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Genomic Approaches to Phenotype Prediction

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To the editor

Methodological considerations raised by Lord and Veenstra-VanderWeele[1] regarding genotype-first approaches to phenotype research are appreciated. In their editorial focusing on autism spectrum disorder, the authors described the importance of considering phenotypic confounds. This letter expands on these considerations with discussion of novel methods increasingly used for predicting and classifying psychiatric phenotypes from genetic data. These developing methods may be further useful in resolving confounds.

There are several approaches to using common genetic variants in prediction. Polygenic risk scores, derived from genome-wide association regression weights, are frequently used to predict case status or quantitative complex traits. Similar methods use the other side of the genome-wide association *P* value distribution to derive scores associated with resistance to disorder. In addition, pathway-based polygenic scoring methods are currently being tested by our group to examine the aggregated weights of thousands of variants within only the molecular pathways demonstrated to be enriched in disorders (specifically, gaussian clustering on pathway scores enriched in cases and contrasting proportions of subtypes within leaves of a regression tree, both accounting for ancestry and sex).[2] Molecular pathway–based scores can reduce the genomic information to a computationally reasonable size, while increasing signal-to-noise ratio.

While these methods have promise, it is important to be realistic about what these analyses might uncover—in many studies, we see common variant heritability estimates plummet in comparison with those from twin studies. However, Lord and Veenstra-VanderWeele[1] point out that the phenotype-first approach to complex, low base rate disorders is often impractical. In these cases, scoring may be useful in at least 2 ways: individual cases can be assigned to a genetic subgroup based on pathway scores and subtypes can then be differentiated phenotypically (A.R.D., D. E. Adkins, PhD, A. C. Edwards, PhD, M. C. Neale, PhD, B. P. Riley, PhD, K. S. Kendler, MD, A. H. Fanous, MD, PhD, and S. A. Bacanu, PhD; unpublished data; December 2015). Additionally, although exploratory

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methods should be used with caution, phenotypic network analyses can be examined across genetic subtypes.

Finally, genetic profile scores can be examined with respect to the entire phenome. Thus, genetic risk across mental health conditions can be used for phenotypically savvy research on quantitative clinical and outcome variables. One example is a report by Krapohl and colleagues,[3] and another could relate to Lord and Veenstra-VanderWeele's discussion of multiple, quantitative phenotypes, such that polygenic risk for autism spectrum disorder within a deletion subtype could be used to predict any number of networks across the phenome. Duplication and deletion information can also be used to subtype, and to maximize the genetic risk accounted for, while simultaneously accounting for ancestry and sex.

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