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Gene–Environment Interplay: Where We Are, Where We Are Going

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Abstract

The idea that both genetic and environmental influences contribute to behavioral outcomes is widely accepted. However, the practice of examining candidate Gene × Environment interaction (cGxE) is controversial. In this article, we summarize some of the key issues involved in cGxE research and provide recommendations for work in this area. Highlighted challenges include the selection of the gene, the development of the cGxE hypothesis, and the coding of the genotype. To address these challenges and gain confidence in cGxE findings, we recommend using empirical data to select and code genes/variants, using theory to develop cGxE hypotheses and a rigorous and transparent approach to hypothesis testing. Family researchers have much to offer to the study of Gene × Environment research in view of their process-oriented theories that are grounded in decades of nuanced measurement of the environment; implementing these best practices will help deliver on that promise.

Keywords

developmental psychology; family research; measurement; methods; research methodologies

In their article, Schlomer, Fosco, Cleveland, Vandenbergh, and Feinberg (2015) tackle the challenging area of integrating genetic information into a longitudinal, multigenerational developmental project. They bring a much-needed biopsychosocial perspective to address the question of "What processes account for the association between characteristics of the interparental relationship and adolescent internalizing?" The authors' hypotheses are rooted in previous theory and evidence concerning the perceptual and cognitive mechanisms that are likely to link interparental relationship characteristics and subsequent adolescent internalizing. Furthermore, they draw on differential susceptibility theory to hypothesize about how these processes may differ as a function of adolescents' *DRD4* genotype.

The sample in which Schlomer et al. tested their hypotheses is impressive; notable strengths include data collected from multiple reporters in over 400 families over a 3-year period.

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However, this study also illustrates the many issues involved in integrating genetic information into family research, and in particular the challenges associated with Gene × Environment interaction (GxE) research. Our goal here is to briefly summarize some of these challenges and to provide recommendations for conducting research in this area. The issues we raise are not intended as a critique of Schlomer et al.'s article specifically; instead, we use their article to begin a discussion of the challenges of candidate Gene × Environment interaction (cGxE) research and to encourage the incorporation of best cGxE methodological practices in family research going forward.

A Bit of History

In the decade since Caspi and colleagues (2002) published their landmark (or notorious, depending on one's view) article documenting that genetic variation in *MAOA* interacted with harsh physical discipline to predict antisocial behavior, there has been a proliferation of interest in examining cGxE across variants in a range of purported risk genes and salient environmental factors (e.g., parenting quality, maltreatment, stressful life events) to predict behavioral outcomes. The idea that both genetic and environmental influences contribute to behavioral outcomes is widely accepted and, conceptually, cGxE research is compelling: Certain environments may change the relationship between one's genotype and the likelihood that that person will express a particular behavior. From the perspective of those of us who are interested in tracing behavioral trajectories across the life span, understanding how genetic predispositions unfold in the context of (changing) environmental influences is critically important and may guide the development of tailored intervention and prevention efforts for those at greatest risk. However, in practice, the study of cGxE is challenging—more challenging than is often appreciated by social scientists, we might argue—and, as a result, has become controversial (Duncan & Keller, 2011).

Challenges in cGxE Research

There are several interrelated conceptual and methodological challenges in cGxE research. Perhaps the biggest challenge when incorporating measured genotypic data into behavioral studies is the question of, "Which gene?" Typically, in the behavioral sciences, a single variant in a handful of "usual suspect" candidate genes that have a purported biological function or are hypothesized to confer sensitivity to one's environment are examined (e.g., *SLC6A4*, *MAOA*, *DRD2*, *DRD4*, and *COMT*). For example, Schlomer et al. selected *DRD4* on the basis that variation in this gene has been previously associated with sensitivity to one's environment. This approach for candidate gene selection is popular; however, it is problematic, for a few reasons. First, history has shown that we have not been very good at identifying plausible candidate genes that confer risk for behavioral outcomes (e.g., internalizing or externalizing behaviors), and very few well-replicated associations have emerged from these hypothesized genes of interest (Bosker et al., 2011; Collins, Kim, Sklar, O'Donovan, & Sullivan, 2012). Exceptions to this include variants in the alcohol dehydrogenase (*ADH*) gene cluster and alcohol outcomes (Gelernter et al., 2013; Thomasson et al., 1991) and nicotinic receptor genes (*CHRNA5–CHRNA3–CHRNB4*) for smoking outcomes (Broms et al., 2012; Tobacco and Genetics Consortium, 2010). Much of cGxE research tests genes thought to be involved in sensitivity to one's environment. Considering

our poor record of selecting genes with effects on complex behavioral outcomes, it may be overly optimistic to think we will be better at guessing genes involved in environmental sensitivity.

Second, although the idea that there are genes that confer sensitivity to one's environment is appealing, there are important measurement issues that make it difficult to make a priori claims that a particular variant operates as a *differential susceptibility locus* (meaning that a genotype confers risk in a negative/risky environment but is associated with especially good outcomes in a positive/protective environment; Belsky et al., 2009). The difficulty in classifying variants as differential susceptibility loci lies in the fact that our measures of the environment do not have a true zero. Thus, in a low-risk sample there may be less variation in interparental conflict compared to a high-risk sample. The range of environments present in any given sample has implications for the shape of the cGxE interaction effect that is likely to be observed. We illustrate this in Figure 1. In a low-risk sample, where the range of interparental conflict is somewhat restricted, we would observe a fan-shaped interaction effect, which is consistent with a diathesis–stress model of cGxE. In a high-risk sample, where there is potentially a greater range of interparental conflict, we would observe a crossover interaction effect, which is consistent with a biological sensitivity to context model of cGxE. Thus, the pattern of effect observed in cGxE studies is closely tied to the nature of the sample and the measurement of the environment.

An important corollary of the question "Which gene?" is "What is the mechanism of GxE?" (Shanahan & Hofer, 2005). The strong theoretical grounding of Schlomer et al.'s article is characteristic of family research and thus illustrates an approach that is much needed in cGxE research. The authors make specific hypotheses about the mechanisms linking interparental relationship characteristics and adolescent internalizing and how these associations may differ as a function of a (purported) differential susceptibility locus, *DRD4*. This theoretically informed approach is much richer than the typical cGxE study, in which the theory regarding the significance of the environment and hypotheses about the mechanism of the GxE effect are often not fully developed. We return to the strengths of this theory-driven approach, and the novel contributions that family researchers can make to this area, in our recommendations below.

A related issue in developing and testing cGxE hypotheses involves the coding of the genotype. Although cGxE analyses are statistical interactions, it is important that the coding of the genotype reflect our understanding of the biology of the underlying gene function; that is, genotypic groups should be collapsed only in instances where it is biologically justifiable. Schlomer et al. discuss the ambiguity of coding *DRD4*, and several of the issues that must be considered when deciding on a genetic model. They draw on functional and gene expression data and the precedent set from the previous literature on differential susceptibility theory in order to justify use of a 7+ versus 7− coding scheme for *DRD4* genotype. This is a reasonable approach in the context of this gene, and probably the best possible strategy; however, the ambiguity surrounding the gene coding and function remains a limitation. For many genetic variants there is not clear functional or expression evidence. Thus, although preliminary analyses may suggest that certain genotypic groups can be

collapsed in order to enhance power, this is not typically a justifiable approach because the statistical model may mismatch the underlying biology and lead to erroneous results.

Setting the Standard for GxE in Family Research

Against this backdrop of conceptual and methodological issues, there has been growing controversy concerning cGxE approaches and their interpretation (Duncan & Keller, 2011; Eaves & Verhulst, 2014). There is no single solution; however, our goal here is to provide some recommendations for moving this area of research forward. We view these as the core issues of which family researchers and journal readers, reviewers, and editors should be cognizant when incorporating genetic data into their studies or evaluating research that includes a measured genetic component. We refer interested readers to an extended discussion of resources and recommendations for navigating this complex area in Dick et al.'s (in press) article. In addition, in collaboration with the National Institutes of Health's Office of Behavioral and Social Science Research, our group has developed a website to assist investigators with conducting cGxE studies. This will be available soon through the Office for Behavioral and Social Science Research's website (http://obssr.od.nih.gov/index.aspx).

There are a number of conceptual and statistical "checks" that should be conducted as part of cGxE studies. At the outset, this involves using a theory-driven approach to select environments and empirical data to select relevant genes/genetic variants. Family researchers are in a unique position to contribute to studies of GxE by using theory-driven approaches to develop hypotheses. This theory-driven approach may help identify novel environments as well as processes through which GxE effects are mediated (an approach illustrated by Schlomer et al.). Studies of latent GxE can also be used to develop hypotheses for cGxE studies. In twin studies, latent GxE is inferred by comparing monozygotic and dizygotic twin pair correlations across different levels of the environment. Studies of adolescent twin samples have found that latent genetic influences for behavioral outcomes are more pronounced in riskier environments, such as those characterized by high levels of peer deviance or low levels of parental monitoring (Button et al., 2007; Dick, Viken, et al., 2007; Hicks, South, DiRago, Iacono, & McGue, 2009). By design, studies of latent GxE examine how environmental factors moderate additive genetic risk for an outcome of interest. Thus, a significant latent GxE effect indicates that the environmental factor changes the association between most genetic variants and the outcome (assuming the outcome is influenced by a large number of small, approximately equal genetic effects), making environments for which there are latent GxE effects promising for follow-up in cGxE studies. We illustrated this strategy for one candidate gene, *GABRA2*, in Dick et al.'s (2009) article.

We strongly encourage researchers to think deeply and critically about the genes they investigate in cGxE studies. Not all candidate genes are created equal. In most cases, it may be time to move away from analyses of the "usual suspect" candidate genes in view of the field's poor track record at selecting (based on theory) the genes that are likely to be important for behavioral outcomes or confer sensitivity to the environment. An alternate strategy is to investigate genes and genetic variants that have been identified through large-

scale gene identification efforts, including genome-wide association study meta- and mega-analyses, such as those conducted by the Psychiatric Genomics Consortium (see www.med.unc.edu/pgc). Translating genes and gene networks identified in model organisms into human studies of cGxE also holds promise. For example, genes that are highly interconnected as part of these networks (i.e., “hub genes”; Wolen et al., 2012) may be high priorities for cGxE studies.

In short, family researchers may do more to advance cGxE research by focusing on genes with more compelling a priori evidence of involvement in behavioral outcomes. The challenge with this approach is that none of these large-scale gene identification efforts are focused on genes that affect susceptibility to the environment, which may be the outcome of greatest interest to family researchers. Nonetheless, we would argue that genes with strong evidence of association with main effects on behavioral outcomes would be ideal candidates for further characterization by social scientists (Thomas, 2010), who have a rich tradition of carefully delineating the mechanisms underlying developmental processes.

We also encourage researchers to take a rigorous and transparent approach to statistical tests for cGxE interaction, which includes checks for robustness of the cGxE effects following nonlinear transformation of the dependent variable. Interaction effects are dependent, in part, on the scale of the outcome variable (Mather & Jinks, 1982). The scales of many of the outcomes in the behavioral sciences (e.g., internalizing and externalizing behavior) are arbitrary in the sense that they have no true zero, and the differences between scores on the scales cannot be interpreted as ratios (i.e., the magnitude of the difference between people scoring 1 and 2 points on a depressive symptom inventory may be not be the same as the magnitude of the difference between people scoring 9 and 10 points). Accordingly, checking for the robustness of cGxE effects following nonlinear transformations of scale (e.g., logarithmic or square root transformations) is important. Neither the transformed nor the untransformed version of the outcome variable is “right”; however, nonlinear transformations of scale reduce heteroscedasticity that may masquerade as cGxE and thus represent a key discriminant test.

Additional considerations include controlling for potential confounders, selecting an appropriate statistical model, using multiple statistical methods to evaluate an effect, and following up significant cGxE effects with replication attempts in independent samples. With respect to controlling for potential confounders, Keller (2014) recommended statistical checks that the cGxE effect holds after including all potential Covariate × Environment and Covariate × Genotype interactions. With respect to model selection, recent simulation studies have indicated that the cross-product approach for testing cGxE for three-category single-nucleotide polymorphisms, where genotype is coded as zero, one, or two copies of a specific allele, may not be appropriate in many cases, and an alternative regression parameterization has been suggested to overcome these limitations (Aliev, Latendresse, Bacanu, Neale, & Dick, 2014).

On a related note, using additional methods to probe the reliability of an observed GxE effect can add to our confidence in it. A strength of Schlomer et al.’s article is the authors’ use of bootstrapping methods to evaluate the reliability of the GxE effect. Bootstrapping

approaches are particularly useful in cases where parametric assumptions may not be met, which can occur when examining statistical interactions in which the normality of residuals assumption may be violated. Finally, efforts to replicate cGxE effects in independent samples is critical to building a weight of evidence for an effect, although we also recognize that family researchers' samples are often unique (e.g., multigenerational and long-term longitudinal studies that include high-cost observational assessments) and are therefore less amenable to direct replication. To the extent that conceptual replications are possible, they are encouraged.

We also encourage family researchers to consider polygenic approaches in future studies of GxE. Polygenic approaches include the effects of many variants of small magnitude across the genome (Plomin, Haworth, & Davis, 2009). Considering multiple genes and variants in aggregate addresses a key issue with candidate gene approaches, which is that examination of single variants in isolation is at odds with our understanding that behavioral outcomes have a polygenic architecture. Now that there are relatively inexpensive methods for genotyping hundreds of thousands of genetic variants across the genome (< 100 USD), researchers can easily calculate polygenic risk scores, which sum across hundreds of thousands of genetic variants in order to capture aggregate genetic risk. These polygenic scores can be carried forward into studies of GxE in which, in theory, the *G* represents a more global index of genetic risk (Salvatore, Aliev, Bucholz, et al., 2014; Salvatore, Aliev, Edwards, et al., 2014). However, we note that using polygenic risk scores in tests of GxE assumes that most of the genes of interest for that trait are moderated in the same way. This may be more reasonable for some hypotheses (e.g., in substance use, where restrictive environments that limit one's access to alcohol would reduce the likelihood of expressing a predisposition toward substance use; Dick, Pagan, et al., 2007) than others (e.g., GxE analyses of stressful life events may be more limited to genes involved in stress response).

Conclusions

Family researchers have much to offer to the study of GxE in view of their process-oriented theories that are grounded in decades of nuanced measurement of the environment. Schlomer et al.'s article, which draws on the emotional security and cognitive appraisal literatures to examine pathways from interparental relationship factors to adolescent internalizing, is an excellent example of this. However, to fully reach this promise, careful attention must be paid to the *G* that gets integrated into studies of GxE, and the methods used to study GxE. Increased awareness and attention to these issues among researchers, journal reviewers, and journal editors will—we hope—increase the quality of cGxE work and the potential of biopsychosocial approaches to inform our understanding of family processes.

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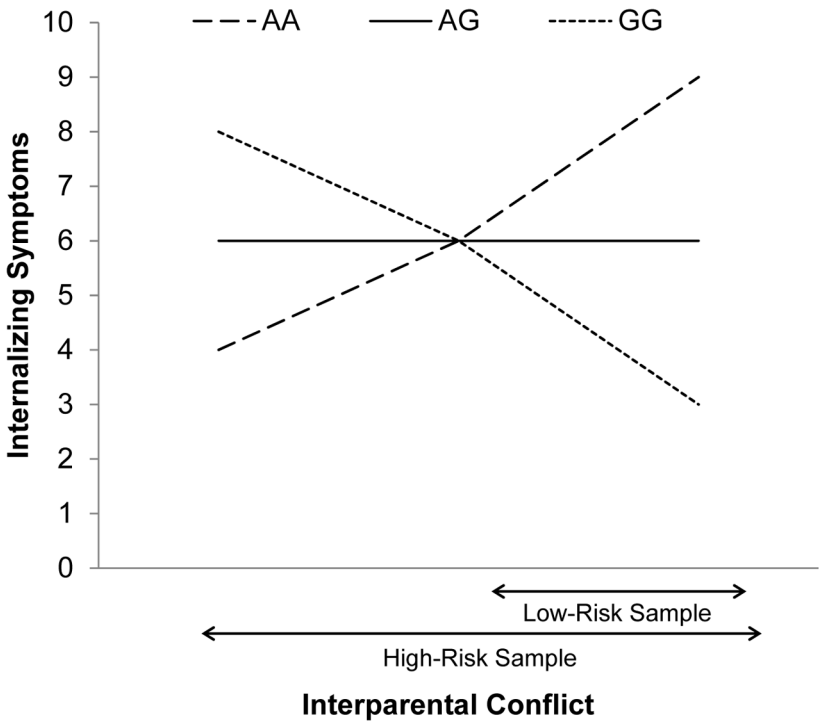

Figure 1.

An Illustration of the Difficulty in Determining Whether a Genetic Variant Confers Differential Susceptibility, Using the Hypothetical Example of Internalizing Symptoms as a Function of Interparental Conflict and a Single Nucleotide Polymorphism.

Note. In the low-risk sample (far right of the *x*-axis), the range of interparental conflict is restricted relative to the high-risk sample. Accordingly, in a low-risk sample we observe a fan-shaped interaction effect, which is consistent with a diathesis–stress model of cGxE. In a high-risk sample, where there is potentially a greater range of interparental conflict, we observe a crossover interaction effect, which is consistent with a differential susceptibility model of cGxE.