Genetics of the Research Domain Criteria (RDoC): genome-wide association study of delay discounting

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ABSTRACT

Delay discounting (**DD**), or the tendency to favor immediate over future rewards, is a form of impulsivity that is present in a constellation of diseases. Here we performed a genome-wide association study of DD using 23,127 research participants of European ancestry. We estimated chip heritability at 12%, and identified significant genetic correlations between DD and neuropsychiatric diseases (attention-deficit/hyperactivity disorder (**ADHD**), schizophrenia, major depression), smoking, personality, cognition, and weight.

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Delay discounting (**DD**) is a fundamental component of impulse control[1] and is exaggerated in patients with diseases including attention-deficit/hyperactivity disorder (**ADHD**)[3], substance use disorders[4] and obesity[5]. DD is included in the National Institute of Mental Health (NIMH)'s Research Domain Criteria (**RDoC**) initiative[6], which focuses on psychiatric disorders as extremes of normal tendencies, based on a biological understanding of behavior. Although the heritability of DD has been established using twin studies (from 46% to 62%)[7], the genetic basis of DD remains ill-defined.

In collaboration with the genetics company 23andMe, Inc., we performed the first genome-wide association study (**GWAS**) of DD. DNA extraction and genotyping were performed on saliva samples by the National Genetics Institute, a CLIA-certified laboratory. Quality control, imputation, and genome-wide analysis were performed by 23andMe (see **Supplementary Table 1** and **Online Methods**). Our sample consisted of 23,217 male and female adult research participants of European ancestry (demographic information is presented in **Supplementary Table 2**). We employed the well-validated Monetary Choice Questionnaire[8] to quantify DD rates (**Supplementary Tables 3** and **4**). The phenotypic correlations between DD and demographic and substance use variables measured in the same cohort are shown in **Supplementary Table 5**. Age was not significantly correlated with DD, however males showed greater DD compared to females ($r = 0.11$, $P < 0.0001$). BMI was positively associated with DD ($r = 0.11$, $P < 0.0001$). Several measures of cigarette and cannabis use were also positively correlated with DD (rs = 0.05-0.09, $P < 0.0001$); however, surprisingly, heaviest lifetime alcohol use in a 30-day period was *negatively* correlated with DD ($r = -0.07$, $P < 0.0001$) and scores on the Alcohol Use Disorder Identification Test (**AUDIT**), which is used to screen for alcoholism, were not correlated with DD ($r = 0.00$, $P > 0.5$), perhaps due to low rates of alcohol use in this population.

Using GCTA[9] we estimated the chip-heritability of DD at 12.2% ($\pm$ 1.7%, $P = 5.84 \times 10^{-14}$). We performed association tests by linear regression assuming an additive model. We included age (inverse-normal transformed), sex, the top four principal components of genotype, and indicator variables for genotype platforms as covariates (**Supplementary Tables 6**). **Figure 1** shows the Manhattan and quantile-quantile (**QQ**) plots for DD.

The most significant association was at rs6528024, located on the X-chromosome ($P = 2.40 \times 10^{-8}$; $\beta = -0.10$, SE = 0.02; minor allele frequency (**MAF**) = 0.03; **Supplementary Fig. 1**). Meta-analysis using an independent cohort of 928 participants in the Genes for Good study strengthened this association ($P = 1.44 \times 10^{-8}$; $\beta = -0.10$, SE = 0.02; **Online Methods**). The association was in an intron of the gene *GPM6B* (Neuronal Membrane Glycoprotein M6B), which is implicated in the internalization of the serotonin transporter[10]. *Gpm6B*-deficient mice exhibit deficient prepulse inhibition and an altered response to the 5-HT2A/C agonist DOI[11]. Similarly, serotonergic signaling has also been strongly implicated in DD[12–14]. Furthermore, *GPM6B* mRNA levels were downregulated in the brains of depressed suicide victims[15]. Because rs6528024 is located on the X chromosome, we performed separate GWAS in males and females. Although the association with rs6528024 was stronger in males ($\beta = -0.11$, SE = 0.02, $P = 9.82 \times 10^{-7}$) than in

females (β = -0.08, SE = 0.03, $P = 5.70 \times 10^{-3}$), a meta-analysis of the males and females supported the original finding (β = -0.10, SE = 0.02, $P = 2.81 \times 10^{-8}$).

Several other SNPs showed suggestive associations (**Supplementary Table 7**), including rs2665993 ($P = 1.40 \times 10^{-7}$, β = -0.04, SE = 0.01; MAF = 0.38; **Supplementary Fig. 2**). Using the Genotype-Tissue Expression Portal (**GTEx**) database, we identified *cis* expression quantitative trait loci (**eQTLs**) for *TEN1*, *CDK3* and *EVPL* that co-localized with rs2665993 (within 500 kb and $r^2 > 0.50$; see **Supplementary Table 8**). We also found evidence of regulatory elements associated with this particular SNP using the Regulome DB[16] (**Supplementary Table 8**).

Our results did not support any of the previously published candidate gene studies of DD (reviewed in[17]; **Supplementary Table 9**).

We used MetaXcan[18] to perform a gene-based association test on the autosomes using reference data from the GTEx project. This approach identified higher predicted expression of *CDK3* in the hippocampus of individuals with higher DD (FDR 0.05; **Supplementary Table 10**).

LD score regression[19] showed a genetic overlap between DD and numerous traits (**Fig. 2 and Supplementary Table 11**). We detected a positive genetic correlation between DD and ADHD and major depressive disorder (**MDD**), and a negative genetic correlation with schizophrenia. With regard to smoking-related behaviors, we observed a positive genetic correlation between DD and lifetime smoking, and a negative genetic correlation with former smoker status. Although genetic correlations cannot disentangle causal pathways, our interpretation of these results is that higher DD facilitates smoking initiation and impedes cessation. We identified a positive correlation between DD and neuroticism. DD showed strongly negative correlations with three cognitive measures: college attainment, years of education and childhood IQ. Finally, DD was genetically correlated with BMI, suggesting that higher DD may promote excessive eating. As expected, height, which is not strongly influenced by an individual's behavior, was not genetically correlated with DD.

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With over 23,000 research participants, ours is by far the largest genetic study of DD that has even been undertaken. Our results indicate that DD is a highly polygenic trait that would likely benefit from an even larger sample size.

Unlike studies of disease traits, which require careful diagnosis and ascertainment, we were able to rapidly obtain a large cohort for which genotype data were available. Phenotypic correlations between DD and both ADHD and drug abuse were already well established[4,20]; we showed, for the first time, that they are also genetically correlated. Furthermore, we identified less intuitive genetic correlations between DD and both schizophrenia and MDD. This approach also provides an important entry point for the use of animal models to explore the fundamental molecular mechanisms that underlie psychiatric diseases characterized by altered DD. Consistent with the core goals of the RDoC initiative, our approach shows how genetic studies of DD can be used to gain insight into the biology of psychiatric diagnoses.

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FIGURE LEGENDS

Figure 1 Results of GWAS on DD. (**a**) Manhattan plot of GWAS results for DD. The horizontal line denotes genome-wide significance ($P < 5 \times 10^{-8}$). (b) QQ plot of DD. The results have been adjusted for a genomic control inflation factor λ=1.022 (sample size = 23,217).

Figure 2 Genetic correlations between DD and several traits. (**a**) neuropsychiatric, (**b**) smoking, (**c**) personality, (**d**) cognition, (**e**) anthropomorphic. * P < 0.05, ** P < 0.01, *** P < 0.0001.

METHODS

Methods, along with Supplemental Information with 12 additional tables, are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

Conceptualization, J.M., A.A.P.; analysis and software, P.F., S.S-R., L.K.D., J.C.G.; writing S.S-R., A.A.P.; review and editing, all authors.

COMPETING FINANCIAL INTERESTS

None to declare.

FIGURE 1

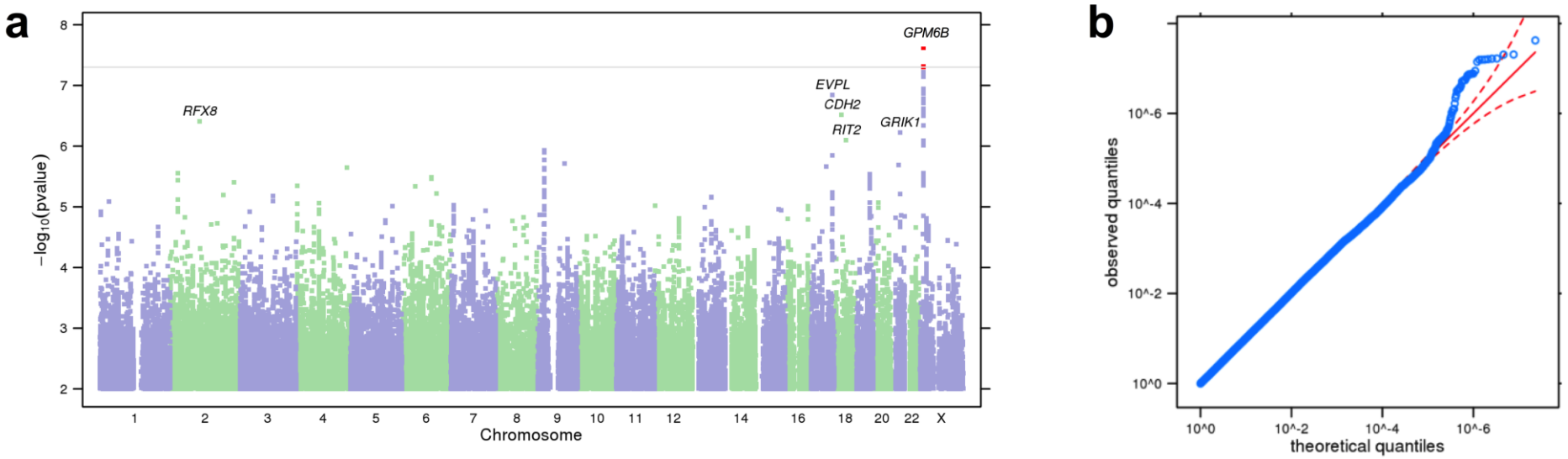
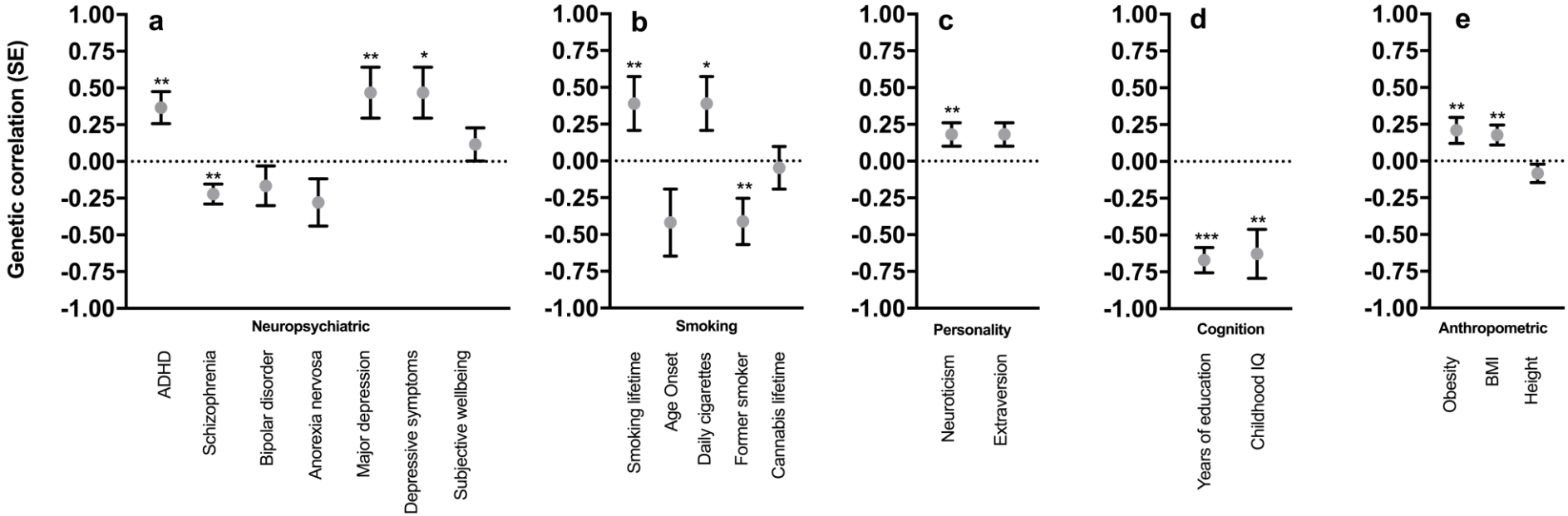

a
b
GPM6B
EVPL
CDH2
RIT2
GRIK1
RFX8
−log10(pvalue)
Chromosome
observed quantiles
theoretical quantiles
10^0
10^-2
10^-4
10^-6

FIGURE 2


Genetic correlation (SE)
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
a
**
**
**
*
Neuropsychiatric
ADHD
Schizophrenia
Bipolar disorder
Anorexia nervosa
Major depression
Depressive symptoms
Subjective wellbeing
b
**
*
**
Smoking
Smoking lifetime
Age Onset
Daily cigarettes
Former smoker
Cannabis lifetime
c
**
Personality
Neuroticism
Extraversion
d
***
**
Cognition
Years of education
Childhood IQ
e
**
**
Anthropometric
Obesity
BMI
Height