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Archival Report

Polygenic Risk Scores Derived From a Tourette Syndrome Genome-wide Association Study Predict Presence of Tics in the Avon Longitudinal Study of Parents and Children Cohort

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ABSTRACT

BACKGROUND: Tourette syndrome (TS) has a well-established genetic background, but its genetic architecture remains largely unknown. The authors investigated the role of polygenic risk scores (PRSs) derived from a TS genome-wide association study in relation to the occurrence of tics and associated traits in a general population cohort.

METHODS: Using the most recent TS genome-wide association study (n = 4819 cases; n = 9488 controls) as the discovery sample, PRSs were calculated in Avon Longitudinal Study of Parents and Children participants (n = 8941). Regression analyses were used to assess whether PRS predicted the presence and chronicity of tics, and symptom severity of obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder in Avon Longitudinal Study of Parents and Children participants.

RESULTS: Following correction for multiple testing, the PRS significantly predicted the presence (R^2 = .48%, p empirical = .01, Q = .04) but not the chronicity (R^2 = .16%, p empirical = .07, Q = .14) of tics in the Avon Longitudinal Study of Parents and Children cohort; it did not predict the severity of obsessive-compulsive disorder (R^2 = .11%, p empirical = .11, Q = .15), attention-deficit/hyperactivity disorder (R^2 = .09%, p empirical = .19, Q = .21), or autism spectrum disorder (R^2 = .12%, p empirical = .09, Q = .14).

CONCLUSIONS: The authors found a significant polygenic component of tics occurring in a general population cohort based on PRS derived from a genome-wide association study of individuals with a TS diagnosis. This finding supports the notion that tics along a spectrum from nonclinical to clinical symptom levels share a similar genetic background.

Keywords: Attention-deficit/hyperactivity disorder, Autism spectrum disorder, Avon Longitudinal Study of Parents and Children (ALSPAC), Obsessive-compulsive disorder, Polygenic risk score, Tourette syndrome

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Tourette syndrome (TS) has a well-established genetic background, with twin study–based heritability estimates in the range of 25%–56% (1,2). While its genetic etiology remains elusive, common polygenic or de novo variation is involved (3,4). The first genome-wide association study (GWAS) of TS did not identify genome-wide significant single nucleotide polymorphisms (SNPs) (5). In line with approaches used in the study of other neuropsychiatric disorders such as schizophrenia (6), an increase in sample size will promote the detection of genome-wide significant SNPs; however, a single SNP explains only a small portion of the total genetic risk of complex heterogeneous disorders such as TS (7). Genome-wide complex trait analysis using data from the first TS GWAS (5) indicated that common variation distributed across the genome accounts for a large proportion of TS heritability (7). Therefore, using subthreshold GWAS signals may offer a better approach in understanding the involvement of common genetic variation in TS.

One method that includes subthreshold GWAS signals is a polygenic risk score (PRS) analysis in which an aggregate score derived from the risk alleles based on a TS GWAS is used to predict tic phenotypes in an independent sample. So far, two TS PRS studies have been conducted, of which the first found that TS PRS (nonsignificantly) predicted 0.6% of the phenotypic variance in a TS case-control target cohort, the nonsignificant prediction probably due to a modest sample size (a target sample of 265 cases and 196 controls) (8). The second study found that TS PRS was significantly associated with a symmetry phenotype (R^2 = .57%), as defined by factor analysis that included items such as evening up and ordering things (4), behaviors that are often seen in participants with TS and obsessive-compulsive disorder (OCD).

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While these studies (4,7,8) pointed to a polygenic component of TS in clinical samples, it is currently not known whether TS-based PRS would predict the broader spectrum of tics in the general population. The notion of a tic disorder spectrum has been supported by some studies that describe a continuum along TS and chronic motor and/or vocal tic disorders (6,9), which also include transient tic disorder (2,10).

The current study investigated whether PRS derived from the most recent GWAS of individuals diagnosed with TS would predict the presence and chronicity of tics in a population-based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) (11,12). We also related the TS GWAS–based PRS to symptoms of OCD, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) within ALSPAC, given the high comorbidity rates between TS and these associated disorders, which suggest at least a partially shared genetic etiology (4,13–15).

METHODS AND MATERIALS

Participants

The ALSPAC is an ongoing population-based birth cohort study of 15,247 mothers and their children residing in the county of Avon (United Kingdom) (11,12,16,17). Participants are assessed in regular intervals from birth, using clinical interviews, self-reported questionnaires, medical records, and physical examinations. The study website contains details of available data through a fully searchable data dictionary: http://www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local research ethics committees. All participants provided written informed consent or assent.

Phenotypic Assessment Within ALSPAC

Tics. The presence of tics was assessed during nine time points: annually between the ages 1.5 and 7.6 years, at age 10.7, and at age 13.8. Parents received a questionnaire in which they reported whether their child "has a tic or twitch" ("Never" = 0, "Less than once a week/once a week or more" = 1), and at age 10 years, whether their child "has any tics or twitches in the past year that he/she can't seem to control" ("No" = 0, "Yes" = 1). At age 13, the presence of specific motor and/or vocal tics was reported by the mothers using a questionnaire containing five questions regarding the presence of repeated movements in the past year of the 1) face and head, 2) neck, shoulder, or trunk, 3) arms, hands, legs, feet; and of 4) repeated noises and sounds and 5) repeated words or phrases; ("not at all" = 0, "definitely" and "probably" = 1). The frequency of these tic symptoms was also assessed ("less than once a month" = 1; "1–3 times a month" = 2; "about once a week" = 3; "more than once a week" = 4; "every day" = 5).

Consistent with the methods in previous ALSPAC publications (18,19), we used three diagnostic constructs to define the presence of tics (0 = absent, 1 = present): 1) The presence of "Tics intermediate" [approximating the "Tourette syndrome/chronic tic disorder intermediate" definition by Scharf *et al.* (18)], which required the presence of motor and/or vocal tics occurring at least once a week at age 13 years and at least one positive response to a tic-screening question between the ages of 1.5 and 7 years and at age 10 years; 2) The presence of "Tics broad" [approximating the "Tourette syndrome/chronic tic disorder broad" definition by Scharf *et al.* (18)], which required only the presence of motor and/or vocal tics occurring at least once a week at age 13 years; and 3) the presence of "Tics all" that required only at least one positive answer to the tic-screening question between the ages 1.5 and 13 years. Moreover, we calculated a chronicity score (possible range 0–13), i.e., the sum score of the number of times tics were present up to age 10.7 years (possible range 0–8) plus the number of different tic symptoms at 13.8 years (possible range 0–5). Consistent with a previous publication of Scharf *et al.* (18), we removed participants who likely had nontic movement such as stereotypies (e.g., only reporting repeated movements of arms, legs, or feet) or isolated echolalia. However, we did not exclude participants based on IQ. Furthermore, we did not use the diagnostic construct "TS/chronic tic narrow" as defined by Scharf *et al.* (18) because of an insufficient sample size of cases ($n < 100$).

OCD Severity. We used the parent-on-child Development and Well-Being Assessment (20) questionnaire data as administered at ages 7.5 and 13.8 years, which has shown high validity to detect obsessions and compulsions (21). A total of 10 OCD symptoms were extracted (e.g., excessive cleaning, checking things) and scored as absent ("no" = 0), "sometimes present" = 1, or "often present" = 2 (11,12,17). OCD symptom severity was based on the highest sum score (i.e., either at age 7.5 or at age 13.8 years, whichever was highest) of all 10 items (possible range 0–20), using prorating in case of less than 30% missing items (11,12).

ADHD Severity. The Development and Well-Being Assessment at age 7.5 years was also used to assess 18 ADHD symptoms reported on a 3-point scale ("no" = 0, "a little more than others" = 1, "a lot more than others" = 2) (20). ADHD symptom severity was calculated as the sum score of all 18 items, again using prorating when <30% of the items were missing (possible range 0–36) (11,12,22).

ASD Severity. The Social Communication Disorders Checklist (23) was used to assess 12 ASD symptoms relating to social and emotional skills (e.g., "not aware of other people's feelings," "does not realize when others are upset or angry") by parental report ("not true" = 0, "quite or sometimes true" = 1, "very often true" = 2) at age 7.5 years. The Social Communication Disorders Checklist has been demonstrated to have excellent internal consistency (0.93) and test-retest reliability (0.81), making it a valid screening questionnaire for autistic traits (23). ASD symptom severity reflected the sum score of all 12 items using prorating (possible range 0–24) (11,12,24,25).

Genotyping

Within ALSPAC, genotype data was available for 9915 children of the total 14,541 ALSPAC participants. Genotyping was done using the Illumina HumanHap550 quad genome-wide SNP genotyping platform (Illumina, San Diego, CA). We applied standard quality controls, including exclusion of individuals

with excessive missingness (i.e., >3%), gender mismatch, excessive or minimal heterozygosity, cryptic relatedness as measured by identity by descent (genome-wide identity by descent >10%), duplicate samples, and non-European ancestry as defined by multidimensional scaling modeling using the HapMap Phase II (release 22) reference populations. SNPs that showed excessive missingness (i.e., call rate <95%), minor allele frequency <1%, or a departure from Hardy-Weinberg equilibrium (p value $< 5 \times 10^{-7}$) were excluded. The data set contained 500,527 SNPs after quality control. To increase the coverage of SNPs, genotype imputation was performed with Impute2 (version 2.2.2) (26) and phasing by ShapeIt (version 2.r727) (27) using the 1000 genomes phase 1 version 3 (release date Mar 21, 2011) as a reference data set. Final quality control checks were performed on the imputed data set; any SNPs with minor allele frequency <1%, excessive missing rate (call rate <95%), Impute2 information quality metric <0.8, and not confirming to Hardy-Weinberg equilibrium (p value $< 5 \times 10^{-7}$) were removed. After data cleaning, a total of 8941 individuals (4580 male 4361 female individuals) and 6,976,085 SNPs remained in the ALSPAC data set. The final number of SNPs eligible for analyses (SNPs present in both the discovery and target data sets) was 6,425,471.

PRS Calculations

PRSs were based on summary statistics of a GWAS of 4819 TS cases (75% male) and 9488 controls (43% male) (28) (Table 1). Cases for the GWAS study had mostly been recruited from TS specialty clinics. The calculation, application, and evaluation of the PRS was performed with PRSice (2.1.2.beta; github.com/choishingwan/PRSice/) (29). PRSice relies on PLINK to perform necessary cleaning steps prior to PRS calculation (29,30). SNPs that were present exclusively in the second GWAS data set or in the ALSPAC data set, as well as strand-ambiguous SNPs, were removed prior to the risk scoring. Clumping was applied to thin SNPs according to linkage disequilibrium and p value: the SNP with the smallest p value in each 250-kilobase window was retained, and all those in linkage disequilibrium ($r^2 > .1$) with this SNP were removed. The major histocompatibility complex (MHC) locus was also removed because of its complex linkage disequilibrium structure.

The PRS was calculated for each individual as a sum of the risk alleles they carried, weighted by the odds ratio estimated by the TS GWAS study. This calculation was performed at different (GWAS) p-value thresholds of the risk alleles (between $p = .0001$ and $p = .9999$). The strength of the polygenic signal was evaluated across all p-value thresholds (Supplemental Figures S1 and S2).

Statistical Analysis

Logistic regression analyses were applied to predict all phenotypic binary outcome measures (i.e., presence of "Tics intermediate," "Tics broad," and "Tics all") and linear regression analyses to predict the continuous outcome measures (chronicity score, OCD, ADHD, and ASD symptom severity). Considering that all continuous outcome measures were highly positively skewed (Supplemental Figure S3), as a sensitivity analysis, we also estimated the regression parameters using a negative binomial regression (Supplemental Table S1). Gender was included as a covariate in all regression models to correct for gender differences. We did not include ancestry-informative dimensions as covariates in the regression models, as we did not find evidence for bias due to population stratification (for results see Supplemental Figures S4–S6 and Supplemental Tables S2 and S3).

We first predicted the presence of tics (according to the "Tics intermediate," "Tics broad," and "Tics all" definitions) and the chronicity score using the TS PRS. We then predicted OCD, ADHD, and ASD symptom severity using TS PRS. Note that all analyses included the total ALSPAC sample, irrespective of comorbidity (tics, OCD, ADHD, ASD). We report the

Table 1. Clinical Characteristics of Study Participants in the Discovery Sample (TS GWAS 2)[a] and Target Sample (ALSPAC)[b]

	Cases			Controls		
Phenotype	*n*	*n* Male	% Male	*n*	*n* Male	% Male
TS GWAS 2[a]	14,307					
TS	4819	3627	75	9488	4073	43
ALSPAC[b]	8941					
Tics intermediate[c]	101	74	73	4712	2325	49
Tics broad[c]	612	395	65	4201	2004	48
Tics all[c]	1043	641	61	3770	1758	47

	n	*n* Male	% Male	Mean	SD	Observed Range
ALSPAC						
Chronicity score[d]	4813	2399	50	0.45	1.06	0–9
OCD symptom severity[e]	6006	3085	51	0.45	1.15	0–16
ADHD symptom severity[f]	6046	3096	51	4.88	6.75	0–36
ASD symptom severity[g]	6019	3088	51	2.82	3.71	0–24

ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; GWAS, genome-wide association study; OCD, obsessive-compulsive disorder; TS, Tourette syndrome.

[a]D. Yu *et al.* (28).

[b]Golding *et al.* (11) and Golding *et al.* (12).

[c]The presence of tics in ALSPAC participants was defined by three different categorizations: "Tics intermediate" [approximating the "TS/chronic tic disorder (CT) intermediate" by Scharf *et al.* (18)], which included individuals who experienced motor and/or vocal tics at least once a week at age 13 years and experienced at least one tic symptom between the ages of 1.5 and 10 years; "Tics broad" [approximating the "TS/CT broad" by Scharf *et al.* (18)], which included individuals who have experienced motor and/or vocal tics occurring at least once a week at age 13 years; and "Tics all," which included individuals who reported at least one positive answer to the tic-screening question between the ages 1.5 and 13 years.

[d]The chronicity score is the sum of the number of times tics were present up to age 10.7 years plus the number of different tic symptoms at 13.8 years (11,12).

[e]Worst-ever OCD symptom severity based on the Development and Well-Being Assessment (20) at age 7 and at age 13 years using 10 items.

[f]Based on the Development and Well-Being Assessment (20) using 18 items.

[g]Based on the Social Communication Disorder Checklist (23) using 12 items.

PRS model with the most predictive p value thresholds as measured by Nagelkerke's pseudo R^2; model fits at different p-value thresholds can be found in Supplemental Figures S1 and S2. Furthermore, to determine whether removal of the MHC locus significantly impacted our analyses, we also performed the analyses with the inclusion of the MHC locus (Supplemental Table S4).

Considering that the PRSs were calculated at many different p-value thresholds, we adjusted for multiple testing and overfitting using the permutation option in PRSice (29); empirical p values were obtained by comparing the uncorrected p values from the regression models with p values obtained from a null distribution generated by permuting the phenotypes 11,000 times. The empirical p values were corrected for multiple testing for the number of p-value thresholds tested and subsequently corrected for the number of phenotypes ($N = 7$) applying the Benjamini–Hochberg false discovery rate method. The significance threshold was met if the false discovery rate–adjusted empirical p value (i.e., Q) was $< .05$; we present both the empirical and the false discovery rate–adjusted empirical p values (Table 2).

RESULTS

Sample Description

Table 1 presents the clinical characteristics of participants from the discovery and target samples for whom both genotype and phenotype data were available. Within the ALSPAC cohort, the prevalence rates of "Tics intermediate," "Tics broad," and "Tics all" were 1.3% (101 of 8941 participants), 6.8% (612 of 8941 participants), and 11.7% (1043 of 8941 participants) (Table 1).

PRS Analyses

Presence of Tics. Following correction for multiple testing for the number of p-value thresholds and for the number of phenotypes tested, PRS based on the TS GWAS predicted the presence of tics in the ALSPAC population cohort as defined by the "Tics broad" criteria ($R^2 = .48\%$; p empirical = .01, Q = .04) and "Tics all" definition ($R^2 = .46\%$; p empirical = .002, Q = .01), but did not predict tics per the "Tics intermediate" definition (p empirical = .95, Q = .95) (Figure 1 and Table 2).

Chronicity Score. There was no significant association between the TS PRS and the chronicity score ($R^2 = .16\%$, p empirical = .07, Q = .14) (Figure 1 and Table 2). Considering that the chronicity score was highly positively skewed (Supplemental Figure S3), we also performed negative binomial regressions and found similar results (Supplemental Table S1).

OCD, ADHD, and ASD Symptom Severity. The TS-derived PRS was not able to predict OCD symptom severity ($R^2 = .11\%$; p empirical = .11, Q = .15), ADHD symptom severity ($R^2 = .09\%$; p empirical = .19, Q = .21), and ASD symptom severity ($R^2 = .12\%$; p empirical = .09, Q = .14) in the ALSPAC cohort (Figure 1 and Table 2). As a sensitivity analysis, we also performed negative binomial regressions and found similar results (Supplemental Table S1).

Finally, we found no significant differences in above-mentioned results when the MHC locus was included in the calculation of the PRS (Supplemental Table S4).

DISCUSSION

This study suggests that polygenic scores derived from a large GWAS of individuals with TS predicts the broader spectrum of tic phenotypes in a population cohort (11,12). Our findings support the involvement of multiple common variants in tic phenotypes in the general population and validate the relevance of the most recent TS GWAS. A similar conclusion was reached in an ADHD PRS study (25) that found a polygenic component for ADHD traits in the ALSPAC sample. Our tic phenotypes ranged from a lenient definition that captured children who experienced at least one (transient) tic symptom to a more narrowly defined phenotype that more closely resembles a diagnosis of a chronic tic disorder. This was done to reflect the notion that individuals with a TS diagnosis represent the extreme end of a spectrum of tic disorders (13). Results were not driven by the subsample containing exclusively the most narrowly defined tic phenotype, underscoring the relationship of the broader tic phenotype with TS-based PRS.

The ALSPAC sample likely included less severe cases compared with the discovery sample; the discovery sample included TS cases mainly recruited through specialty clinics

Table 2. Number of SNPs Contributing to the Prediction of Each Phenotype at the p-Value Threshold of the Best-Fitted Polygenic Risk Score Model

Phenotype[a]	Best-Fitting p_T	n SNPs at p_T	β	Nagelkerke's Pseudo R^2	p Empirical[b]	FDR Q Value[c]
Tics Intermediate	.0001	162	17.3	.0013	.95	.95
Tics Broad	.0022	2386	111.2	.0048	.01	.04
Tics All	.0022	8448	98.2	.0046	.002	.01
Chronicity Score	.0724	40120	152.4	.0016	.07	.14
OCD Symptom Severity	.003	470	22.7	.0011	.11	.15
ADHD Symptom Severity	.00015	262	85.9	.0009	.19	.21
ASD Symptom Severity	.0016	1969	169	.0012	.09	.14

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; FDR, false discovery rate; OCD, obsessive-compulsive disorder; p_T, p-value threshold; SNP, single nucleotide polymorphism.

[a]For a definition of the outcome measures Tics intermediate, Tics broad, and Tics all, see Table 1.

[b]Empirical p-value corrected for the number of p-value threshold tested by permuting the phenotype 11,000 times.

[c]Empirical p-value corrected for the number of phenotypes tested using the Benjamini–Hochberg false discovery rate (37).

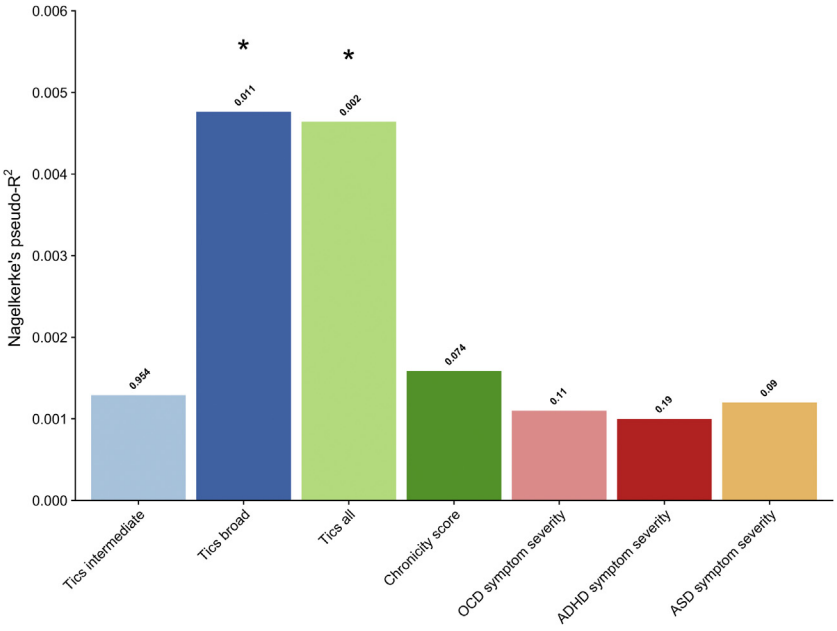

Figure 1. Variance explained by the polygenic risk score for each tested phenotype in the Avon Longitudinal Study of Parents and Children target sample (8,9), based on the second Tourette syndrome (TS) genome-wide association study (TS GWAS 2) (28) as discovery sample. The presence of tics was defined by three different categorizations: "Tics intermediate" [approximating "TS/chronic tic disorder (CT) intermediate" by Scharf *et al.* (18)], which included individuals who experienced motor and/or vocal tics at least once a week at age 13 years and experienced at least one tic symptom between the ages of 1.5 and 10 years; "Tics broad" [approximating "TS/CT broad" by Scharf *et al.* (18)], which included individuals who have experienced motor and/or vocal tics occurring at least once a week at age 13 years; and "Tics all," which included individuals who reported at least one positive answer to the tic-screening question between the ages 1.5 and 13 years. The chronicity score is the sum of the number of times tics were present up to age 10.7 years plus the number of different tic symptoms at 13.8 years (11,12). The risk scores were calculated at different *p*-value thresholds ($p < .0001$ with increments of .00005 to $p < 1$), and the model that explained the most variance is reported. *Significance after correction for multiple testing of the different *p*-value thresholds and for the number of phenotypes tested using the false discovery rate ($Q < .05$). ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder.

(28). The prevalence rates of the "Tics broad" and the "Tics all" groups were markedly higher than was reported for TS (0.3%–5.7%) (31), indicating that these groups likely included more individuals on the subclinical end of the tic disorder spectrum. Despite differences in case severity and in the prevalence of co-occurring OCD and ADHD between the discovery and the target (18) data sets, we were able to find a significant polygenic signal, suggesting that severe and less severe tic cases share a common genetic etiology.

We observed that the tic group that comes closest to a TS diagnosis ("Tics intermediate") was poorly predicted, which may be due to a low prevalence in the ALSPAC cohort. As we moved toward broader tic definitions, we saw an improvement of prediction, probably because of a higher prevalence (and therefore more statistical power) of these phenotypes (i.e., "Tics broad," also resembling a chronic tic disorder but not necessarily with an early onset, and "Tics all," covering at least one tic symptom) in the ALSPAC cohort.

The TS PRS did not predict OCD, ADHD, and ASD symptom severity in the ALSPAC sample, suggesting that different genes underlie these comorbid disorders than those involved in the genetic architecture of tic disorders. It is also possible that the TS PRS derived from a fairly clinical sample is not suitable for predicting OCD, ADHD, and ASD symptom severity in a population cohort that includes less severe cases. Furthermore, the TS GWAS sample size may have been too low in relation to cross-disorder comparisons. In line with our finding, Yu *et al.* (7) found that TS-based PRS did not predict OCD status, perhaps again due to a small TS discovery sample ($N = 776$ cases) and the restriction of the polygenic risk scores to only SNPs with a minor allele frequency >5% (7). Still, one PRS study (4) and three heritability studies (6,14,32) suggested a shared genetic background between TS and OCD. Little is known about the possible genetic overlap between TS and ADHD, with one PRS study agreeing with our finding of no overlap (4) and two heritability studies (14,33) suggesting overlap. Lastly, consistent with our findings, Anttila *et al.* (14) found no evidence for shared genetic risk factors between TS and ASD. Nevertheless, a few candidate gene studies implicated the same genes in both ASD and TS (e.g., *IMMP2L* and *NRXN1*) (34,35). We conclude that larger samples are needed to investigate similarities and dissimilarities in the genetic architecture of tic and associated disorders.

A strength of our study was the use of a currently relatively large discovery and target sample (11,12). Furthermore, the participants in the ALSPAC sample were all from the same geographical location, and the MDS plots indicated that they are homogenous in terms of ancestry (17). A limitation of PRS studies is that they capture only common variants of small effect sizes and miss rare genetic variants with larger effect sizes, hence providing an incomplete picture of the full genetic architecture of neuropsychiatric disorders. Rare de novo damaging variants may contribute to the risk of TS in ≤12% of all clinical cases (3). We underscore that the explained variance found in our study was small yet in line with what previously has been found in other neuropsychiatric disorders (between 0.1% and 0.7% explained variance) within the ALSPAC sample (22,25,36). Another limitation is that tics were reported by parents and not by clinicians. In conclusion, we were able to discriminate between children with and without tics in a general population cohort using PRS derived from the most recent TS GWAS. Our findings support the notion that tics along a spectrum from nonclinical to clinical levels share a similar genetic background. We did not find evidence for a shared genetic etiology of tic, OCD, ADHD, and ASD symptoms. Future PRS studies will greatly benefit from the increasing

sample sizes of GWASs, as they will enhance the predictive capabilities of PRS models. Furthermore, PRS can serve as an excellent starting point for gene–environment interaction studies.

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