Biological Psychiatry: Celebrating 50 Years

Common (Genetic) Links Between Clinics and the Community: New Evidence From a Tourette Syndrome Polygenic Score

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In this issue of *Biological Psychiatry*, Abdulkadir *et al.* (1) test whether a new genome-wide polygenic score (GPS) for Tourette syndrome (TS) predicted the presence and chronicity of tics in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. This new GPS for TS stems from a new genome-wide association study (GWAS)—the second and largest GWAS of TS to date (2). The GPS was found to predict the presence but not the chronicity of tics after correcting for multiple testing.

Demonstration that the TS GPS derived from a clinical sample significantly predicts the presence of tics in a community sample is a reliable form of biological evidence for overlap in common additive genetic influences between clinical and subclinical forms of tics. In the GWAS from which the GPS was created, participants were recruited largely from clinics that specialize in TS, which means that the sample includes severe cases of TS (2). As Abdulkadir *et al.* (1) note, the ALSPAC sample was recruited through the community and is a general population cohort; as such, it includes more individuals with milder forms of TS and the full spectrum of tic severity (1). For example, Abdulkadir *et al.* (1) found that the TS GPS significantly predicted a broader phenotype they termed "tics all." "Tics all" included any individuals between 1.5 and 13 years of age who had at least one positive answer to the tic screening questions in the ALSPAC cohort. As such, this is intentionally a much broader phenotype than a clinical diagnosis of TS. The TS GPS predicted 0.78% in itself (in the same disorder) in an independent sample (2); in comparison, it predicted 0.46% variance in "tics all" in the ALSPAC cohort (1).

In further analyses, Abdulkadir *et al.* (1) reported that the TS GPS did not significantly predict other psychopathology traits in the ALSPAC cohort—namely, symptom severity of obsessive-compulsive disorder assessed at either 7 or 13 years of age and both attention-deficit/hyperactivity disorder–like traits and social communication impairment traits at 7 years of age. It is interesting to consider why significant predictions of the TS GPS with chronicity of tics and with other forms of psychopathology severity were not found. Within psychiatric genetics, significant genetic correlations between different forms of psychopathology are becoming pervasive in both twin and DNA-based studies. The power to predict other traits in GPS analyses is strongly dependent on the reliability of the GPS, which in turn depends on the sample size of the GWAS from which it was generated. It is possible to imagine that, as has been found for other phenotypes (3,4), a GPS that is derived from an even larger GWAS of TS might predict chronicity of tics as well as other forms of psychopathology.

Why is evidence for a genetic link between clinical TS and less severe tics important? One practical reason is that this type of evidence helps inform practitioners, genetic counselors, and families that TS and milder forms of subclinical tics are likely to run in the same families.

More broadly, within psychiatry and psychology there has been longstanding interest in whether psychopathology traits seen to varying degrees in the community are linked to clinical diagnoses. Family studies have shown that relatives of individuals with a clinical psychiatric disorder show elevated traits related to that disorder compared with relatives of control participants. Typical family studies cannot, however, disentangle whether such familiality is due to the family environment or due to shared genetic influences among relatives. Twin studies have shown that the heritability of traits within psychopathology does not change across the severity continuum, and there appears to be a genetic link between severe psychopathology traits and those in the normal range (4). Finally, literature reviews have noted that the same environmental risk factors show associations with both disorders and less severe manifestations of symptoms—for example, for schizophrenia and psychotic-like experiences (5).

The results reported by Abdulkadir *et al.* (1) provide another source of evidence, at the measured genotype level, for overlap in causal influences between milder and more severe forms of psychopathology. To put it in context, Table 1

Table 1. Effect Sizes of Genome-wide Polygenic Score Predictions for Four Psychiatric Disorders and Their Related Dimensional Traits

Disorder GPS	Related Trait	Variance Predicted in Disorder Itself by GPS (A)	Variance Predicted in Related Trait by Disorder GPS (B)	B/A
Autism	Autistic traits	1.13% (6)	0.1% (6)	9%
Schizophrenia	Negative symptom traits	7% (3)	0.7% (7)	10%
Depression	Depressive traits	0.72% (8)	0.11% (9)	15%
ADHD	ADHD traits	3.71% (10)	0.8% (10)	22%

ADHD, attention-deficit/hyperactivity disorder; GPS, genome-wide polygenic score.

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https://doi.org/10.1016/j.biopsych.2018.12.006
ISSN: 0006-3223

summarizes what has been reported for four psychiatric disorders from recent GWAS studies. The "Variance predicted in disorder itself by disorder GPS" column shows the amount of variance in liability that the GPS predicts in the same disorder in an independent sample. The "Variance predicted in related trait by disorder GPS" column shows the percent variance in a related trait that the disorder GPS predicts in an independent community sample. If we divide the second value by the first, the relative predictive power of the GPS to predict a related trait compared with predicting the disorder itself is demonstrated. For these four psychiatric disorders, the amount of variance that the disorder GPS currently predicts in the related trait is 10% to 20% compared with what it predicts in itself (Table 1) (4). Nevertheless, for these four disorders, and now also for TS, we appear to have evidence of some overlap in common additive genetic influences between milder subclinical and more severe clinically recognized forms of psychopathology.

Why do disorder GPSs not predict as much variance in traits as they do in themselves (i.e., the same disorder) in an independent sample? One possible reason is that disorder diagnoses tend to include more than simply scoring high on trait scales. Diagnoses often require specific combinations of multiple symptoms as well as criteria relating to impairment in functioning brought about by the symptoms. Traits are often measured at a single age, whereas diagnoses depend on symptoms' having been persistent over a period of time before diagnoses are made.

Abdulkadir *et al.* (1) expand our understanding of the links between subclinical and clinical manifestations of psychopathology and make a valuable new contribution to the growing field of the molecular genetics of TS.

Acknowledgments and Disclosures

AR has received fees for consultancy writing for the National Childbirth Trust.

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Received Dec 6, 2018; accepted Dec 7, 2018.

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