Genetic Association Study of Childhood Aggression across raters, instruments and age

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Abstract

Background

Human aggressive behavior (AGG) has a substantial genetic component. Here we present a large genome-wide association meta-analysis (GWAMA) of childhood AGG.

Methods

We analyzed assessments of AGG for a total of 328,935 observations from 87,485 children (aged 1.5 – 18 years), from multiple assessors, instruments, and ages, while accounting for sample overlap. We performed an overall analysis and meta-analyzed subsets of the data within rater, instrument, and age.

Results

Heritability based on the overall meta-analysis (AGG_{all}) that could be attributed to Single Nucleotide Polymorphisms (SNPs) was 3.31% (SE=0.0038). No single SNP reached genome-wide significance, but gene-based analysis returned three significant genes: *ST3GAL3* (*P*=1.6E-06), *PCDH7* (*P*=2.0E-06) and *IPO13* (*P*=2.5E-06). All three genes have previously been associated with educational traits. Polygenic scores based on our GWAMA significantly predicted aggression in a holdout sample of children and in retrospectively assessed childhood aggression. We obtained moderate-to-strong genetic correlations (r_g's) with selected phenotypes from multiple domains, but hardly with any of the classical biomarkers thought to be associated with AGG. Significant genetic correlations were observed with most psychiatric and psychological traits (range $|r_g|$: 0.19 – 1.00), except for obsessive-compulsive disorder. Aggression had a negative genetic correlation (r_g=~-0.5) with cognitive traits and age at first birth. Aggression was strongly genetically correlated with smoking phenotypes (range $|r_g|$: 0.46 – 0.60). Genetic correlations between AGG and psychiatric disorders were strongest for mother- and self-reported AGG.

Conclusions

The current GWAMA of childhood aggression provides a powerful tool to interrogate the genetic etiology of AGG by creating individual polygenic scores and genetic correlations with psychiatric traits.

Introduction

Phenotypic definitions of aggressive behavior (AGG) range from broadly defined externalizing problems to narrow conceptualizations like chronic physical aggression (1). Generally, any action performed with the intention to harm another organism can be viewed as AGG (2,3). AGG is considered a common human behavior (4), with people varying in the degree of AGG they exhibit (5). AGG is part of numerous disorders (6), including oppositional defiant disorder (ODD) and conduct disorder (CD)(7). In its extreme forms, AGG may be considered a disorder by itself – inflicting a huge personal and financial burden on the individual, their close ones, and society as a whole (8). In general population studies, AGG is commonly treated as a quantitative trait where pathological AGG lies at the extreme end of the continuum (9–11).

AGG typically is displayed early in life, after which symptoms tend to diminish (12,13) – although in some individuals, AGG persists into adulthood (14). Childhood AGG co-occurs with many other behavioral, emotional, and social problems (15,16); and is associated with increased risk of developing negative outcomes later in life, including cannabis abuse (17), criminal convictions (18), anxiety disorder (19), and antisocial personality disorder (20). Not all associated outcomes are harmful (21). For example, children who learn to control their impulses and apply aggressive acts as a well-timed coercion strategy are generally more liked by their peers and score higher on social dominance (22).

Despite a heritability of ~50% (5,23), genome-wide association studies (GWASs) on AGG(-related traits) have not identified genome-wide significant loci that replicated (1). Childhood cohorts often have rich longitudinal data and assessments from multiple informants. In AGG, twin studies have reported moderate-to-high genetic correlations (r_g's) among instruments, raters, and age (24–26); and the power to detect genomic loci for AGG might increase via a multivariate genome-wide association meta-analysis (GWAMA) (27,28). Childhood behavior is context-dependent. At home, parents share part of their genome with their offspring and, most often, a household. Parental genomes can influence the home

environment, and it is predominantly within this context that parents observe the child's behavior. At school, teachers are typically unrelated to the child; and observe the child in the context of a structured classroom, where they can judge the child's behavior against that of other pupils. These considerations support an approach in which all AGG data are simultaneously analyzed, while retaining the ability to analyze the data by rater or age. We developed an approach that allowed inclusion of repeated observations on the same subject – e.g. from multiple raters at multiple ages – and resolved issues of sample overlap at the meta-analysis level. By doing so, we make full use of all available data and maximize statistical power for gene discovery. By aggregating data at level of the meta-analysis, however, we simultaneously retain the flexibility to explore the genetic architecture of specific aspects of AGG.

Data on AGG from parent-, teacher-, and self-report in boys and girls aged 1.5 to 18 years were collected in 29 cohorts from Europe, USA, Australia, and New-Zealand; resulting in 328,935 observations from 87,485 participants. First, we combined all data to produce the largest GWAMA on childhood aggressive behavior to date. We computed polygenic scores (PGSs) to test out-of-sample prediction of AGG and explore the usefulness of the GWAMA results in future research (29). To assess genetic pleiotropy between AGG and associated traits, we estimated r_g's between our GWAMA and a preselected set of phenotypes from multiple domains. Second, meta-analyses were done by rater, instrument, and age. We subsequently estimated r_g's across these assessments of AGG. To identify context-specific genetic overlap with other phenotypes, r_g's were also estimated between rater-specific assessments of AGG and these phenotypes.

Methodology

Data description

Extended description of the cohorts and phenotypes is supplied in the Supplemental Text and Supplementary Tables 1–9. Cohorts with assessment of AGG in genotyped children and adolescents took part in the meta-analysis. AGG was assessed on continuous scales, with higher scores indicating higher levels of AGG. Within cohort, samples were stratified by (a) rater, (b) instrument, and (c) age, maintaining at least 450 observations in each stratum. Cohorts ran a univariate GWAS for each stratum within each cohort. To account for dependence within cohort during the meta-analysis (see Supplementary Text), each cohort supplied the phenotypic covariance matrix between the AGG measures (Supplementary Table 10) and the degree of sample overlap (Supplementary Table 11) between the different strata. We assumed no sample overlap across cohorts, and set phenotypic correlations among cohorts to zero. Phenotypic correlations of zero within cohort correspond to independent sub-samples. Supplementary Figure 1 shows the distribution of phenotypic correlations across all AGG measures, with phenotypic correlations of zero omitted from the figure. Overall, phenotypic correlations ranged between 0.1 and 0.4, with a median value of 0.29. When stratified by rater, phenotypic correlations were more heavily centered around 0.4. The maximum number of correlations within a specific age is three based on four raters, with the largest number of observations within age-bin around age 12 years. Within this age group, phenotypic correlations among raters ranged between 0.22 and 0.65, with a median of 0.34. The lowest phenotypic correlations were observed between teachers and parents. We restricted analyses to individuals of European ancestry, since limited data were available on individuals of non-European ancestry.

In total, 29 cohorts contributed 163 univariate GWASs, based on 328,935 observations from 87,485 unique individuals (Supplementary Table 2). Children were 1.5 to 18 years old at assessment, or retrospectively assessed at within these ages. Cohorts supplied between 1 and 26 GWASs. Approximately 50% of the subjects was male. Most GWASs were based on maternal- (52.4%) and self-assessment (25.1%), with the remainder based on teacher (12.4%) and paternal report (10.1%). After

296 quality control on the univariate GWASs (see Supplementary Text), between 3.47M SNPs and 7.28M
297 SNPs were available for meta-analysis (see Supplementary Figure 2 and Supplementary Table 9).
298
299 **Meta-analysis**
300 Within cohort, measures of AGG may be dependent due to including repeated measures of AGG over
301 age and assessments from multiple raters. To account for the effect of sample overlap, we applied a
302 modified version of the multivariate meta-analysis approach developed by Baselmans *et al* (28) (see
303 Table 1). Instead of directly estimating the dependence among GWAS test statistics using the cross-trait-
304 intercept (CTI) with Linkage Disequilibrium SCore regression (LDSC)(30,31), the expected pairwise CTI
305 value was calculated (Table 1) using the observed sample overlap and phenotypic covariance. Effective
306 sample sizes (N_{eff}) were approximated using the third formula in Table 1. When there is no sample
307 overlap (or phenotypic correlation equal to zero) between all GWASs – i.e. CTI is an identity matrix – N_{eff}
308 is equal to the sum of sample sizes.
309 First, we meta-analyzed all available GWAS results (AGG_{all}). Second, we meta-analyzed the
310 available data within rater (rater-specific GWAMAs). Third, rater-specific age-bins were created for
311 mother- and self-reported AGG based on the mean ages of the subjects in each GWAS (age-specific
312 GWAMA; see Supplementary Text and Supplementary Table 12). To ensure that the age-specific
313 GWAMAs would have sufficient power for subsequent analyses, age-bins were created such that the
314 *univariate* number of observations (N_{obs}) exceeded 15,000. For father- and teacher-reported AGG there
315 were insufficient data to run age-specific GWAMAs. Fourth, we performed instrument-specific GWAMAs
316 for (a) the ASEBA scales and (b) for the SDQ, because for these two instruments the total *univariate* N_{obs}
317 exceeded 15,000.
318 SNPs that had MAF<0.01, N_{eff}<15,000, or were observed in only one cohort were removed from
319 further analyses. SNP-heritabilities (h^2_{SNP}) and r_g's were estimated using LDSC (30,31). To ensure

320 sufficient power, r_g's across stratified assessments of AGG were only calculated if the Z-score of the

321 h^2_{SNP} for the corresponding GWAMA was 4 or higher (30).

322

323 **Gene-based tests**

324 For AGG_{all} a gene-based analysis was performed in MAGMA (32). The gene-based test combined *P*-

325 values from multiple SNPs to obtain a test statistic for each gene, while accounting for LD between the

326 SNPs. From the MAGMA website (see URLs) we obtained (a) a list of 18,087 genes and their start- and

327 end-positions, and (b) pre-formatted European genotypes from 1,000 Genomes phase 3 or the

328 reference LD. We applied a Bonferroni correction for multiple testing at α=0.05/18,087. A lookup for

329 significant results was performed in GWAS Catalog and PhenoScanner (see URLs).

330

331 **Polygenic scores**

332 All data were meta-analyzed twice more, once omitting all data from the Netherlands Twin Register

333 (NTR) and once omitting all Australian data (Queensland Institute for Medical Research [QIMR] and

334 Mater-University of Queensland Study of Pregnancy [MUSP]). For the target sample in the NTR we

335 considered mother-reported AGG at age 7 (*N*=4,491), which represents the largest NTR univariate

336 dataset. In the QIMR participants (*N*=10,706), we tested whether a childhood AGG PGS predicted adult

337 retrospective assessment of their own CD behavior during adolescence. Polygenic score analyses were

338 carried out by each cohort (see Supplementary Text). Briefly, in the NTR, 16 sets of clumped PGSs were

339 created based on *P*-value thresholds between 1 and 1.0E-05. To account for relatedness within the

340 target sample, prediction was performed using generalized equation estimation (GEE)(33). Age, age^2,

341 sex, dummy variables for genotyping array, first five ancestry-based principal components, and

342 interaction terms between sex and age, and sex and age^2 were included as fixed effects. To correct for

343 multiple testing, we applied a False Discovery Rate (FDR) correction at α=0.05 for 16 tests. QIMR

344 calculated different PGSs for seven *P*-value thresholds. Linear mixed models were fitted, which
345 controlled for relatedness using a genetic relatedness matrix; and sex, age, two dummy variables for the
346 GWAS array used, and first five ancestry-based principal components as covariates.
347
348 **Genetic correlation with external phenotypes**
349 We computed r_g's between AGG_{all} and a set of preselected outcomes (*N*=46; collectively referred to as
350 "external phenotypes"; Supplementary Table 14). Phenotypes were selected based on established
351 hypotheses with AGG and the availability of sufficiently powered GWAS summary statistics. We
352 restricted r_g's to phenotypes for which the Z-scores of the LDSC-based $h^2_{SNP} \geq 4$ (30). Next, we
353 estimated r_g's for all rater-specific assessments of AGG (except for father-reported AGG). Genomic
354 Structural Equation Modelling (Genomic SEM)(34) was applied to test if r_g's were significantly different
355 across raters. Specifically, for every phenotype, we tested whether (a) all three r_g's between phenotype
356 and rater-specific assessment of AGG – i.e. mother, teacher, and self-ratings – could be constrained at
357 zero, and (b) whether the r_g's could be constrained to be equal across raters. A χ^2 difference test was
358 applied to assess whether imposing the constraints resulted in a significant worse model fit compared to
359 a model where the r_g's between the phenotype and three rater-specific assessment of AGG were
360 allowed to differ. We applied a FDR correction at α=0.05 over two models for 46 phenotypes, for a total
361 of 92 tests. A FDR correction for 4 x 4 = 184 tests was applied to correct for multiple testing of whether
362 the genetic correlations were significantly different from zero.
363
364 ## Results
365 **GWAMA** of all GWAS results (AGG_{all})
366 We first meta-analyzed the effect of each SNP across all available univariate GWASs. Assuming a N_{eff} of
367 151,741, the h^2_{SNP} of AGG_{all} was estimated at 3.31% (SE=0.0038). The mean χ^2-statistic was 1.12 along

368 with an LDSC-intercept of 1.02 (SE=0.01). This indicated that a small, but significant, part of the inflation
369 in test statistic might have been due to confounding biases, which can either reflect population
370 stratification or subtle misspecification of sample overlap within cohorts. No genome-wide significant
371 hits were found for AGG_{all} (Figure 1). The list of suggestive associations (*P*<1.0E-05) is provided in
372 Supplementary Table 15. SNPs were annotated with SNPnexus (see URLs). The strongest association, in
373 terms of significance, was located on chromosome 2 (rs2570485; *P*=2.0E-07). The SNP is located inside a
374 gene desert, without any gene in 400Kbp in any direction. The second strongest independent
375 association was found with rs113599846 (*P*=4.3E-07), which is located inside an intronic region of
376 *TNRC18* on chromosome 7. None of the suggestive associations have previously been reported for AGG
377 or AGG-related traits (1).
378 We performed a lookup of previously reported genome-wide significant hits for AGG and AGG-
379 related traits in AGG_{all}. We restricted lookup to associations with autosomal SNPs that were reported in
380 samples of European ancestry, resulting in three loci (1). One genome-wide significant hit has previously
381 been reported for adult antisocial personality disorder (rs4714329; OR=0.63[1]; *P*=1.64E-09)(35). The
382 same SNP, however, had an opposite direction of effect in AGG_{all} (β=0.0022; *P*=0.41). Two genome-wide
383 significant hits have also been reported for antisocial behavior (36), one on chromosome 1 (rs2764450)
384 and one on chromosome 11 (rs11215217). While both SNPs have the same direction of effect, neither
385 SNP is associated with AGG_{all} (both *P*>0.5).
386
387 **Gene-based analysis**
388 After correction for multiple testing, the gene-based analysis returned three significant results
389 (Supplementary Table 16): *ST3GAL3* (ST3 beta-galactoside alpha-2,3-sialyltransferase3; *P*=1.6E-06),
390 *PCDH7* (protocadherin 7; *P*=2.0E-06) and *IPO13* (importin 13; *P*=2.5E-06). *ST3GAL3* codes for a type II

[1] Odds ratio was signed to the other allele in the original study

391 membrane protein that is involved in catalyzing the transfer of sialic acid from CMP-sialic acid to
392 galactose-containing substrates. *ST3GAL3* has been implicated in 107 GWASs, most notably on
393 intelligence and educational attainment. The top SNP in *ST3GAL3* (rs2485997; *P*=2.48E-06) is in strong
394 LD (r^2>0.8) with several other SNPs inside the gene body of *ST3GAL3* and in moderate LD (r^2>0.6) with
395 SNPs in several neighboring genes (Supplementary Figure 3). *PCDH7* codes for a protein that is
396 hypothesized to function in cell-cell recognition and adhesion. *PCDH7* has been implicated in 196
397 previous GWASs, including educational attainment and adventurousness. The top SNP for *PCDH7*
398 (rs13138213; *P*=1.44E-06) is in strong LD (r^2>0.8) with a small number of other closely located SNPs and
399 the signal for the gene-based test appears to be driven by two independent loci (Supplementary Figure
400 4). *IPO13* codes for a nuclear transport protein. *IPO13* has been implicated in the UKB GWASs on
401 whether a person holds a college or university degree and intelligence. The top SNP (rs3791116;
402 *P*=1.19E-05) is in moderate to strong LD with multiple SNPs (Supplementary Figure 5), including SNPs in
403 the neighboring *ST3GAL3* gene.
404
405 **Polygenic prediction**
406 After correction for multiple testing, 11 out of 16 PGSs were significantly correlated with mother-
407 reported AGG in 7-year-olds (Figure 2A). The scores explained between 0.036% and 0.44% of the
408 phenotypic variance. The significant correlations consistently emerged when scores including SNPs with
409 *P*>0.002 in the discovery GWAMA were considered. In the retrospective assessments of adolescent CD,
410 the PGSs calculated at various thresholds explained up to 0.2% of the variance in symptom sum scores
411 (Figure 2B). Generally, CD is significantly predicted at most thresholds, although, as we would expect
412 based on the SNP-heritability of AGG_{all}, the proportion of explained variance is small.
413
414 **Genetic correlation with other phenotypes**

415 Genetic correlations between AGG_{all} and a set of preselected phenotypes are shown in Figure 3 and
416 Supplementary Table 17. These phenotypes can broadly be grouped into psychiatric and psychological
417 traits, substance use, cognitive ability, anthropometric traits, classic biomarkers of AGG, reproductive
418 traits, and sleeping behavior. We included childhood phenotypes (e.g. birth weight and childhood IQ)
419 and disorders (e.g. ADHD and autism spectrum disorder [ASD]), but the majority of phenotypes were
420 adult characteristics or characteristics measured in adult samples. After correction for multiple testing,
421 36 phenotypes showed a significant r_g with AGG_{all} (P<0.02). Generally, the strongest positive r_g's were
422 seen with psychiatric traits – most notably ADHD, ASD, and major depressive disorder (MDD). The
423 strongest negative r_g's were found for age at smoking initiation, childhood IQ, and age at first birth.
424 Surprisingly, very small r_g's were observed between AGG_{all} and classical biomarkers of AGG (i.e. lipid
425 levels, heart rate, heart rate variability, and testosterone levels), with in many cases the sign of the
426 genetic correlation opposite to what was expected based on the literature on biomarkers of AGG.
427

428 **Stratified assessment of childhood aggressive behavior**

429 Separate meta-analyses were performed for raters, instruments, and age. None of these GWAMAs
430 returned genome-wide significant hits. Manhattan plots for the four rater-specific GWAMAs are shown
431 in Supplementary Figure 6. Estimates of h^2_{SNP} for rater-specific assessment of AGG are shown in
432 Supplementary Table 18. The lowest and highest h^2_{SNP} was observed for father-reported AGG
433 (h^2_{SNP}=0.04; SE=0.03) and teacher-reported AGG (h^2_{SNP}=0.08; SE=0.02), respectively. We estimated r_g's
434 between all rater-specific assessments of AGG, except for father-reported AGG, because of its non-
435 significant h^2_{SNP}. Genetic correlations were 0.67 (SE=0.10) between AGG_{Mother} and AGG_{Self}, and 0.81
436 (SE=0.11) between AGG_{Mother} and $AGG_{Teacher}$; and in both cases were significantly lower than 1. A
437 moderate r_g was observed between AGG_{Self} and $AGG_{Teacher}$ (r_g=0.46; SE=0.13).

We further performed two separate GWAMAs across all GWASs with commonly used rating scales – i.e. any ASEBA scale (AGG_{ASEBA}) and the SDQ (AGG_{SDQ}). SNP-heritabilities for AGG_{ASEBA} and AGG_{SDQ} were 0.031 (SE=0.0099) and 0.026 (SE=0.0086), respectively. The GWAMAs were insufficiently powered to estimate r_g across instrument-specific assessment of AGG.

Age-specific GWAMAs were performed for mother- and self-reported AGG, which made up 77.5% of the data. The mother- and self-reported data were split into respectively seven and three age-bins (Supplementary Table 12). Estimates of the SNP-heritabilities for each age-specific GWAMA are shown in Supplementary Table 19. For mother-reported AGG, h^2_{SNP} ranged between 0.012 and 0.078. For self-reported AGG, the highest h^2_{SNP} was seen for the retrospective data (h^2_{SNP}=0.12; SE=0.03), which also showed a significantly inflated intercept (1.05; SE=0.01). Genetic correlations could be estimated between AGG_{M17}, AGG_{S13} and AGG_{SR} (Supplementary Table 20).

Genetic correlation between rater-specific assessment of AGG and other phenotypes

We estimated rater-specific r_g's with other phenotypes, except for father-reported AGG, and tested if these r_g's could be constrained to be equal across mother-, teacher-, and self-reported AGG. For ADHD, ASD, MDD, schizophrenia, wellbeing, and self-reported health, constraining the r_g's to be equal across rater resulted in significantly worse model fit (Supplementary Table 21). For all these phenotypes, r_g's with teacher-reported AGG were consistently lower compared to mother- and self-reported AGG (Supplementary Figure 7 and Supplementary Table 17). For lifetime cannabis use, genetic correlations also could not be constrained to be equal across raters. Here, a relatively strong r_g was found with self-reported AGG (r_g=0.36; SE=0.08) compared to teacher- (r_g=0.13; SE=0.07) and mother-reported AGG (r_g=0.08; SE=0.08).

462 **Discussion**

463 We present the largest genome-wide association meta-analysis of childhood aggressive behavior to
464 date. Gene-based analysis implicated three genes – *PCDH7*, *ST3GAL3* and *IPO13* – based on the overall
465 meta-analysis (AGG_{all}), which did not return genome-wide significant SNPs. Lead SNPs in these genes
466 have previously been associated with educational outcomes. However, as these SNPs did not reach
467 genome-wide significance levels, further evidence is needed before considering them as risk variants for
468 AGG. Polygenic scores significantly predicted childhood AGG and retrospectively assessed adolescent
469 CD. Stratified analyses within AGG generally returned moderate to strong genetic correlations across
470 raters. We found substantial genetic correlations between AGG_{all} and a list of preselected external
471 phenotypes from various domains – including psychiatry and psychology, cognition, and anthropometric
472 and reproductive traits. Most notably was the perfect r_g between AGG_{all} and ADHD (r_g=1.00; SE=0.07).
473 This is in line with the moderate-to-strong phenotypic correlations that have consistently been found
474 across sex-, rater-, age- and instrument-specific assessment of AGG with attention problems and
475 hyperactivity (15). Significant genetic correlations were further observed with other psychiatric and
476 psychological traits (range $|r_g|$: 0.19 – 0.55). Negative genetic correlations (r_g=~-0.5) were found with all
477 three traits from the cognitive domain. Genetic correlations were positive with smoking initiation
478 (r_g=0.55; SE=0.04) and smoking quantity (r_g=0.46; SE=0.06), and negative with age at smoking initiation
479 (r_g=-0.60; SE=0.09).

480 We examined r_g's with classical biomarkers of AGG. Higher levels of aggression have been
481 associated with lower levels of LDL (37) and lower resting heart rate (38,39). We reported a positive,
482 albeit weak, r_g between AGG_{all} and LDL levels (r_g=0.15; SE=0.07), which has an opposite direction than
483 what was expected based on the literature. More broadly, except for HDL (r_g=-0.13; SE=0.07), all
484 measures of lipid levels returned significant positive r_g's with AGG_{all}, albeit weakly (r_g<0.2). No heart
485 rate measure showed a significant r_g with AGG_{all}. The relationship between testosterone levels and

486 (childhood) AGG in the literature is, at best, unclear. A positive association between AGG and
487 testosterone is often assumed, but both positive and negative phenotypic correlations have been
488 reported and seem context-dependent (40,41). We found significant negative r_g's between AGG_{all} and
489 testosterone levels in males and females ($|r_g|$<0.15). These r_g's should be interpreted with some caution
490 due to the design of the GWA studies: AGG was measured in children and young adolescents whereas
491 testosterone levels were measured in adults in the UK Biobank (42), and genetic stability of testosterone
492 levels might be low, at least for males (43). Genetic correlations with reproductive traits showed a
493 positive relation with having more children (r_g=0.27; SE=0.08) and having offspring earlier in life (r_g=-
494 0.60; SE=0.06), tending to confirm that not all associated outcomes are harmful.
495 The stratified design of our study also allowed for examination of the genetic etiology of AGG in
496 subsets of the data and examination of genetic correlations among raters. The r_g between AGG_{Mother} and
497 $AGG_{Teacher}$ (r_g=0.81; SE=0.11) was high, but less than unity, and is in line with previous findings of rater-
498 specific additive genetic effects in childhood AGG (44). Most external phenotypes showed comparable
499 r_g's with mother-, self-, and teacher-reported AGG. For ADHD, ASD, MDD, schizophrenia, wellbeing, and
500 self-reported health, r_g's differed significantly across raters. Weaker r_g's were consistently found in
501 teacher-reported AGG compared to mother- and self-reported AGG. These findings indicated the
502 presence of rater-specific effects when considering the genetic correlation of AGG with other outcomes.
503 r_g's are generally stronger in the psychopathology and psychological domains. A lack of power, however,
504 seems insufficient to explain why we found weaker r_g's between $AGG_{Teacher}$ and phenotypes from these
505 two domains. Other phenotypes, like smoking behavior, educational attainment, or age at first birth,
506 are, like psychopathological phenotypes, highly genetically correlated with AGG_{all}, but, unlike
507 psychopathologies, have near identical r_g's across raters. The rater-specific effects on r_g's between
508 childhood AGG and external phenotypes might be limited to psychopathologies, and future research

509 into the genetics of childhood psychopathology should consider these nuances in effects of assessment
510 of childhood AGG from various sources, be that multiple raters, instruments, or ages.

511 Despite the considerable sample sizes, we were still underpowered to compute genetic
512 correlations with other phenotypes while stratifying AGG over age or instrument. Age-stratified GWASs
513 in larger samples across development are a desirable target for future research. Because genetic
514 correlations can be computed between phenotypes for which a well-powered GWAS is available, age-
515 stratified GWAS of many developmental phenotypes, behavioral, cognitive, and neuroscientific can be
516 leveraged to better understand development of childhood traits.

517 We note that multivariate results should be interpreted with some caution. While combining
518 data from correlated traits can indeed improve power to identify genome-wide associations,
519 interpreting the phenotype may become less straightforward. In the current GWAMA, we have referred
520 to "aggressive behavior" and interpreted the results accordingly. Aggressive behavior, however, is an
521 umbrella term that has been used to identify a wide range of distinct – though correlated – traits and
522 behaviors (1).

523 Genome-wide association studies are increasingly successful in identifying genomic loci for
524 complex human traits and also in psychiatry, genetic biomarkers are increasingly thought of as
525 promising for both research and treatment (45). Genetic risk prediction holds promise for adult
526 psychiatric disorders (29) and it seems reasonable to expect the same for childhood disorders. Here we
527 found that polygenic scores explain up to 0.44% of the phenotypic variance in AGG in 7-year-olds and
528 0.2% of the variance in retrospectively reported adolescent CD. Future studies may explore the utility of
529 these PGSs in illuminating pleiotropy between AGG_{all} and other traits. A limiting factor in this regard was
530 the relatively low SNP-heritability, which puts an upper bound on the predictive accuracy of PGSs.
531 Sample sizes for AGG and other developmental phenotypes may need to increase by several orders of
532 magnitude before PGS become useful for individual patients.

533 Even in the absence of genome-wide significant SNPs, GWASs aid in clarifying the biology behind
534 complex traits. Our results show that, even without genome-wide significant hits, a GWAS can be
535 powerful enough to illuminate the genetic etiology of a trait in the form of r_g's with other complex
536 traits. Non-significant associations are expected to capture part of the polygenicity of a trait (31) and
537 various follow up-analyses have been developed for GWASs that do not require, but are aided by,
538 genome-wide significant hits (46). Polygenic scores aggregate SNP effects into a weighted sum that
539 indicates a person's genetic liability to develop a disorder. While their clinical application is still limited
540 in psychiatric disorders, they can already aid in understanding the pleiotropy among psychiatric and
541 other traits. Similarly, summary statistics-based genetic correlations (r_g) provide insight into the genetic
542 overlap between complex traits (30,47).
543

544 **URLs**

545 MAGMA: https://ctg.cncr.nl/software/magma
546 SNPnexus: https://www.snp-nexus.org/index.html (accessed on 28-8-2019)
547 GWAS Catalog: https://www.ebi.ac.uk/gwas/ (accessed on 29-8-2019)
548 PhenoScanner: http://www.phenoscanner.medschl.cam.ac.uk/ (accessed on 29-8-2019)
549

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556

557 **Author contributions** may be found in Supplemental Text

558

559 **Conflict of interests**

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569

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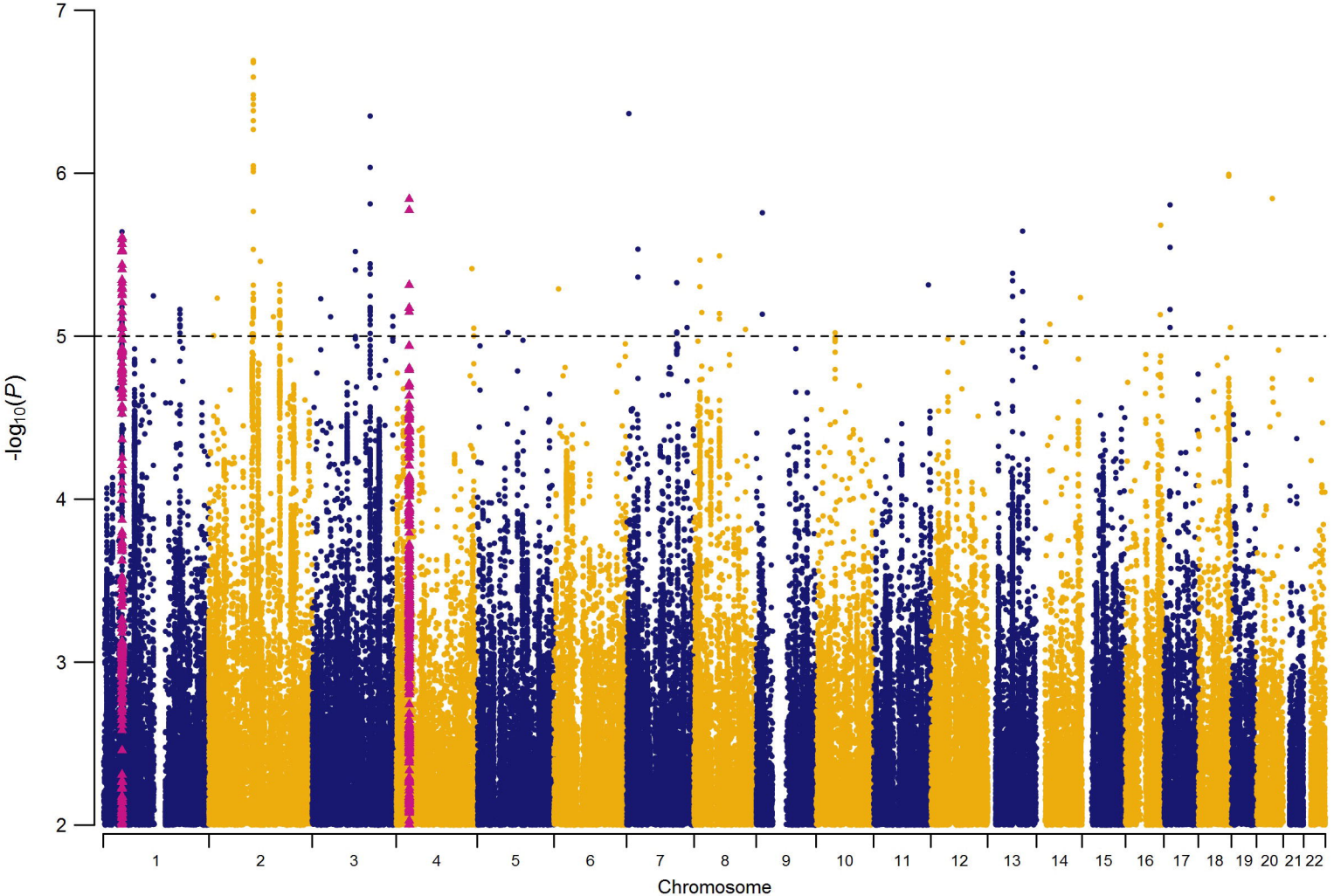
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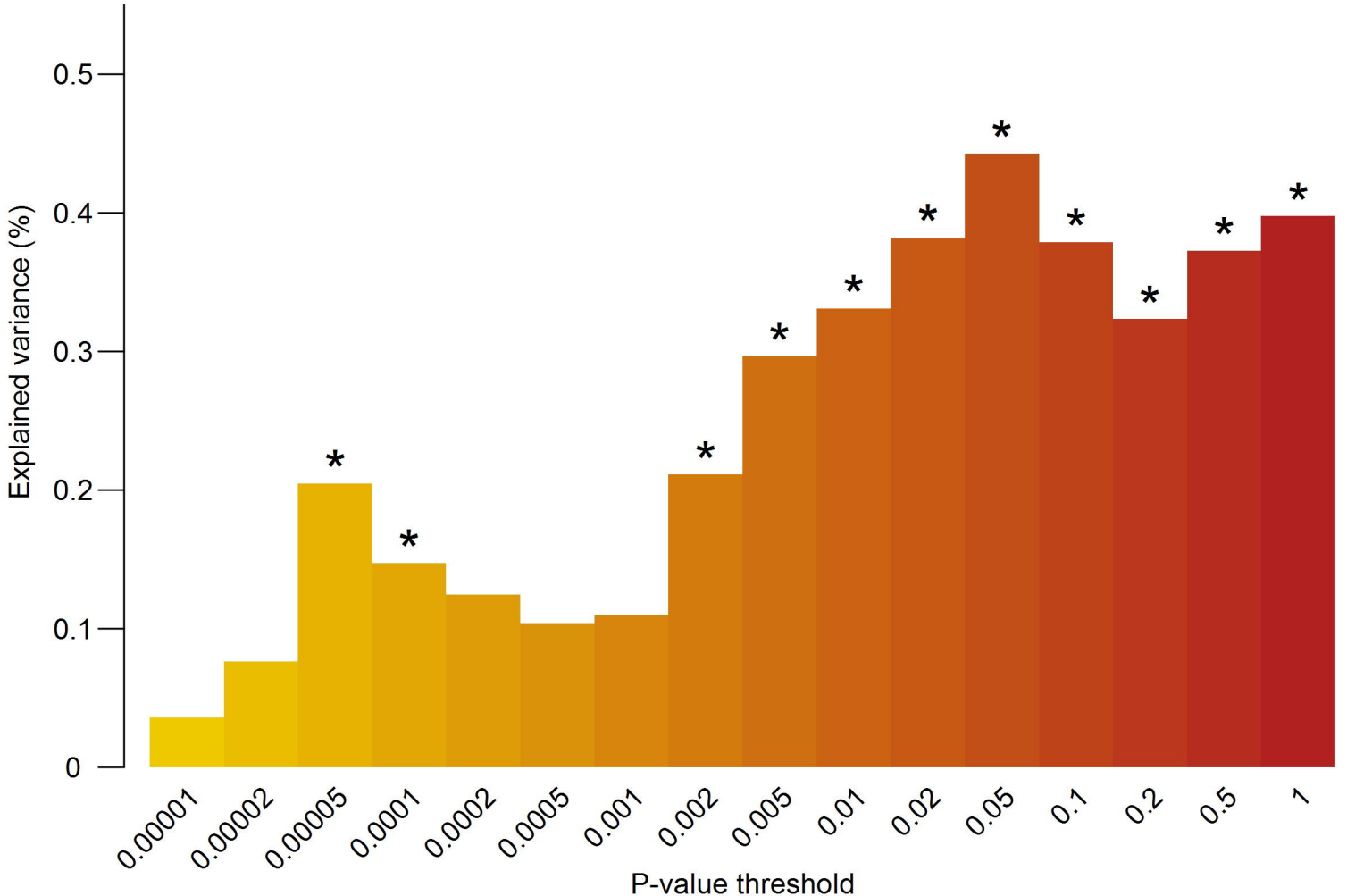
Explained variance (%)
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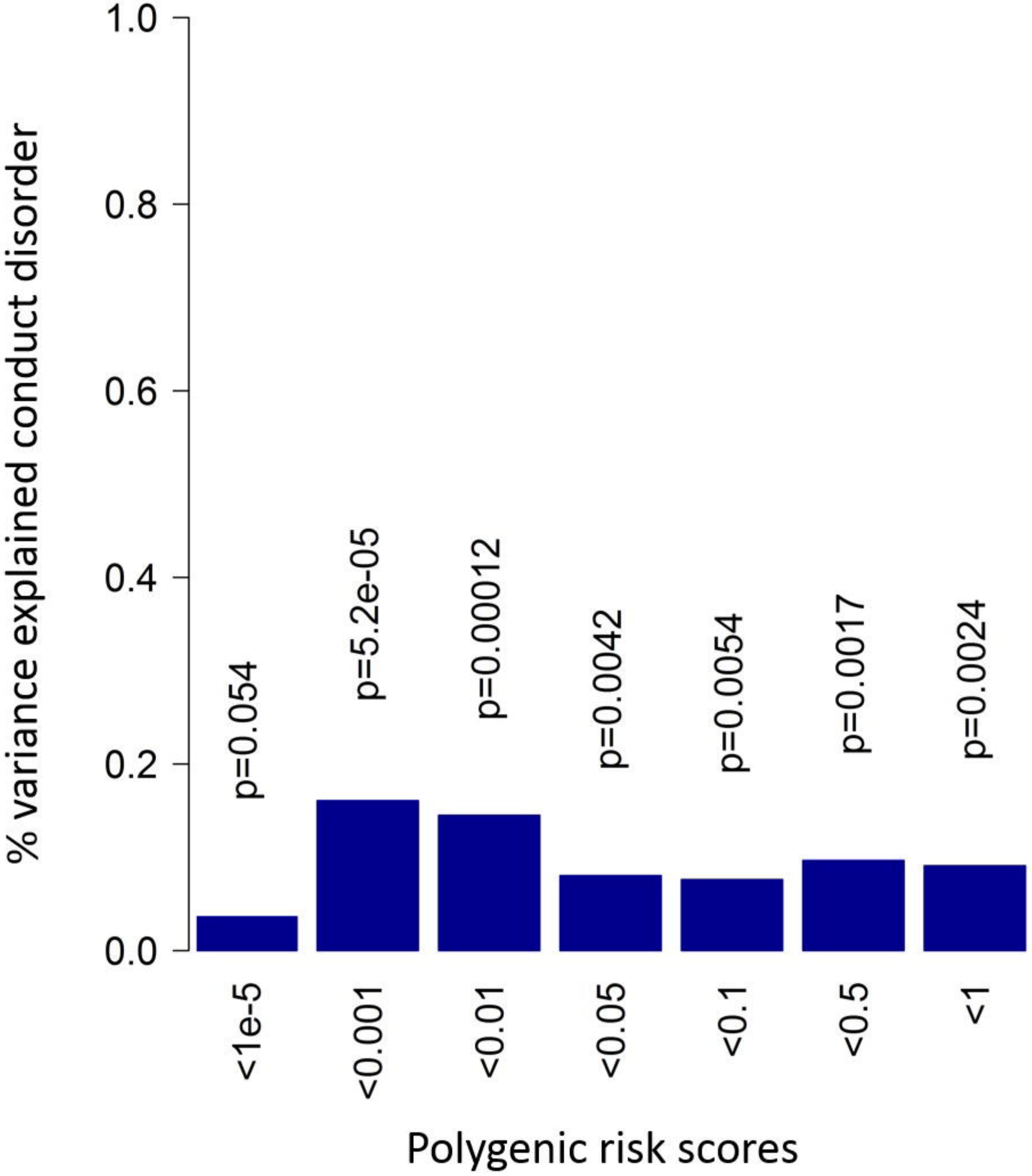
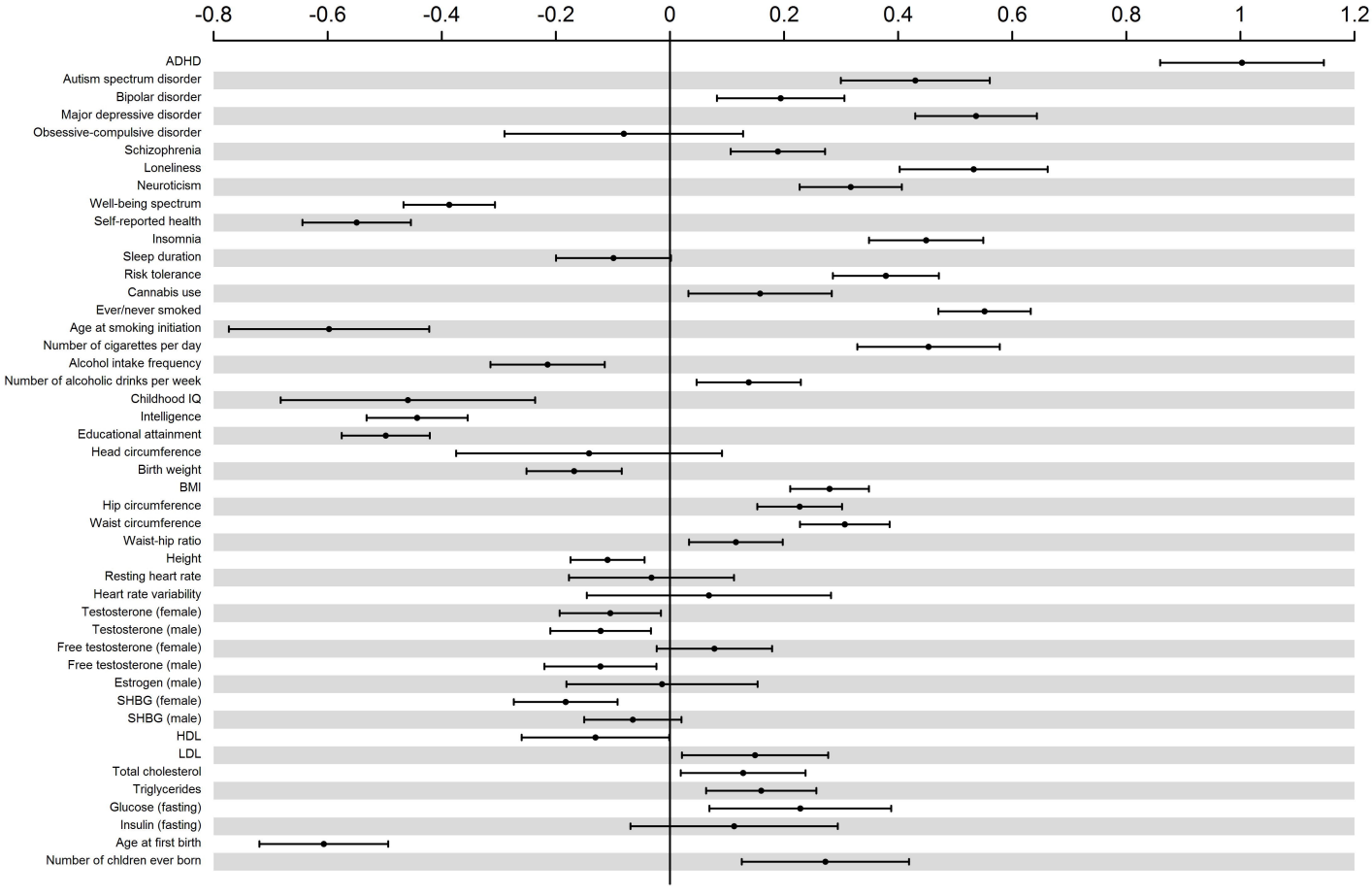
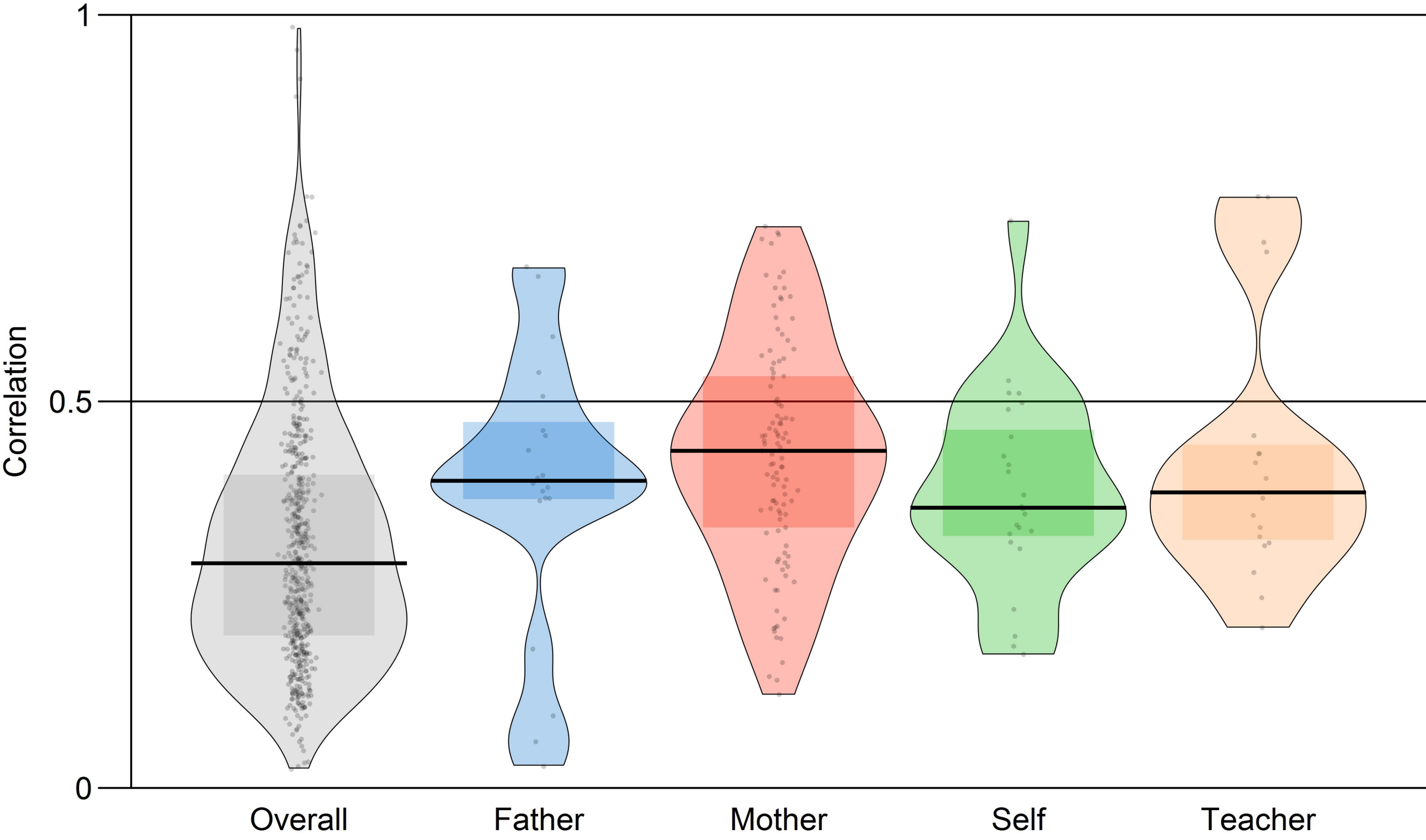
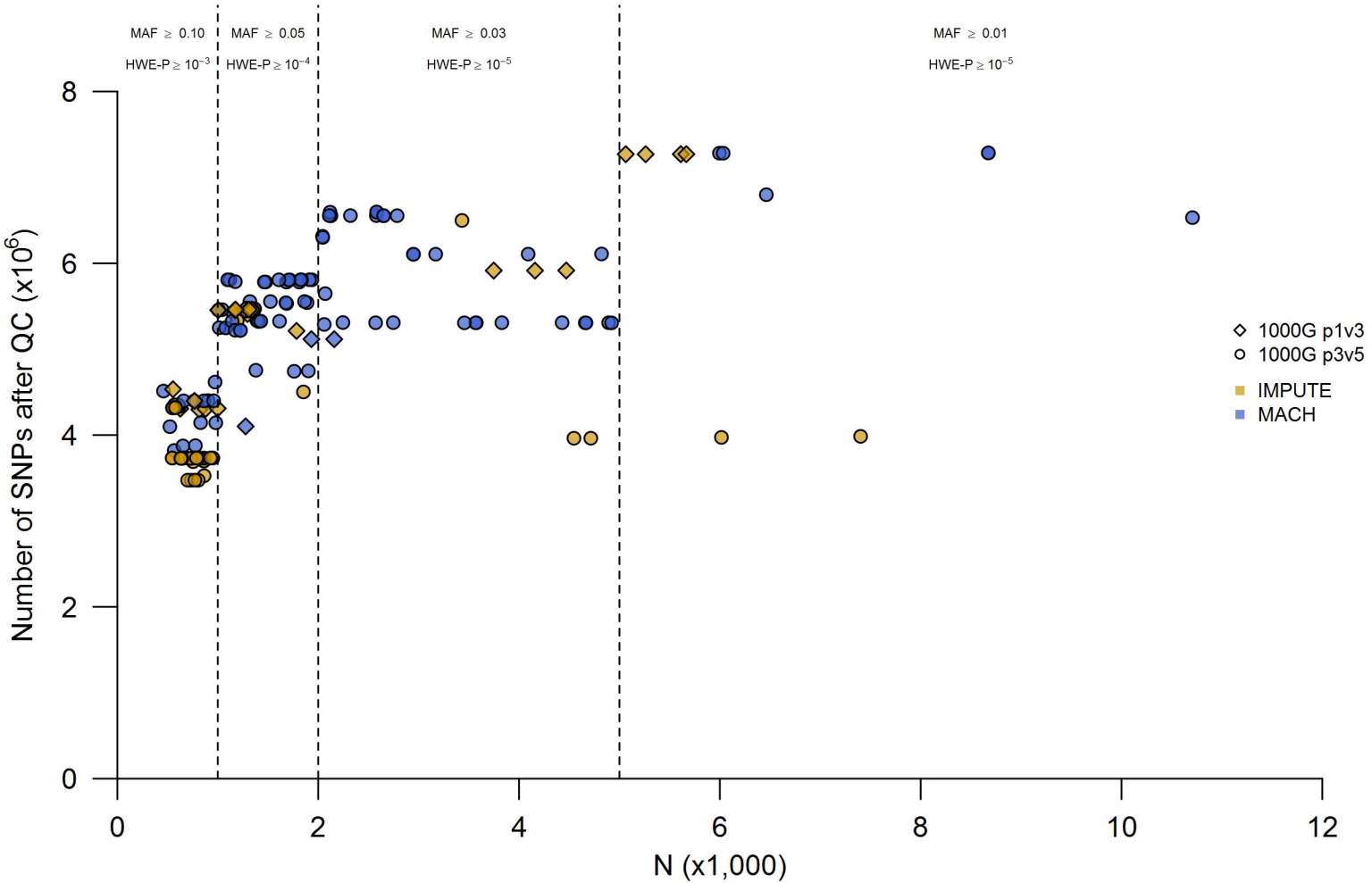
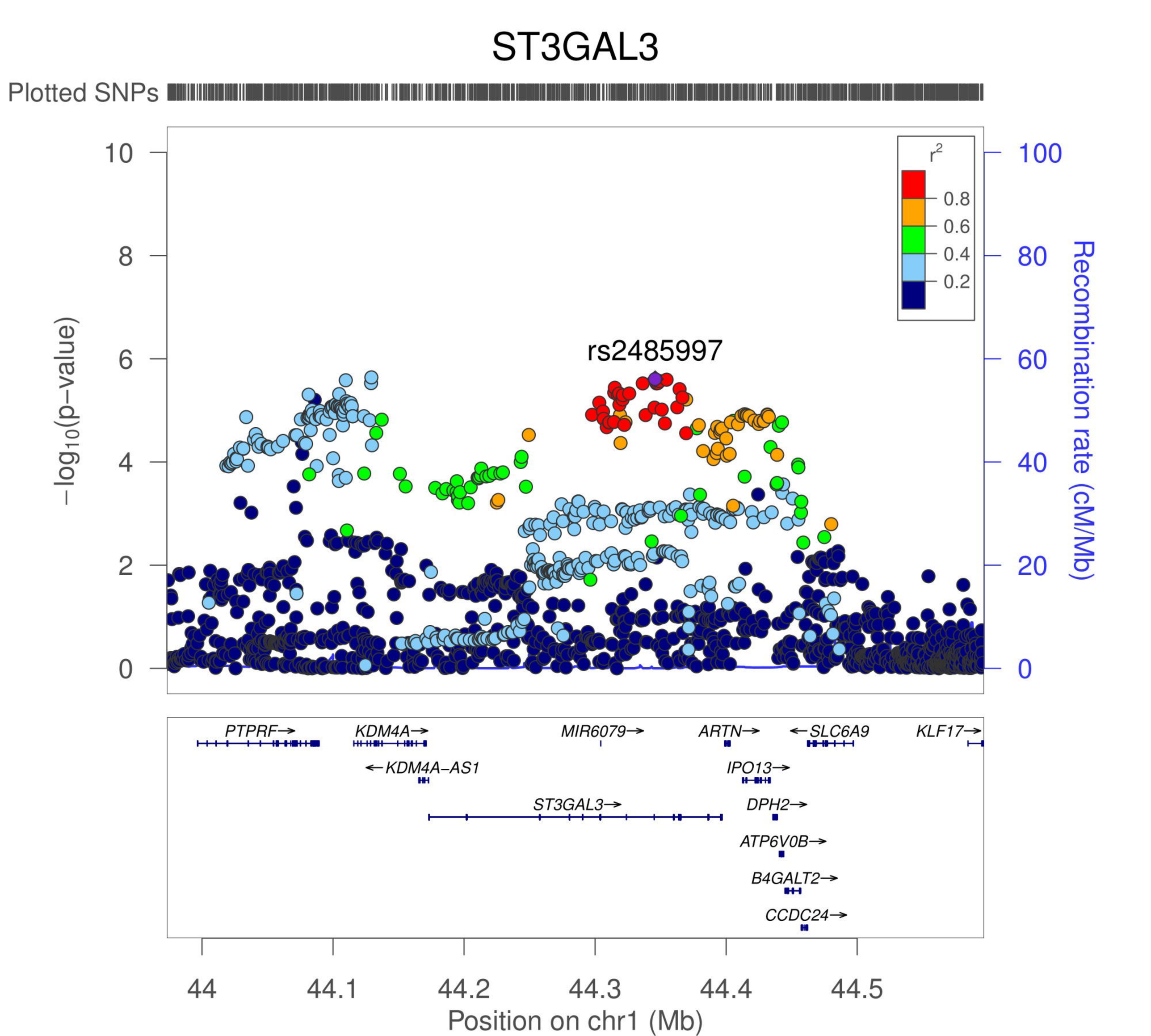
0.1
0.2
0.5
1
P-value threshold

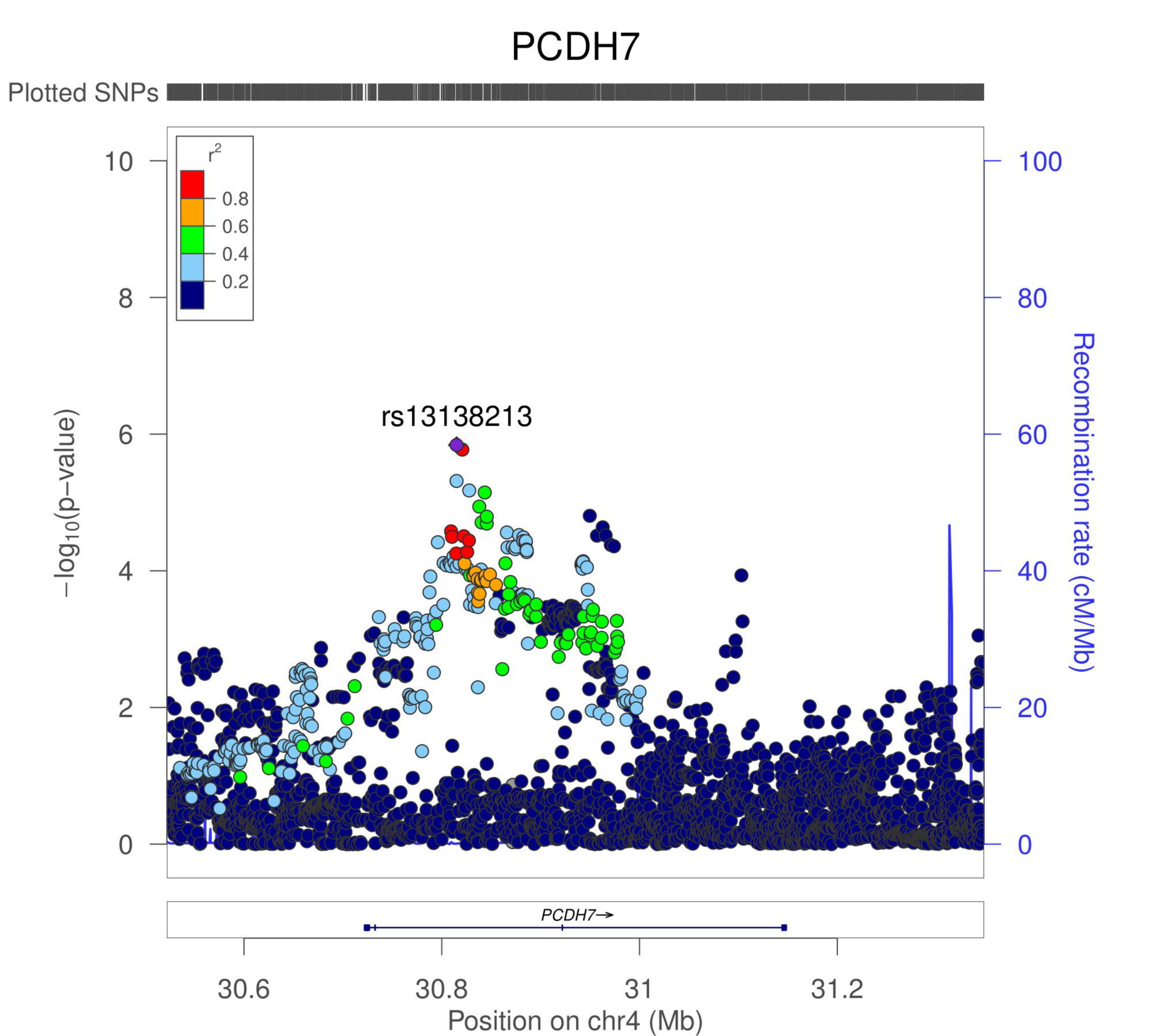

% variance explained conduct disorder
1.0
0.8
0.6
0.4
0.2
0.0
p=0.054
p=5.2e-05
p=0.00012
p=0.0042
p=0.0054
p=0.0017
p=0.0024
<1e-5
<0.001
<0.01
<0.05
<0.1
<0.5
<1
Polygenic risk scores

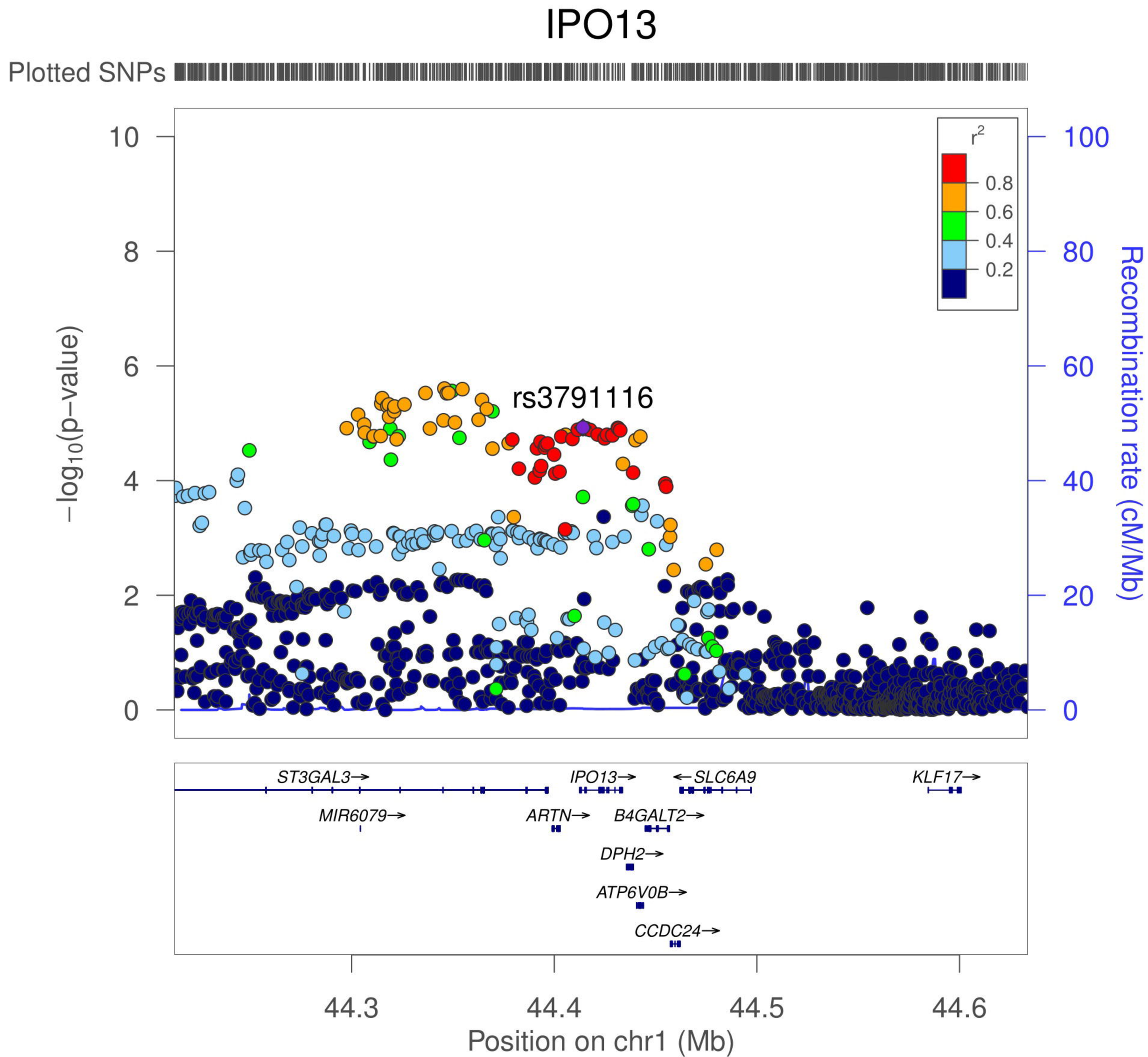

-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
1.2
ADHD
Autism spectrum disorder
Bipolar disorder
Major depressive disorder
Obsessive-compulsive disorder
Schizophrenia
Loneliness
Neuroticism
Well-being spectrum
Self-reported health
Insomnia
Sleep duration
Risk tolerance
Cannabis use
Ever/never smoked
Age at smoking initiation
Number of cigarettes per day
Alcohol intake frequency
Number of alcoholic drinks per week
Childhood IQ
Intelligence
Educational attainment
Head circumference
Birth weight
BMI
Hip circumference
Waist circumference
Waist-hip ratio
Height
Resting heart rate
Heart rate variability
Testosterone (female)
Testosterone (male)
Free testosterone (female)
Free testosterone (male)
Estrogen (male)
SHBG (female)
SHBG (male)
HDL
LDL
Total cholesterol
Triglycerides
Glucose (fasting)
Insulin (fasting)
Age at first birth
Number of chldren ever born

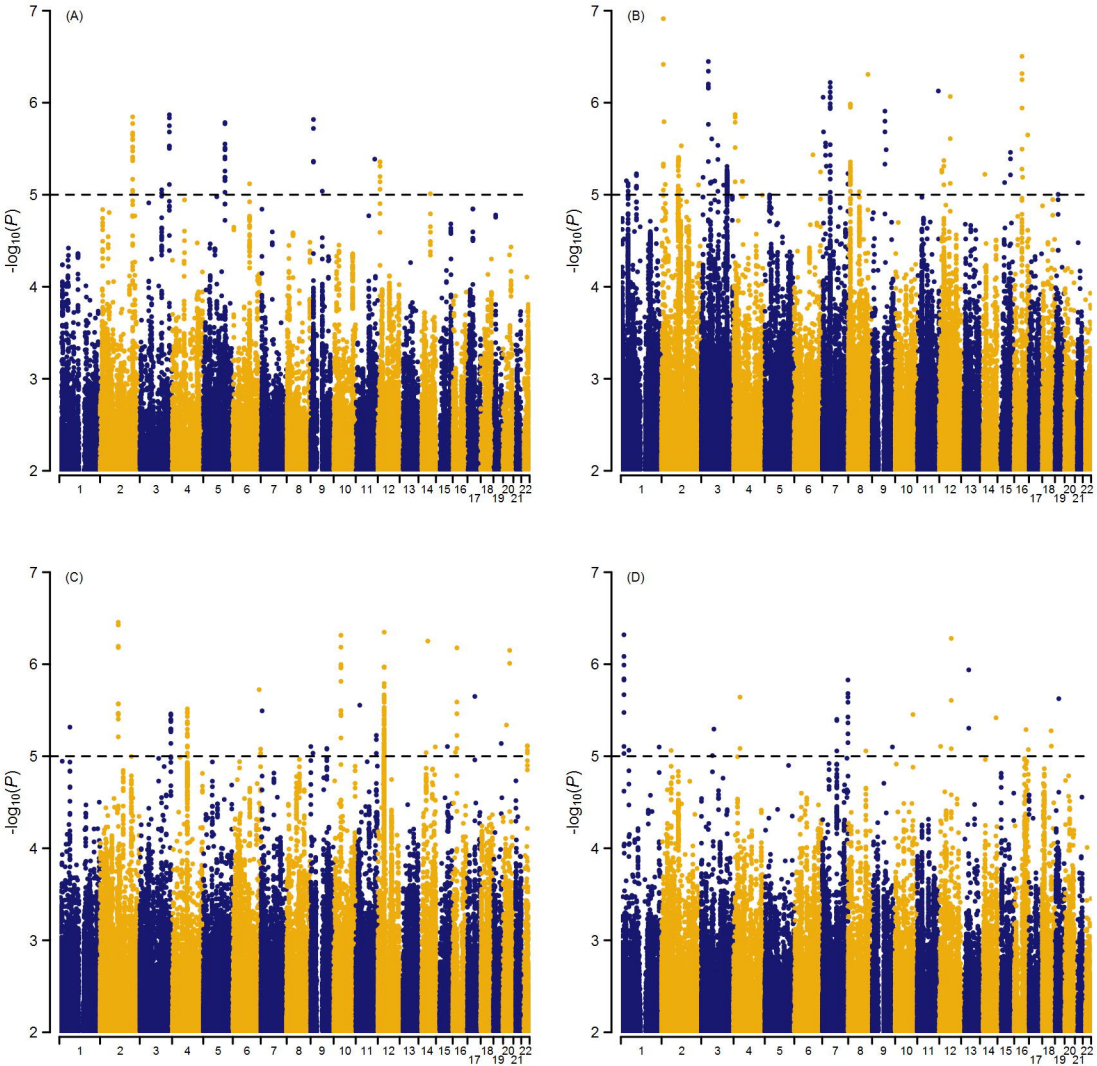

1
0.5
0
Correlation
Overall
Father
Mother
Self
Teacher

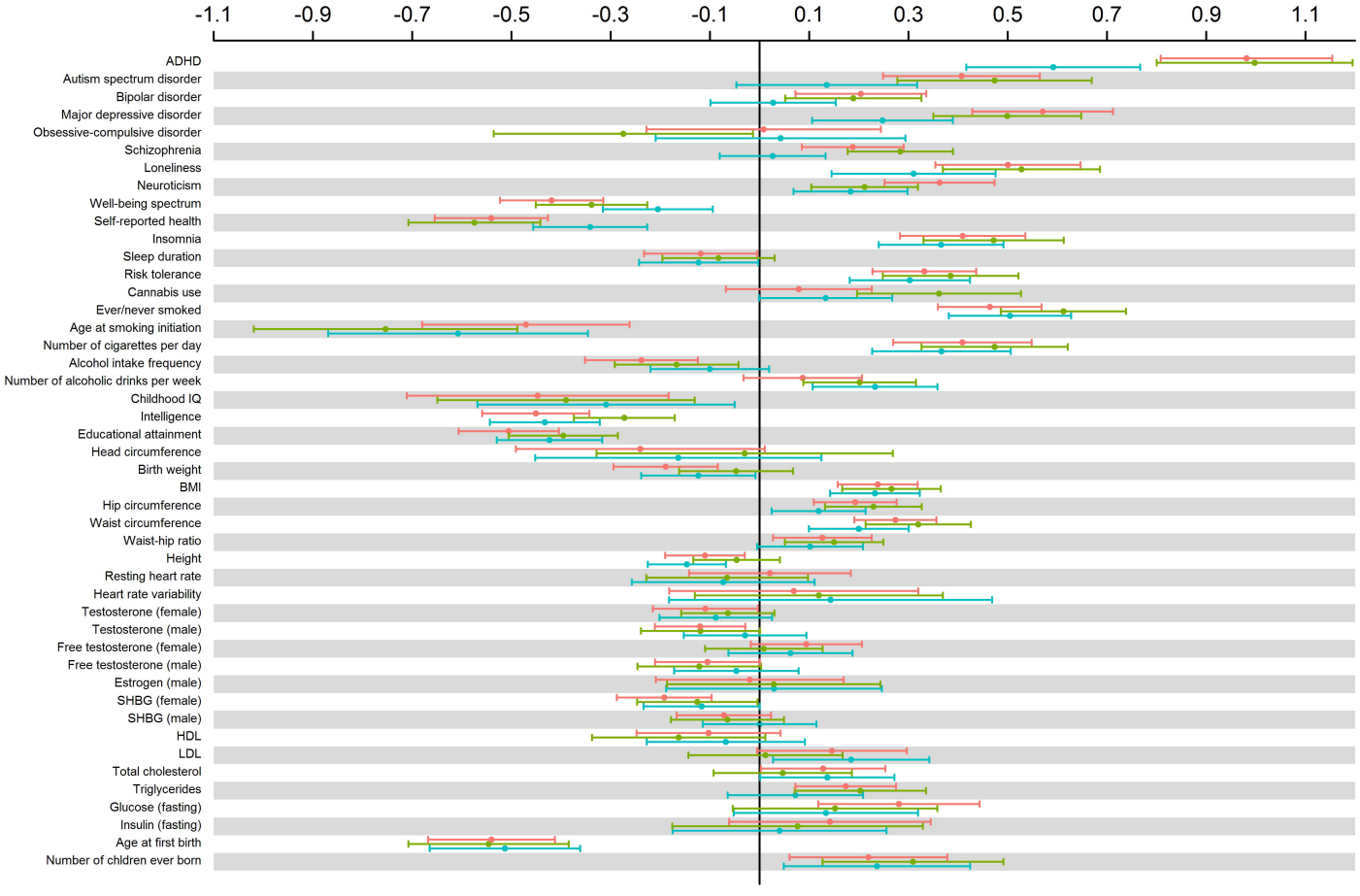

MAF ≥ 0.10
HWE-P ≥ 10⁻³
MAF ≥ 0.05
HWE-P ≥ 10⁻⁴
MAF ≥ 0.03
HWE-P ≥ 10⁻⁵
MAF ≥ 0.01
HWE-P ≥ 10⁻⁵
Number of SNPs after QC (x10⁶)
N (x1,000)
0
2
4
6
8
10
12
1000G p1v3
1000G p3v5
IMPUTE
MACH


ST3GAL3
Plotted SNPs
rs2485997
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
PTPRF
KDM4A
MIR6079
ARTN
SLC6A9
KLF17
KDM4A−AS1
IPO13
ST3GAL3
DPH2
ATP6V0B
B4GALT2
CCDC24
Position on chr1 (Mb)


PCDH7
Plotted SNPs
r2
0.8
0.6
0.4
0.2
rs13138213
−log10(p−value)
Recombination rate (cM/Mb)
PCDH7→
Position on chr4 (Mb)
30.6
30.8
31
31.2
0
2
4
6
8
10
0
20
40
60
80
100


IPO13
Plotted SNPs
rs3791116
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
10
8
6
4
2
0
100
80
60
40
20
0
ST3GAL3→
IPO13→
←SLC6A9
KLF17→
MIR6079→
ARTN→
B4GALT2→
DPH2→
ATP6V0B→
CCDC24→
44.3
44.4
44.5
44.6
Position on chr1 (Mb)


(A)
(B)
(C)
(D)
-log10(P)
7
6
5
4
3
2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22


-1.1
-0.9
-0.7
-0.5
-0.3
-0.1
0.1
0.3
0.5
0.7
0.9
1.1
ADHD
Autism spectrum disorder
Bipolar disorder
Major depressive disorder
Obsessive-compulsive disorder
Schizophrenia
Loneliness
Neuroticism
Well-being spectrum
Self-reported health
Insomnia
Sleep duration
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Waist circumference
Waist-hip ratio
Height
Resting heart rate
Heart rate variability
Testosterone (female)
Testosterone (male)
Free testosterone (female)
Free testosterone (male)
Estrogen (male)
SHBG (female)
SHBG (male)
HDL
LDL
Total cholesterol
Triglycerides
Glucose (fasting)
Insulin (fasting)
Age at first birth
Number of chldren ever born