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Common (genetic) links between clinics and the community: new evidence from a Tourette Syndrome polygenic score --Manuscript Draft--

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Common (genetic) links between clinics and the community: new evidence from a
Tourette Syndrome polygenic score

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Commentary

In Abdulkadir et al (1), the authors test whether a new genome-wide polygenic score for Tourette syndrome predicted presence and chronicity of tics in the ALSPAC cohort. This new genome-wide polygenic score (GPS) for Tourette syndrome stems from a new genome-wide association study (GWAS) - the second and largest GWAS of Tourette syndrome to date. The GPS was found to predict presence but not chronicity of tics after correcting for multiple testing.

Demonstration that the Tourette syndrome GPS derived from a clinical sample significantly predicts 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 Tourette syndrome specialty clinics, which will mean that the sample will include severe cases of Tourette syndrome (2). The ALSPAC sample, as the authors note, was recruited through the community and is a general population cohort; as such it will include more individuals with milder forms of Tourette syndrome and the full spectrum of tic severity (1). For example, the authors found that the Tourette syndrome GPS significantly predicted a broader phenotype they termed “tics all”. “Tics all” included any individuals with at least one positive answer to the tic screening questions between the ages of 1.5 and 13 years in the ALSPAC cohort. As such this is intentionally a much broader phenotype than a clinical diagnosis of Tourettes. The Tourette syndrome GPS predicted .78% in itself in an independent sample (2); in comparison it predicted .48% variance in “tics all” in ALSPAC (1).

In some further analyses, the authors reported that the Tourette syndrome GPS did not significantly predict other psychopathology traits in ALSPAC, namely, symptom severity of OCD assessed at either 7 or 13 years, and ADHD-like traits and social-communication impairment traits both at age 7. It is interesting to consider why a significant prediction of the Tourette syndrome GPS with chronicity of tics and with other forms of psychopathology severity was not found. Within psychiatric genetics, significant genetic correlations between different forms of psychopathology are becoming pervasive in both twin and DNA-based studies. 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. As such 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 Tourette syndrome might predict chronicity and other forms of psychopathology.

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

More broadly within psychiatry and psychology, there has been a long-standing interest in whether psychopathology traits seen to varying degrees in the community are linked to clinical diagnoses. In past work, family studies have shown that relatives of individuals with a clinical psychiatric disorder show elevated traits related to that disorder more often compared to relatives of controls. Typical family studies

cannot however disentangle whether such familiarity is due to the family environment or 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 see e.g., (4). Finally, reviews of the literature have noted that the same environmental risk factors show associations with both disorders and less severe manifestations of symptoms - see, for example, for schizophrenia and psychotic-like experiences (5).

The results reported in this journal's new paper (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 summarises what has been reported for four psychiatric disorders from recent GWAS studies. The "percent variance predicted in disorder itself by GPS" column shows the amount of variance in liability that the GPS predicts in the same disorder in an independent sample. The "percent variance predicted in related trait by disorder GPS" 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 to predicting the disorder itself is demonstrated. For these four psychiatric disorders, GPS associated with each disorder currently predicts 10-20% variance in the related trait compared to what it predicts in itself (Table 1) (4). Nevertheless, for all these four disorders, and now also for Tourette syndrome, we appear to have evidence of some overlap in common additive genetic influences between milder subclinical and more severe clinically-recognised forms of psychopathology.

Why do disorder GPS 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 disorders tend to include more than simply scoring high on trait scales. Disorder 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's new paper in *Biological Psychiatry* expands our understanding of the links between subclinical and clinical manifestations of psychopathology, and makes a valuable new contribution to the growing field of the molecular genetics of Tourette's syndrome.

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Table 1. Effect sizes of genome-wide polygenic score predictions for four psychiatric disorders and their related dimensional traits

| Disorder | Related trait | Variance predicted in disorder itself by disorder GPS (%) (A) | Variance predicted in related trait by disorder GPS (%) (B) | B/A |
|---------------|-------------------------|---|---|-----|
| Autism | Autistic traits | 1.13% (6) | .1% (6) | 9% |
| Schizophrenia | Negative symptom traits | 7% (3) | .7% (7) | 10% |
| Depression | Depressive traits | .72% (8) | .11% (9) | 15% |
| ADHD | ADHD traits | 3.71% (10) | .8% (10) | 22% |