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Genome-Wide Association Studies of a Broad Spectrum of Antisocial Behavior

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IMPORTANCE Antisocial behavior (ASB) places a large burden on perpetrators, survivors, and society. Twin studies indicate that half of the variation in this trait is genetic. Specific causal genetic variants have, however, not been identified.

OBJECTIVES To estimate the single-nucleotide polymorphism–based heritability of ASB; to identify novel genetic risk variants, genes, or biological pathways; to test for pleiotropic associations with other psychiatric traits; and to reevaluate the candidate gene era data through the Broad Antisocial Behavior Consortium.

DESIGN, SETTING, AND PARTICIPANTS Genome-wide association data from 5 large population-based cohorts and 3 target samples with genome-wide genotype and ASB data were used for meta-analysis from March 1, 2014, to May 1, 2016. All data sets used quantitative phenotypes, except for the Finnish Crime Study, which applied a case-control design (370 patients and 5850 control individuals).

MAIN OUTCOME AND MEASURES This study adopted relatively broad inclusion criteria to achieve a quantitative measure of ASB derived from multiple measures, maximizing the sample size over different age ranges.

RESULTS The discovery samples comprised 16 400 individuals, whereas the target samples consisted of 9381 individuals (all individuals were of European descent), including child and adult samples (mean age range, 6.7-56.1 years). Three promising loci with sex-discordant associations were found (8535 female individuals, chromosome 1: rs2764450, chromosome 11: rs11215217; 7772 male individuals, chromosome X, rs41456347). Polygenic risk score analyses showed prognostication of antisocial phenotypes in an independent Finnish Crime Study (2536 male individuals and 3684 female individuals) and shared genetic origin with conduct problems in a population-based sample (394 male individuals and 431 female individuals) but not with conduct disorder in a substance-dependent sample (950 male individuals and 1386 female individuals) (R^2 = 0.0017 in the most optimal model, P = 0.03). Significant inverse genetic correlation of ASB with educational attainment (r = −0.52, P = .005) was detected.

CONCLUSIONS AND RELEVANCE The Broad Antisocial Behavior Consortium entails the largest collaboration to date on the genetic architecture of ASB, and the first results suggest that ASB may be highly polygenic and has potential heterogeneous genetic effects across sex.

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Supplemental content

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Antisocial behavior (ASB) covers a range of inappropriate behaviors that cause harm to others, the community, and the environment. These behaviors include aggression, hostility, theft, deceitfulness, and violent felonies. In addition to the monetary effects,[1] violent criminal behavior also has significant social and emotional costs. Communities with high rates of crime often face high rates of unemployment, drug and alcohol abuse, poverty, and other social pathologic conditions.[2] Survivors of crime often experience emotional trauma and can develop serious mental health problems, such as posttraumatic stress disorder.[3] In addition, ASB has high comorbidity with other psychiatric traits and maladaptive behaviors.[4,5] Therefore, identification of the causal mechanisms that underlie ASB is important to identify prevention and treatment modalities. Accumulated evidence from quantitative and molecular genetic studies[6,7] reveals the substantial influence of genetic factors in the etiology of ASB. Most evidence of a role of genetics is derived from twin studies and, to a lesser extent, adoption studies[7,8] and indicates that approximately half of the variance in ASB can be explained by genetic factors, whereas the remainder can be explained by unique and common environmental factors.[6-8] A twin study[9] further determined that the association between ASB and cognitive and psychiatric traits is in part attributable to common genetic factors, indicating there may be shared biological mechanisms that underlie these behaviors. Early candidate gene studies[9-11] identified a number of genetic polymorphisms involved in serotonergic and catecholaminergic function, among others, that may be involved in ASB. However, a systematic review and meta-analysis[12] of most published genetic association studies on aggression and violence failed to reveal a significant overall association between any of the previously reported candidate genes and aggression. The lack of replication of candidate genes for ASB is consistent with other candidate gene findings in psychiatry, which for the most part have failed to identify reproducible and clinically useful genetic variants.[13] This is attributable in part to the a priori inferences of the classic candidate gene approach, which increases the chances of false-positive findings in the typically small sample sizes of the individual studies.[14]

Genome-wide association studies (GWASs) can overcome these limitations. To date, relatively few GWASs have focused on antisocial phenotypes. One study,[15] performed on childhood conduct disorder in an American sample (872 patients and 3091 control individuals), detected 3 genome-wide significant loci. However, none of the other published GWASs[16-19] reported evidence of a genome-wide association with any genetic variants.

This lack of positive results from GWASs is most likely attributable to low statistical power to detect small effects.[20] For example, recent work of the Schizophrenia Working Group of the Psychiatric Genomics Consortium revealed the direct association between sample size and success in detecting genetic variants. Their latest GWASs, including 36 989 patients and 113 075 controls, identified 108 genome-wide significant independent genomic loci, providing new insights in the pathology of schizophrenia,[21] whereas earlier studies by Purcell et al[22] (N = 6909 [3322 patients]) and Ripke et al[23] (N = 59 318 [21 246 patients]) detected 1 and 13 genome-wide significant single-nucleotide polymorphisms (SNPs), respectively.

Key Points

Questions Which genetic variants are associated with antisocial behavior, are they sex specific, and do they correlate with other traits?

Findings In this study of genome-wide association data from 5 population-based cohorts and 3 target samples, antisocial behavior was associated with polygenic traits, demonstrating pleiotropic genetic associations with educational attainment and distinct genetic effects across sex.

Meaning Larger samples, divided by sex, are needed to validly identify genetic variants associated with antisocial behavior.

To increase sample sizes for gene finding for ASB, we initiated the Broad Antisocial Behavior Consortium (BroadABC). BroadABC represents a collaborative research initiative to conduct genetic analyses on a larger scale to identify biological mechanisms that underlie the course of ASB. In designing BroadABC's gene-discovery strategies, we weighed the benefits and costs of outcome measure heterogeneity in relation to the total sample size. We chose to maximize sample size by pooling the heterogeneous measures of the individual cohorts, including different age ranges, and jointly analyzing their data. Our rationale is supported by a genetically informative longitudinal study[24] demonstrating evidence of genetic continuity (the continuity in ASB during childhood and adolescence is explained largely by genetic factors). Moreover, a prior study[25] examining the etiologic connections between the externalizing spectrum found that additive genetic factors account for 81% of the variance in externalizing behavior. Lastly, previous meta-analytical GWASs have successfully applied this joint analysis approach by identifying additional loci associated with depressive symptoms and neuroticism.[26]

Methods

BroadABC focuses on the broad spectrum of ASB and currently consists of 5 discovery cohorts (a combined 16 400 individuals) and 3 independent prediction and replication samples: (1) a population-based sample (n = 825), (2) a forensic sample (n = 6220), and (3) and a substance-dependent sample (n = 2336). In total, BroadABC has genotypic and phenotypic data from 25 781 individuals across 8 unique samples and, to our knowledge, is the largest collective sample available to estimate the effects of genome-wide genetic variants for ASB and testing for genetic overlap with other traits. All participants provided written informed consent. All data were deidentified. Because of the extra perceived vulnerability of the Finnish Crime Study participants, multiple committees, including the Ethics Committee for Pediatrics, Adolescent Medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa, and Criminal Sanctions Agency, approved this study.[27]

Table 1. Study Design, Sample Sizes, and Phenotypes for Genome-Wide Association Study Cohorts

Sample	Study Design	Antisocial Measure	Total Sample Size (M/F), No.	Age, Mean (SD), y
Discovery samples				
ALSPAC	Prospective pregnancy cohort (family design)	Development and Well-being Assessment, conduct disorder scale	4336 (2065/2271)	13.1 (0.1)
COGA	Alcohol dependence case-control sample (family design)	Count of the number of antisocial personality disorder criteria	1379 (739/640)	43.8 (11.7)
GENR	Population based (family design)	Rule-breaking behavior, Teacher Report Form	1420 (718/702)	6.7 (4.2)
TEDS	Population based (family design)	Antisocial Process Screening Device	2734 (1257/1477)	12.5 (.2)
QIMR	Population based (twin-family design)	Retrospective conduct disorder	6531 (2993/3538)	33.8 (2.4)
Target samples				
Finnish Crime Study	Case-control (prisoners sample)	Structured Clinical Interview for *DSM-IV* disorders	6220 (2536/3684)	56.1 (12.8)
MSUTR	Population based (family design)	Child Behavioral Checklist: conduct problems (reported by mother)	825 (394/431)	8.2 (1.5)
Yale-Penn	Substance-dependent sample	*DSM-IV* conduct disorder criteria	2336 (950/1386)	41.0 (8.2)

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; COGA, Collaborative Studies on Genetics of Alcoholism; GENR, Generation Rotterdam; MSUTR, Michigan State University Twin Registry; QIMR, Queensland Institute of Medical Research; TEDS, Twins Early Development Study.

Cohorts and Phenotypes

Except for the Finnish Crime Study, which used a dichotomized outcome measure, all studies used a continuous scale to increase statistical power.[28] To maximize sample size, we included studies with a broad range of antisocial measures, including aggressive and nonaggressive domains of ASB and using study-specific scales in different age groups (**Table 1** and eAppendix 1 in the Supplement). Five large population-based discovery cohorts and 3 target samples (all participants were of European descent) were included in this study from March 1, 2014, to May 1, 2016 (see Table 1 for cohort-specific details). The discovery samples comprised 16 400 individuals, whereas the target samples consisted of 9381 individuals. All participants were recruited from different regions; thus, sample overlap was highly unlikely.

Genotyping

Genome-wide genotyping was performed independently in the cohorts using commercially available genotyping arrays. All cohorts imputed their genotype data to the 1000 Genomes phase 1 version 3 (build 37, hg19) reference panel using the standard software package MACH[29] or IMPUTE2[30] except for the Finnish Crime Study and Michigan State University Twin Registry (MSUTR), which were not imputed. Additional details and cohort-specific procedures concerning the genotyping process, imputation, and quality control are provided in eTable 1 and eTable 2 in the Supplement.

Statistical Analysis

GWASs at the Cohort Level

Analyses of the GWASs were performed at the cohort level according to a prespecified analysis plan (standard operating procedures). Each cohort uploaded sex-specific and combined GWAS results to the BroadABC server as input for the meta-analyses. All analyses were restricted to samples of European ancestry. For sex-pooled analysis of the X chromosome, males were treated as homozygous females. Quality control and meta-analysis of the GWAS summary results were performed by 2 of us (J.J.T. and A.J.) following a strict analysis protocol. Additional details on the standard operating procedure analysis plan and quality control are provided in eAppendix 2 in the Supplement and on the BroadABC website (http://broadabc.ctglab.nl/).

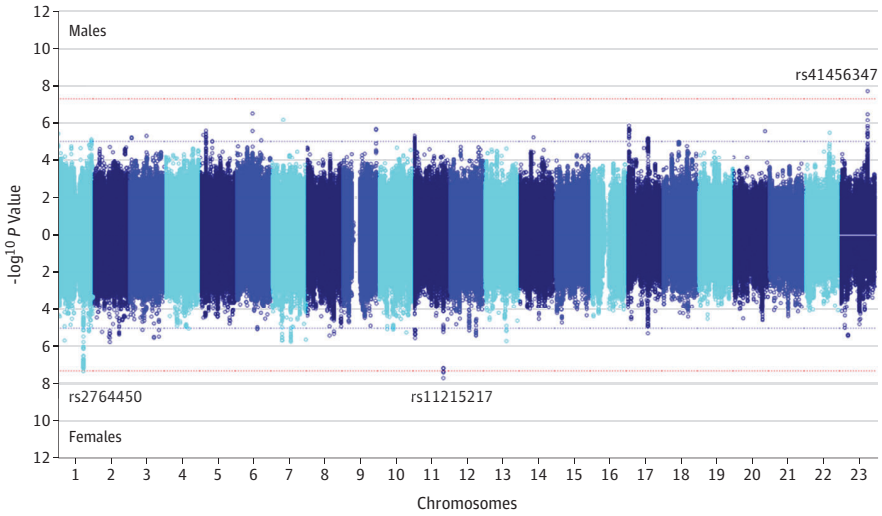
Meta-analysis of Discovery Cohorts

The meta-analysis across discovery cohorts was run for the pooled male-female GWAS results (N = 16 400), as well as separately for the sexes (8535 female individuals and 7772 male individuals), using a fixed-effects model with *z* scores weighted by sample size as implemented in the software METAL.[31] We only reported and interpreted the results of polymorphisms with a total sample size greater than 10 000 (across all samples) and 5000 (sex specific). The genome-wide significance threshold was set at 1.67×10^{-8} because we performed 3 meta-analyses; polymorphisms with $P<10^{-6}$ were considered to be promising findings.

Polygenic Risk Scores

We performed a polygenic risk score (PRS) analysis in the Finnish Crime Study to test whether a genetic risk for ASB could significantly discriminate between prisoners and matched controls. We used the software package PRSice to estimate the best-fit PRS at a broad range of *P* value thresholds. For clumping, the linkage disequilibrium (LD) threshold was set to an R^2 of 0.25 and a 500-kb distance. The PRS analyses were conducted based on the sex-combined samples and the male-specific samples (given the overrepresentation of male prisoners), and sex, age, and 4 principal components were included as covariates. In addition, to evaluate evidence for shared genetic origin, we used the summary-summary statistic-based analysis as implemented in PRSice, using the sex-combined, male-specific, and female-specific samples in MSUTR and Yale-Penn samples after applying more stringent clumping thresholds (R^2 = 0.05, 300-kb distance).

Figure 1. Miami Plot Showing *P* Values of the Single-Nucleotide Polymorphism Associations With Antisocial Behavior in Males and Females



The threshold for genome-wide significance ($P < 1.67 \times 10^{-8}$) is indicated by the red dotted line, and the threshold for promising findings ($P < 1.0 \times 10^{-5}$) is indicated by the blue dotted line.

LD Regression Score Heritability and Correlation Analyses

To calculate the SNP heritability and estimate the genetic correlation between ASB and a range of cognitive, psychiatric, and reproductive traits, we used the (cross-trait) LD score regression method. The LD score method disentangles the contribution of true polygenic signal and bias caused by population stratification to the inflated test statistics in GWASs and optionally calculates a genetic correlation (r_g) among different traits.[32] This method is particularly useful because it only requires GWAS summary statistics and is not biased by sample overlap.[33] Genetic correlations of ASB were calculated with cognitive and psychiatric traits previously reported to be comorbid with ASB using summary results from attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and bipolar disorder[21,34,35] that are publicly available on the Psychiatric Genomics Consortium webpage (https://www.med.unc.edu/pgc/results-and-downloads). The summary statistics of neuroticism and educational attainment (defined as number of years in the educational system) were provided by the Social Science Genetic Association Consortium.[26,36] The genetic correlations of ASB with reproductive traits were computed from a centralized database of summary-level GWASs.[37]

The methods and results regarding the functional annotation, gene analysis, gene-set analyses, replication analysis, and tests for enrichment in loci previously related to antisocial phenotypes are reported in eAppendixes 3 through 6, eTables 3 through 10, and eFigure 1 and eFigure 2 in the Supplement).

Results

The discovery samples comprised 16 400 individuals, whereas the target samples consisted of 9381 individuals (all individuals were of European descent), including child and adult samples (mean age range, 6.7-56.1 years). We removed 2 134 049 SNPs because of insufficient total sample size (N<10 000), resulting in 7 392 849 SNPs available for analyses. There were no discrepancies between the results files of the 2 analysts at the cohort or meta-analysis level. The genomic inflation factors were 1.015 for the combined analysis, 1.012 for the male analysis, and 1.001 for the female analysis, which are as expected under a polygenic model given the sample size, prevalence, and heritability of ASB (eFigure 3 in the Supplement).

Meta-analysis of GWAS

The combined discovery meta-analysis incorporating both sexes did not identify genetic variants of genome-wide significance (n = 16 400, lowest $P = 6.1 \times 10^{-7}$). The strongest associations were located on chromosome 20, followed by chromosomes 1, 19, 22, and 6 (eFigure 4 in the Supplement). The SNPs yielding *P* values smaller than 1.0×10^{-6} were considered promising (eTables 11, 12, and 13 in the Supplement).

The GWAS meta-analysis for females only (n = 8535) (eTable 12 in the Supplement) revealed 2 promising loci on chromosome 1 (rs2764450, $R^2 = 0.35\%$, $P = 4.8 \times 10^{-8}$) and chromosome 11 (rs11215217, $R^2 = 0.37\%$, $P = 2.1 \times 10^{-8}$), whereas the meta-analysis for males (n = 7772) (eTable 13 in the Supplement) identified a near genome-wide signal on chromosome X (rs41456347, $R^2 = 0.41\%$, $P = 2.0 \times 10^{-8}$). We found no evidence of heterogeneity ($I^2 = 0$) across discovery samples in the association of rs2764450 ($\chi^2_3 = 2.62$, $P = .45$), rs11215217 ($\chi^2_4 = 3.01$, $P = .54$), and rs41456347 ($\chi^2_4 = 2.72$, $P = .60$) with ASB (eFigure 5 in the Supplement). Functional annotation was performed for the top 3 loci to gain insight into possible causal genes (eAppendix 6 and eAppendix 7 and eFigure 1 in the Supplement). Top signals were located differently across sex (**Figure 1** and eTable 14 in the Supplement). We tested whether the signs of the regression coefficients were consistently in the same direction between the SNPs for males and females. The sign tests showed no consistent directions of effect (proportions were 0.51, 0.50, and 0.50) for SNPs selected for

different *P* value thresholds (0.05, 0.001, and 0.0001, respectively). Moreover, Fisher exact tests found no evidence for enrichment of SNPs with low *P* values across sex regardless of sign (odds ratio [OR], 0.9; *P* = .05 for males; OR, 1.1; *P* = .001 for females) (eTable 15 in the Supplement).

The sex-specific signals were supported by a large number of promising SNPs, which were in incomplete LD with the lead SNP (eFigure 4). Imputation quality for the lead SNPs was high for rs41456347 (mean R^2 = 99.7), rs2764450 (mean R^2 = 93.8), and rs11215217 (mean R^2 = 86.8). Gene-based and gene-set analyses yielded no significant genes (top gene was centromeric protein I [OMIM 300065], $P = 3.2 \times 10^{-5}$) (eTables 3-9, and 14 and eFigure 1 in the Supplement) or gene sets (top gene-set was Reactome cell communication, $P = 3.6 \times 10^{-4}$) (eTable 6 in the Supplement). None of the traditional candidate genes on ASB were significantly associated with ASB (top gene was tyrosine hydroxylase [OMIM 191290], *P* = 0.08 for correlation) (eTables 7, 8, and 9 in the Supplement).

Polygenic Risk Scores

The BroadABC antisocial genetic risk scores were associated with case-control status of antisocial personality disorder in the Finnish Crime Study (sex combined, R^2 = 0.0017, *P* = .03; male-specific R^2 = 0.0018, *P* = .05) (**Figure 2**A and B). Nevertheless, the analyses revealed low Nagelkerke R^2 estimates (R^2 = 0.0019 in the most optimal model) not exceeding the Bonferroni-corrected threshold for significance. Using summary statistics in PRSice software, we found that the genetic effect from the females-only ASB analysis significantly overlapped with genetic effects in the expected direction on conduct problems in MSUTR (R^2 = 0.021 for the most optimal model, *P* = .004) but not with the sex-combined and males-only analyses (Figure 2C-E). No significant genetic overlap was found with conduct disorder in Yale-Penn sample, although a nominal significant effect (R^2 = 0.0022, *P* = .04) in the expected direction was found in the males-only analysis (Figure 2E-H).

SNP Heritability and Genetic Correlation of ASB With Other Traits

The estimated proportion of the phenotypic variance in ASB explained by all SNPs was 5.2%, with an SE of 2.7% (*P* = .03). Sample sizes were too small in the sex-specific meta-analyses to be used to estimate SNP heritability (h^2) for the male and female samples separately. We found a significant (corrected α = .006) and moderate negative genetic correlation between ASB and educational attainment (*r* = −0.52, *P* = .005). Follow-up analyses using the Fisher exact test revealed evidence of enrichment of low *P* (*P* < .001) in the same SNPs for ASB and educational attainment (OR = 3.26, *P* = .001). Moreover, we found a promising positive genetic correlation with neuroticism (*r* = 0.29, *P* = .02) and support for a negative genetic correlation between ASB and age at menopause (*r* = −0.49, *P* = .01), age of first birth (*r* = −0.43, *P* = .008), and a positive genetic correlation with number of children ever born (*r* = 0.42, *P* = .03)[38] (**Table 2**). There was no evidence for genetic overlap between ASB and schizophrenia, bipolar disorder, ADHD, or age at menarche.

Discussion

To our knowledge, this study represents the largest investigation on the genetic architecture of ASB to date. Our meta-analyses of diverse continuous measures of ASB found that ASB is heritable and highly polygenic and suggests that part of the genetic architecture is sex specific. This finding is not surprising in view of the sex-influenced phenotypic expression. We also found a strong inverse correlation of ASB with genetic variants for educational attainment and some reproductive traits and a positive genetic correlation with neuroticism but not with schizophrenia, bipolar disorder, or ADHD.

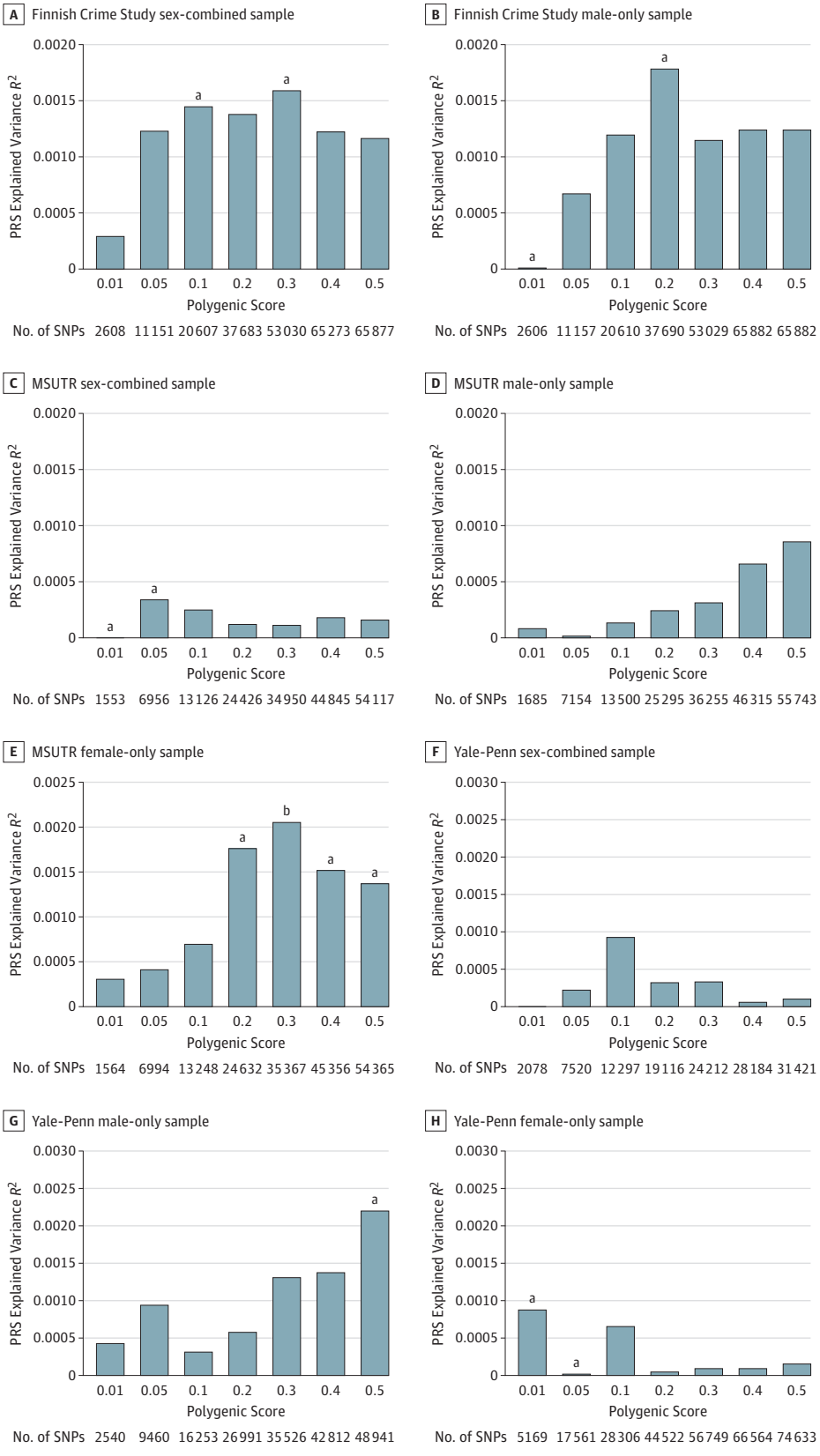
The SNP heritability analyses found that the collective effect of the measured SNPs accounted for 5% of the variance or 10% of the heritability of approximately 50%, as estimated from family-based studies. Recent GWASs on other complex traits, such as height, body mass index, and schizophrenia, demonstrated that with greater sample sizes, the SNP h^2 increases. The relatively small total GWAS discovery sample size yielded limited power to detect small genetic effects, which could explain in part the high missing heritability in our study, although we cannot rule out that most of the genetic variance in ASB is attributable to rare alleles. Taken together, we suspect that with greater sample sizes and better imputation and coverage of the common and rare allele spectrum, over time, SNP heritability in ASB could approach the family-based estimates.

Polygenic risk score analysis, based on a broad conceptualization of ASB, could reliably determine some of the variation in antisocial personality disorder in a forensic cohort, demonstrating that population-based genetic association studies can also be informative for samples that are at risk. Nevertheless, effect sizes were small, indicating limited prognostication accuracy and clinical utility for the current GWAS outcomes.

Despite the small but significant collective genetic effect on ASB, none of the individual genetic variants exceeded the significance threshold in our overall meta-analysis. The sex-specific meta-analyses, however, revealed 3 promising loci. Moreover, stronger polygenic risk effects were found for the sex-specific analyses. Given the substantial differences in prevalence, age at onset, and severity of ASB between males and females,[39] which might in part reflect sex differences in genetic architecture, it is important to account for those effects in genetic research designs.[40] Our current results suggest the presence of at least some sex-specific genetic effects. Even though sample sizes were smaller, the sex-specific analyses yielded increased specificity because potential noise attributable to different genetic loci driving the genetic component of ASB in male and female individuals was removed.

Our genetic correlation analyses revealed a promising positive genetic correlation of ASB with neuroticism, a finding that is concordant with previous twin research demonstrating a shared genetic origin of externalizing behavior and negative emotionality.[41] Moreover, we found significant genetic overlap between ASB and educational attainment, indicating a common underlying genetic architecture that influenced both phenotypes. The negative genetic correlation with educational

Figure 2. Polygenic Risk Scores (PRSs) in the Finnish Crime Study, Michigan State University Twin Registry (MSUTR), and Yale-Penn Samples



The PRSs for antisocial personality disorder (ASPD) among patients with antisocial behavior (ASB) in the Finnish Crime Study using sex-combined (A) and male-only (B) samples. Summary-summary statistic–based results plotting the explained variance in ASB within the MSUTR (sex combined [C], males only [D], and females only [E]) and Yale-Penn (sex combined [F], males only [G], and females only [H]) samples. The proportion of variance explained (Nagelkerke R^2) was computed by comparison of a full model (covariates plus PRS) score with a reduced model (covariates only). Seven different *P* value thresholds for selecting risk alleles are denoted by the color of each bar. The number of single-nucleotide polymorphisms (SNPs) per threshold is displayed below each bar.

[a] Statistical significance at $P < .05$.

[b] Statistical significance after correcting for multiple testing at $P < .006$.

Table 2. Genetic Correlation Estimates for 9 Traits With Broad Antisocial Behavior

Phenotype	Sample Size	SNP h2[a]	r_g (SE)[b]	*P* Value
Educational attainment	293 723	0.099	-0.52 (0.18)	.005
Neuroticism	170 911	0.094	0.29 (0.13)	.02
Schizophrenia	150 064	0.576	0.07 (0.15)	.64
Bipolar disorder	17 091	0.516	0.17 (0.20)	.41
Attention-deficit/hyperactivity disorder	9152	0.156	0.002 (0.29)	.99
Age at menarche	87 802	0.207	−0.04 (0.09)	.68
Age at menopause	69 360	0.134	−0.49 (0.19)	.01
Age at first birth	251 151	0.061	−0.43 (0.16)	.008
No. of children ever born	343 072	0.025	0.42 (0.19)	.03

Abbreviations: SNP h2, single-nucleotide polymorphism heritability.

[a] SNP h^2 is the estimation of narrow-sense heritability.

[b] r_g is the genetic correlation and is calculated with the linkage disequilibrium score regression software package using precalculated linkage disequilibrium scores from Finucane et al.[38]

attainment is consistent with a previous epidemiologic study[42] that reported a negative association between academic performance and delinquency. This finding is important because it may provide insight into the developmental pathways that underlie the association between academic failure and ASB.[43] Of interest, ASB also correlated with reproductive traits, thus fitting to the unified evolutionary theory that Boutwell and colleagues proposed.[44] Their theory suggests that increased criminality represents a faster life history approach—one that would be significantly calibrated by genes.

Limitations

Given the nature of ASB with no accepted gold standard for measuring the trait, our attempt to bring together large historic collections is possibly burdened by measurement diversity. The consortium includes adult and child samples, and within the adult samples, some focus on lifetime antisocial behavior and others focus on retrospective reports of child behavior. Nevertheless, previous studies[45-47] have demonstrated stable and unique genetic influences on ASB during the lifespan. Moreover, despite the broad conceptualization of ASB in the current study, the sample size is relatively small for gene-finding purposes. Still, we found a polygenic signal, and our correlation analyses further reflect the validity and usefulness of our approach. To identify individual SNPs or genes associated with ASB, we found that even larger samples are needed.

Conclusions

Our study suggests that ASB may be highly polygenic and has potential heterogeneous genetic associations across sex. As large-scale initiatives, such as the BroadABC, continue to increase, these collaborative efforts will also facilitate the conduct of epidemiologic studies that incorporate genome-wide data and environmental factors in a joint analysis.[48] Discoveries obtained from such gene-environment-wide interaction studies may contribute to more advanced explanatory models of the complex origin of ASB, thereby ultimately aiding prevention and intervention strategies.[49]

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