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Looking Forward in Candidate Gene Research: Concerns and Suggestions

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Abstract

Candidate Gene × Environment (cGxE) interaction research holds promise for helping us understand for whom and why environments matter for families and development. In their commentary on our target article (G. L. Schlomer, G. M. Fosco, H. H. Cleveland, D. J. Vandenbergh, & M. E. Feinberg, 2015), J. E. Salvatore and D. M. Dick (2015) present their view of the current state and future of cGxE research and frame the debate regarding its merits for advancing knowledge of gene–environment interplay. In this reply, we discuss points of agreement and departure and provide a list of 5 domains by which the quality of cGxE research should be evaluated. Our hope is that researchers will use this list as a guide for their own work.

Keywords

candidate gene; GxE; sociobiology; susceptibility

We are grateful to the *Journal of Marriage and Family* for this forum in which to discuss important issues in candidate Gene × Environment (cGxE) family research and to Drs. Salvatore and Dick (2015) for sharing their expertise and their thoughtful and balanced commentary on our article (Schlomer, Fosco, Cleveland, Vandenbergh, & Feinberg, 2015). We found many points of agreement in their commentary and believe that differences in our views are a matter of degree and emphasis rather than contrast.

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We agree with Salvatore and Dick that a major challenge in cGxE research is "which gene." We differ, however, with the suggestion that considering the "usual suspects" is necessarily problematic. Although this strategy should not be exclusively pursued, there is now a decades-old literature on these usual-suspect markers (e.g., *SLC6A4*, *DRD4*, *MAOA*, *CHRNA5*), including genomic function, neurological/hormonal correlates, endophenotypes, psychological/behavioral outcomes, and environmental moderation. It is *because* these markers have been well characterized, at multiple analytic levels, that they have been incorporated into family/developmental research. Given adequate sophistication and care (see Cleveland et al., in press), research with these genes can provide valuable insights into gene–environment interplay.

Salvatore and Dick note that genome-wide association studies (GWAS) have shown inconsistent associations with psychiatric phenotypes and suggest we should be no better at "guessing" sensitivity genes. Our own skepticism (Schlomer et al., 2014) has been somewhat abated, however, by the growing number of studies that have found cGxE patterns consistent with plasticity theories (i.e., differential susceptibility theory, diathesis–stress, vantage sensitivity), including compelling evidence from experimental studies (e.g.,van IJzendoorn & Bakermans-Kranenburg, in press) and prevention/intervention studies that use random assignment (e.g., Brody Beach, Philibert, Chen, & Murry, 2009). Two additional experimental studies of *DRD4* and alcohol use (Creswell et al., 2012; Larsen et al., 2010) have made a particularly strong case that some genes deserve the status of a usual suspect.

GWAS and cGxE approaches have unique strengths, and neither should be dismissed on the basis of their limitations. GWAS analyses are greatly important for discovering gene–phenotype links. However, the inconsistency noted by Salvatore and Dick may be the result of the search for population-level main effects. Because they require large samples, GWAS findings likely reflect a gene's average effect over the wide range of environments from which the samples were drawn. However, if a genetic effect is larger in one environment and smaller in others, the overall main effect may be small and thus difficult to detect statistically. The solution to this problem has been to increase power through sample size. Interaction-based work underscores a reality that in many cases (based on the shape of the interaction and the distribution of the environments sampled) a null main effect may hide an interaction, as exemplified in our findings (Schlomer et al., 2015). Thus, in conventional GWAS a null main effect overlooks the possibility that an allelic association may be environmentally contingent. The remedy for inconsistent GWAS findings may include more than increasing sample size, such as considering conditional associations (i.e., moderation).

Moving Forward in cGxE Research

Our view of the future of cGxE research is optimistic, tempered by the need for careful and critical evaluation of this work. To assist in this process, we emphasize five domains in which cGxE research should be evaluated: Design, Measurement, Theory, Biological Role, and Population Structure.

Design

There are substantial benefits of applying randomized designs to cGxE research. In epidemiological studies, causality is difficult to determine because experience–outcome associations may equally reflect causal environmental influences or self-selection into those environmental experiences. These niche-picking processes reduce both the ability to infer cause (see G. J. Duncan, Magnuson, & Ludwig, 2004) and the statistical power to identify interactions. Prevention/intervention trials, owing to randomization, eliminate nonrandom selection to the environment (i.e., intervention vs. control) and create a unique opportunity to examine cGxE interactions without confounds due to gene–environment correlation (rGE). Moreover, randomized intervention designs offer substantially more power to detect interactions in cGxE than other designs (see Bakermans-Kranenberg & van IJzendoorn, 2015; McClelland & Judd, 1993).

Measurement

Researchers should be wary of categorically dismissive conclusions about cGxE research. For example, some of the strongest critiques of cGxE research have emerged from research reviews (e.g., L. E. Duncan & Keller, 2011; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009) that include studies that vary in measurement quality. We, along with others (e.g., Karg, Burmeister, Shedden, & Sen, 2011; Rutter,Thapar, &Pickles,2009; Uher&McGuffin, 2008), disagree with conclusions drawn by these reviews, including the notion that all cGxE research should be considered suspect (see Gildersleeve, Haselton, & Fales, 2014). Family and developmental researchers are in a unique position to capitalize on high-quality measurement, which, among other strengths, can increase statistical power to a greater extent than increasing sample size (Manchia et al., 2013).

Theory

We agree with Salvatore and Dick that using theory to shape cGxE research questions is critical. Not only can theory direct researchers toward the most relevant constructs to consider, but it also can play an important role in helping researchers avoid searching for findings and leveraging chance results.

Biological Role

Equally important to theory is considering the underlying biological processes for genetic associations or environmental interactions. We suggest that the “which gene” decision be made on a range of levels, from broad to narrow, that demonstrate a cogent role for the marker vis-à-vis both the phenotype and environment. For instance, one might start by examining literature that demonstrates a gene is associated with behavioral outcomes, proceeding to more narrow associations (e.g., perceptual, neurocognitive) and, finally, to the physiological and molecular level (e.g., cell activity and gene expression). It is additionally important to be cognizant of allele coding schemes across analyses (e.g., dominant, additive). For an application of these criteria see Cleveland et al. (in press).

Population Structure

Because allele frequencies can vary across populations, inattention to population structure (e.g., genetic ancestry) can lead to spurious results (Knowler, Williams, Pettitt, & Steinberg, 1988). The best strategies to address population structure confounds will vary by sample size, sample diversity, genes examined, outcomes considered, and the combination of these that pose threats to internal validity. Helpful readings on this topic area include Ziv and Gonzalez-Burchard (2003) and Keller (2014).

Conclusion

By considering these five areas necessary for comprehensive cGxE research, a more nuanced —and, we hope, explanatory—set of results will lead the field forward. Although it may be difficult for any single study to maximize quality in each domain, how these domains are addressed as a whole strongly influences validity and generalizability of results. We agree with Salvatore and Dick that research into family processes is likely to be a rich and productive avenue and reveal much about gene–environment interplay.

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