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Why Behavioral Genetics Matters: Comment on Plomin et al. (2016)

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Behavioral genetics has occupied a unique position within psychology, repeatedly inciting acrimonious debates over many of the discipline's defining issues. In their article published in this issue of *Perspectives on Psychological Science*, Plomin, DeFries, Knopik, and Neiderhiser (2016) push the academic controversies to the side and show how behavioral-genetic research has fundamentally altered our understanding of the nature of individual differences in psychological traits. They are to be commended for their comprehensive summary of enduring results. Indeed, in the midst of the ongoing "replicability crisis," their review can be read as a celebration of the field's maturity and accomplishments.

Plomin, DeFries, Knopik, and Neiderhiser (PDKN) organize their review around 10 robustly replicated "big" findings. Those whose view of behavioral genetics is anchored in the nature–nurture debates of the 20th Century will be surprised by the broad scope of the topics covered. PDKN describe how behavioral-genetic research has enriched our understanding of psychological development and even the nosology of mental illness. Significantly, four of their findings have very little to do with genetics at all, being specifically concerned with the nature of environmental influence. Elsewhere, these authors have made the point that some of the strongest evidence for the existence of environmental influences derives from behavioral-genetic research, and for good reason. Furthermore, they justly emphasize that strong causal interpretations of behavioral-genetic findings are indeed warranted. Because drawing causal inferences from observational data can be so often fraught with difficulty, one of the attractions of behavioral genetics for the larger field of psychology is that it offers a set of complementary research designs justifying strong inference in observational settings (Lee, 2012; McGue, Osler, & Christensen, 2010).

But is behavioral genetics really less susceptible to false-positive findings than other areas of psychology? PDKN believe so, and they provide five reasons to justify that belief. Ironically, the first of these, which they designate "Controversy," owes as much to the critics of the field as to behavioral geneticists themselves. Over the past 50 years, psychology has viewed behavioral genetics with a fair degree of skepticism. The doubts of their colleagues have forced behavioral geneticists to adopt high standards of proof—large sample sizes, converging evidence from complementary research designs, transparent multisite collaborations, and attention to alternative explanations. Making common cause with their colleagues in human genetics studying diseases and anthropometric traits, behavioral geneticists at the molecular frontier have mustered the will to stamp out nonreplicability, and the resulting culture has turned the broad endeavor of gene-trait mapping into one of the most trustworthy fields in all of biomedical and social science (Ioannidis, 2013). Seeing that uncritical acceptance of research findings has proven a major impediment to scientific progress elsewhere (Duarte et al., 2015), behavioral geneticists may perhaps owe a debt to those who have challenged their methods and interpretations.

The benefits of being "blessed by brilliant enemies," as E. O. Wilson put it, can be appreciated by virtue of their absence from an area of behavioral-genetic research that did not make PDKN's list: gene–environment interaction (G×E). There is general recognition that G×E effects on behavior are pervasive. The downside of this recognition, in our view, is that reports of G×E are not met with the same skepticism as findings from other areas of behavioral genetics. Over the past 15 years, there has been a consequent explosion of published G×E research in psychology. Unfortunately, much of this research has been susceptible to the same limitations with which other areas of psychology are struggling—small samples, ad hoc analytical decisions, multiple model tests, etc. And the result? G×E research has a rather poor record of replicability, leading to calls for its claims to meet the same standards of proof that have been established in other areas of genetics (Duncan & Keller, 2011).

The only place where we might quibble with PDKN's conclusions is their analysis of the search for marginal

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genetic effects. Over the past 20 years, psychologists who have sought to identify the specific genetic variants that influence individual differences in behavior have primarily used a candidate-gene approach. This approach involves testing for an association between a behavioral phenotype and genetic variation in a specific gene, selected because it is hypothesized to be biologically relevant to the trait in question. We agree with PDKN's doubts about the replicability of candidate-gene studies in behavioral research. Indeed, concerns over the robustness of candidate-gene studies are not limited to behavioral research, as the false discovery rate of such studies in human genetics generally has been estimated to be as high as 95% (Colhoun, McKeigue, & Davey Smith, 2003).

Despite the general failure of the candidate-gene approach, the search for marginal genetic effects is advancing rapidly with the advent of genome-wide association studies (GWAS). GWAS are hypothesis-free searches of the entire genome for genetic association. Each of 1 million or more single nucleotide polymorphisms (SNPs) is tested for phenotypic association with appropriate controls for multiple testing. GWAS of diverse medical, behavioral, and physical traits have revealed a fairly general pattern: Single genetic variants can be identified but the marginal effect of any single variant is very small, accounting for much less than 1% of the phenotypic variance. These small individual effects lead PDKN to emphasize the estimation of aggregate quantities such as variance components and polygenic scores. We believe this emphasis is misplaced, as well-conducted GWAS of behavioral traits now produce highly credible results despite the small sizes of the individual effects.

For instance, in an as-yet unpublished study adding ~164,000 individuals to an original sample of ~125,000 (Okbay et al., 2015), we have replicated the associations reported by Rietveld et al. (2013) between three SNPs and educational attainment. (Among the millions of SNPs tested in the larger sample, we have also uncovered many more novel associations.) These findings are not only statistically significant but biologically significant. The first of these SNPs, rs9320913, is located near the gene *POU3F2*, a transcription factor regulating pathways responsible for neurogenesis and the migration of newly born neurons to the upper layers of the cerebral cortex. The second, rs11584700, is strongly correlated with a nonsynonymous SNP in the gene *LRRN2*, which encodes a leucine-rich repeat expressed strongly in neurons. The third, rs4851266, is located near *CHST10*, which encodes a sulfotransferase involved in the synthesis of a carbohydrate with roles in brain development and synaptic plasticity. Although the necessary sample sizes are formidable, GWAS results provide essential biological insights into a broad range of behavioral phenotypes.

As we have said, much of the credit for the thriving state of the field belongs to its practitioners (and detractors), but perhaps we are fortunate to some extent. At any point in the history of science, it may be that we can only discover what Nature is ready to reveal. And when Nature is choosing what genes to assemble together into populations of organisms, she is essentially limited to the same information available to human scientists pursuing GWAS: whether a given allele is correlated with the phenotype (which, in this case, is fitness) to the resolution afforded by size of the population (Fisher, 1941). Nevertheless, looking around at the exquisite adaptedness of living things, we can be confident that Nature correctly picks out alleles for their causal effects on fitness often enough (Lee, 2012; Lee & Chow, 2013). If we live in a world that is simple enough for natural selection to be robust, than perhaps it is not surprising that we can make progress by duplicating Nature's strategy of using large sample sizes to detect small DNA-trait correlations.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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