genotype–environment correlations by design, ensuring that any observed relationship between the exposure and the outcome will not be subject to genetic confounding. Mendelian randomization capitalizes on situations in which genes are correlated with exposures but not outcomes, to test causal hypotheses about the relationship between exposure and outcome.[30]

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Table 1

Weighted [VC6]mean heritability across studies of common psychosocial risk factors for psychiatric illness

Constructs	Total no. (or range)	Weighted mean heritability
Stressful life events		
• Total life events	6197	0.28
• Independent life events	5056	0.17
• Dependent life events	4459	0.31
• Exposure to trauma	6558	0.36
• Divorce	5692	0.35
Child-based reports of parenting[a]		
• Warmth	2264–3446	0.34–0.37
• Control	1448–2330	0.15–0.17
• Negativity	377	0.12
• Protectiveness	2198	0.20–0.26
Parent-based reports of parenting		
• Warmth	1690	0.35
• Control	433	0.20
• Negativity	4766	0.19
• Protectiveness	1477	0.23
Observer-based reports of parenting		
• Affection	1695	0.14
• Control	639	0.12
• Negativity	635	0.06
Family environment[b]	1428–1911	0.18–0.30
Social support[c]	2860–5402	0.17–0.38
Peer deviance	3012	0.21
Marital quality[d]	752–1985	0.13–0.28

Adapted from Kendler and Baker.[6]

[a]Range reflects children's reports of maternal and paternal parenting.

[b]Range includes measures of cohesion/connectedness, conflict, organization, expressiveness, active, and control.

[c]Range includes measures of friend problems, relative problems, friend support, relative support, confidants, and social integration.

[d]Range includes measures of marital satisfaction, marital conflict, and marital warmth.