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Predicting Sensation Seeking From Dopamine Genes: Use and Misuse of Genetic Prediction

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In a recent study reported in *Psychological Science*, “Predicting Sensation Seeking From Dopamine Genes: A Candidate-System Approach,” Derringer et al. (2010) attempted to use a relatively new technique called genetic prediction to demonstrate that dopaminergic genes influence the personality trait of sensation seeking. In this Commentary, we outline the rationale for genetic prediction and how it can be correctly implemented. We then explain why we believe that Derringer et al. used genetic prediction incorrectly, thus invalidating their conclusions.

The recent availability of high-density genotype information has enabled researchers to test for associations between hundreds of thousands of single-nucleotide polymorphisms (SNPs) and any given trait. Although these genome-wide association (GWA) studies have been successful in identifying SNPs associated with common diseases (e.g., Burton et al., 2007), they have failed to identify any SNPs reliably associated with personality traits (e.g., the Big Five: Costa & McCrae, 1994; Eysenck personality scales: Eysenck, Eysenck, & Barrett, 1985; and Cloninger’s temperament scales: Cloninger, Przybeck, & Svrakic, 1991; see also Hettema, van den Oord, An, Kendler, & Chen, 2009; Shifman et al., 2008; Terracciano et al., 2009; Verweij et al., 2010). However, twin, family, and adoption studies have shown that personality traits are substantially influenced by genetic factors (Jang, Livesley, & Vernon, 1996; Keller, Coventry, Heath, & Martin, 2005; Koopmans, Boomsma, Heath, & Van Doornen, 1995; Loehlin, 1992). This disparity suggests that variation in personality traits is likely to be influenced by a large number of SNPs, each of which has effects that are individually too small to statistically identify using current sample sizes (Maher, 2008; Manolio et al., 2009; Verweij et al., 2010).

Statistical models that sum the effects over multiple SNPs is an alternative approach that can be used to detect their combined influence on a trait. This approach is commonly referred to as genetic prediction (Evans, Visscher, & Wray, 2009; Goddard, Wray, Verbyla, & Visscher, 2009; Manolio, 2010; Wray, Goddard, & Visscher, 2007) or genomic profiling


(Janssens et al., 2008). Genetic prediction typically involves using standard GWA analysis to identify the SNPs most strongly associated with a trait (e.g., the 5% of SNPs with the lowest p values) in a discovery sample. The effects of those top SNPs are then combined in a regression model to predict the trait in an independent sample. The use of an independent sample is crucial. In the absence of any true effects, the top-ranked SNPs represent the variables that show the strongest association with the trait on the basis of error variation. These SNPs could predict the trait in the same sample simply as a function of the association between their error variation and the trait (a situation termed model overfitting); this will always result in better predictive ability of a model that includes these top SNPs compared with a baseline model that excludes these SNPs, even if the null hypothesis is true. To avoid overfitting, and to test whether there is a true effect of the SNPs on the trait, researchers need to establish whether they can predict the trait to a degree significantly better than chance in an independent sample. When only a single sample is available, K -fold cross-validation methods can be used to guard against testing hypotheses that are suggested by the data (Evans et al., 2009; Purcell et al., 2009).

Derringer et al. (2010) tested genetic data from eight dopaminergic genes for associations with the personality trait of sensation seeking in 635 unrelated individuals. Subsequently, Derringer et al. attempted to use SNPs that were identified in the association study to predict the genetic risk of sensation seeking in the same sample. We believe that this incorrect application of genetic prediction methodology invalidates their conclusions.

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Instead of using hundreds of thousands of SNPs across the whole genome (i.e., performing a GWA analysis), Derringer et al. tested 273 SNPs within eight candidate genes involved in the dopamine system. The use of a candidate-gene approach, rather than GWA, does not change the underlying principles of genetic prediction. Twelve of the 273 SNPs were statistically associated with sensation seeking ($p < .05$)—fewer than would be expected by chance. In the absence of any true effects, we would expect approximately 14 (i.e., $273 \times .05$) SNPs to show associations at this significance level purely by chance. To infer true effects, researchers must correctly account for multiple testing. Derringer et al. attempted to use false discovery rate to correct for multiple testing, but they erroneously used the number of genes (8) in the formula (their Equation 1) rather than the number of true independent tests (273 adjusted for correlation between SNPs). If standard methods of accounting for multiple testing in genetic association studies are correctly applied (Moskvina & Schmidt, 2008; Nyholt, 2004), none of the 12 SNPs reach study-wide significance. After applying these methods, we found no evidence for truly significant associations between any of the 273 SNPs and sensation seeking.

Derringer et al. also tested whether an aggregate regression model that included these 12 SNPs showed a greater ability to predict sensation seeking than a model that excluded these SNPs; their critical error was that they performed this testing in the same sample in which the SNPs were identified. In this situation, a model including the top SNPs will always improve predictive ability compared with a model excluding those SNPs, regardless of any true effects. However, Derringer et al. incorrectly claimed that their results “indicated that dopamine genes are associated with sensation-seeking behavior at the system level” (p. 1287).

In summary, the conclusions drawn by Derringer et al. are highly misleading. Their claim that dopamine genes influence sensation seeking is not supported by their data. Sensation seeking is an important trait because of its association with externalizing disorders and drug use; the claims made by Derringer et al. confuse and misdirect attempts to unravel the genetic and biological basis of the trait and these related disorders. Furthermore, their misuse of methodology could lead to confusion regarding genetic prediction studies in general and may lead to other similarly flawed studies on other traits.

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The two authors contributed equally to this Commentary.

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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