Title

Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa

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Genome-Wide Association Study Reveals First Locus for Anorexia Nervosa and Metabolic Correlations

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Abstract

Objective—To conduct a genome-wide association study (GWAS) of anorexia nervosa and to calculate genetic correlations with a series of psychiatric, educational, and metabolic phenotypes.

Method—Following uniform quality control and imputation using the 1000 Genomes Project (phase 3) in 12 case-control cohorts comprising 3,495 anorexia nervosa cases and 10,982 controls, we performed standard association analysis followed by a meta-analysis across cohorts. Linkage disequilibrium score regression (LDSC) was used to calculate genome-wide common variant heritability [h^2_{SNP}, partitioned heritability, and genetic correlations (r_g)] between anorexia nervosa and other phenotypes.

Results—Results were obtained for 10,641,224 single nucleotide polymorphisms (SNPs) and insertion-deletion variants with minor allele frequency > 1% and imputation quality scores > 0.6. The $\mathrm{h}^2_{\mathrm{SNP}}$ of anorexia nervosa was 0.20 (SE=0.02), suggesting that a substantial fraction of the twin-based heritability arises from common genetic variation. We identified one genome-wide significant locus on chromosome 12 (rs4622308, $p=4.3\times10^{-9}$) in a region harboring a previously reported type 1 diabetes and autoimmune disorder locus. Significant positive genetic correlations were observed between anorexia nervosa and schizophrenia, neuroticism, educational attainment, and high density lipoprotein (HDL) cholesterol, and significant negative genetic correlations between anorexia nervosa and body mass index, insulin, glucose, and lipid phenotypes.

Conclusions—Anorexia nervosa is a complex heritable phenotype for which we have found the first genome-wide significant locus. Anorexia nervosa also has large and significant genetic correlations with both psychiatric phenotypes and metabolic traits. Our results encourage a

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URLs

SNP results, https://www.med.unc.edu/pgc.

Author contributions - See **Supplementary Table S6**

reconceptualization of this frequently lethal disorder as one with both psychiatric and metabolic etiology.

Introduction

Anorexia nervosa is a serious eating disorder characterized by restriction of energy intake relative to requirements, resulting in abnormally low body weight. It has a lifetime prevalence of approximately 1%, disproportionately affects females (1, 2), and has no well replicated evidence of effective pharmacologic or psychological treatments, despite high morbidity and mortality (3, 4). Twin studies consistently support a genetic basis for the observed familial aggregation in anorexia nervosa, with heritability estimates of 48%-74% (5). Although initial genome-wide association studies (GWASs) were underpowered (6, 7), the available evidence strongly suggested that signals for anorexia nervosa would be detected with increased sample size (6).

The aim of the current study was to combine existing samples to conduct a more powerful GWAS of anorexia nervosa. To further characterize the nature of the illness, we applied linkage disequilibrium score regression (LDSC) (8) to calculate genome-wide common variant heritability (h^2_{SNP}), partitioned heritability, and genetic correlations (r_g) between anorexia nervosa and other phenotypes. These include the other major psychiatric disorders with large GWAS, namely schizophrenia, bipolar disorder, major depressive disorder, autism, and attention deficit hyperactivity disorder (ADHD). We then used r_g estimates between anorexia nervosa and 159 additional phenotypes (as described below) to characterize the phenome-wide genetic architecture of AN.

Methods

Cases and controls

Our sample included 3,495 anorexia nervosa cases and 10,982 controls. Case definition required a diagnosis of lifetime anorexia nervosa (restricting or binge–purge subtype) or lifetime eating disorders ‘not otherwise specified’ anorexia nervosa-subtype (i.e., exhibiting the core features of anorexia nervosa). A lifetime history of bulimia nervosa was allowed given the frequency of diagnostic crossover (9). Amenorrhea was not required as it does not increase diagnostic specificity (10) [it has been removed as a diagnostic criterion in the DSM-5 (11)]. Extensive information on diagnostic and consensus procedures for the samples included in the Children’s Hospital of Philadelphia/Price Foundation Collaborative Group (CHOP/PFCG) cohort are available in (12). The cases included from the Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC3) GWAS came from 12 previously collected clinical or population cohorts. Given that these were archived samples, the calculation of reliability statistics on diagnoses was not possible. Mitigating that concern, however, is that anorexia nervosa is a highly homogeneous phenotype with typical kappa values ranging from .81-.97 (13). Moreover, the approach taken here is consistent with successful GWAS meta-analysis efforts across psychiatric diagnoses, in which larger samples have overcome the challenges posed by imperfect diagnoses and small individual variant effect sizes.

Individuals with conditions including schizophrenia, intellectual disability, and medical or neurological conditions causing weight loss were excluded, as per previous reports (6, 7). All sites had documented permission from local ethical committees and all participants provided informed consent.

Consistent with procedures established by the Psychiatric Genomics Consortium (PGC) (14, 15), we collected individual-level genotype (GWAS array) and phenotype (binary case-control status) data from contributing previous GWAS consortia and groups (for a description see Supplementary Table S1). In particular, the previous reports on anorexia nervosa GWAS from CHOP/PFCG data (7) and the GCAN/WTTTC3 (6) provide further details about cohort ascertainment and participant characteristics not described below or in the Supplementary Text.

Although most of the cases included in the published anorexia nervosa GWASs were included in this analysis, many of the controls used in previous GWAS could not be used for subsequent analyses. To summarize, our analysis includes the CHOP/PFCG data (7) plus *cases* from 12 of the 15 strata included in the GCAN/WTCCC3 analysis of anorexia nervosa (6). Three datasets (Italy-North, Sweden, and Poland) in Boraska et al. were dropped from our analysis because appropriately matched controls could not be found and/or where case plus control numbers were < 100. After removing these three datasets and combining the US and Canadian cases, we included 11 GCAN/WTCCC3-based datasets plus the CHOP/PFCG dataset in our analyses. For the nine datasets requiring new controls, we first evaluated diverse control datasets from Psychiatric Genomics Consortium (PGC) collaborators for potentially suitable controls based on geographic location and Illumina genotyping. We then performed quality control (QC) steps (below, and with additional details in the Supplementary Text), using visual inspection of principal components plots (comparing cases to controls) as well as QQ and Manhattan plots (for evidence of systematic bias) to identify suitably matched controls. All samples in this report are of European ancestry. As shown in Supplementary Figure S1, all of the datasets (except for Finland) form a gradient of clusters when visualized in a scatter plot of the first two principal components, as expected based on known population genetic features (16).

Quality control and analysis

Following uniform quality control and imputation using the 1000 Genomes Project (phase 3) (17) in the anorexia nervosa case-control cohorts, we performed association analysis using an additive model using the dosage data for each cohort. Following adjustment for unbalanced case and control numbers across our 12 strata [see (18)], our summed effective balanced sample size was 5082 cases and 5082 controls. Accordingly, our power was 83.1% for a genotype relative risk of 1.25, at an allele frequency of 0.2 at $p<5\times10^{-8}$ (http://zzz.bwh.harvard.edu/gpc). Analysis within datasets was performed in PLINK with the first ten principal components as covariates. METAL (18) was used to conduct fixed-effects meta-analysis across the twelve datasets using inverse-variance weighting. Results were obtained for 10,641,224 single nucleotide polymorphisms (SNPs) and insertion-deletion variants with minor allele frequency > 1% and imputation quality scores > 0.6 [see Supplementary Figure S2 for quantile-quantile (QQ) plot]. The GWAS statistic inflation (λ)

was 1.080 with a sample size adjusted λ_{1000} of 1.008, consistent with minimal population stratification or other systematic biases. Plotting was performed in R (19) (see Supplementary Text for additional methods and quality control details and Supplementary Table S1 for individual study details).

Statistical significance

The primary analysis in this paper is the GWAS, which analyzes each SNP for association to phenotype. The international standard for statistical significance is $p<5\times10^{-8}$, which corrects for the approximately one million independent statistical tests conducted. Focused secondary analyses are now the expectation for primary GWAS reports, and we describe statistical significance thresholds for them individually. We used the accepted and expected methods of multiple testing correction. Gene-based and pathway analyses were also conducted. For these analyses, statistical significance was set using the Bonferroni correction, which is conservative given non-independence among the gene-based and pathway statistical tests. For the gene-based analyses, we defined statistical significance as gene p-value $< 2.6\times10^{-6}$ (0.05/19,222 genes tested). For pathway analyses: p-value $<1.8\times10^{-5}$ (0.05/2,714 pathways tested).

Analytical methods for estimating heritability and genetic correlations, and for gene-based and pathway analyses, are presented in the Supplementary Text. Regarding the rationale for these particular secondary analyses, we note that these are often considered to be standard analyses for GWAS reports across medicine. In this particular application, we estimate SNP heritability for anorexia nervosa because it is important to quantify the combined effects of common variants on anorexia nervosa and compare it with other complex disorders and traits, within and outside psychiatry.

Results

GWAS

One locus achieved genome-wide significance for a single variant, as shown in the Manhattan plot in Figure 1, in which the threshold for significance, $p<5\times10^{-8}$, is denoted with dotted line. The top locus (chromosome 12q13.2) overlaps six genes (*IKZF4*, *RPS26*, *ERBB3, PA2G4, RPL41*, and *ZC3H10*), and is located near six additional genes (*ESYT1, SUOX, RAB5B, CDK2*, *PMEL*, and *DGKA*). The top SNP was rs4622308 ($p=4.3\times10^{-9}$, odds ratio (OR)=1.2, standard error (SE)=0.03, minor allele frequency in cases (MAF_{cases})=0.48, minor allele frequency in controls ($MAF_{controls}$)=0.44). We found no evidence for heterogeneity in effect sizes across cohorts (Q=12.58, p=.32) and estimated that 12.59 percent of variation was due to heterogeneity instead of chance (I^2=12.59). The effects across studies are shown in the forest plot of rs4622308 in Supplementary Figure S3.

The results of conditional regression analyses are consistent with the existence of one signal at the top locus (see Supplementary Figure S4). The top SNP rs4622308 is in high linkage disequilibrium (LD) (r^2=0.86; D'>0.99) with rs11171739, which has been found to be associated in GWASs of type 1 diabetes (20) and rheumatoid arthritis (21). The risk associated alleles of both SNPs (C–C) are typically found on the same haplotype, i.e., the

direction of effect for the risk allele is consistent across anorexia nervosa and these other disorders. Several other immune-related phenotypes: vitiligo, alopecia areata, and asthma (see Supplementary Figure S5) also have associations in the region, although these are (somewhat) LD independent of rs4622308.

Information for the top ten loci is given in Supplementary Table S2. The second (rs200312312 on chromosome 5, $p=6.7\times10^{-8}$), third (rs117957029 on chromosome 12, $p=1.6\times10^{-7}$), and fourth (rs11174202 on chromosome 12, $p=3.1\times10^{-7}$) most significant loci in our analyses also have consistent evidence for association across multiple cohorts (see Supplementary Figure S6 for area plots of these loci). The fourth best locus is intronic in the *FAM19A2* gene.

Gene-based and pathway analyses

Multiple genes, all but one of which were in the region around the top SNP (rs4622308), reached gene-based significance (reflecting the high LD in the region). The remaining significant gene was *FAM19A2*, a putative chemokine/cytokine, and the 4th best locus in our SNP based analyses. No pathways were significant (see Supplementary Table S3 for the complete gene-based and pathway analysis results). As has typically been reported for other psychiatric disorders, candidate genes from previous studies did not reach gene-based significance [or in our other analyses; for a detailed review of the candidate gene literature see (5)].

Gene expression

Interrogation of databases such as GTeX (22) did not indicate that any of the genes in the top region have distinct patterns of brain gene expression. Searches using both GTeX and the SNP tag lookup function in MRbase (www.mrbase.org/beta) indicated that that the top SNP (rs4622308) is not, directly or via LD tagging, an eQTL or mQTL. In addition, differential expression in an exploratory mouse model did not suggest a distinct pattern of gene expression (Supplementary Figure S7).

Linkage disequilibrium score regression (LDSC)

LDSC (8, 23) was used to calculate h^2_{SNP}, partitioned heritability, and r_g between anorexia nervosa and other psychiatric, medical, and educational phenotypes. Heritability estimates reported here afford comparison of AN to other major psychiatric disorders. We made comparisons to the psychiatric disorders that have been examined with adequately sized GWAS to afford reliable estimates of heritability, including schizophrenia, bipolar disorder, major depressive disorder, autism, and ADHD. The genetic correlation estimates between AN and 159 additional phenotypes (with publically available GWAS summary statistics) further characterize the genetic architecture of AN, by providing the magnitude and direction of shared genetic effects between AN and diverse psychological, medical, metabolic, and educational phenotypes.

In our cohort, h^2_{SNP} for anorexia nervosa was 0.20 (SE=0.021), comparable to h^2_{SNP} estimates for other psychiatric disorders (see Supplementary Figure S8). Partitioned heritability

estimates for annotation categories and cell types were not significant after multiple testing correction (for complete results see Supplementary Table S4).

A wide range of genetic correlations between anorexia nervosa and other phenotypes were statistically significant. Of 159 phenotypes tested, 29 had false discovery rate (FDR)<0.05 (uncorrected p-values reported below). See Figure 2 for depiction of these genetic correlations and text below for selected examples. All 159 genetic correlations and relevant references are available in Supplementary Table S5.

Notable significant genetic correlations between anorexia nervosa and psychiatric traits and disorders included neuroticism (r_g =0.39, SE=0.14, p=4.4×10^{-3}), schizophrenia (r_g =0.29, SE=0.07, p=4.4×10^{-5}), and results from a meta-analysis across psychiatric phenotypes (r_g =0.22, SE=0.07, p=3.4×10^{-3}). Genetic correlations between anorexia nervosa and educational phenotypes such as years of education (r_g =0.34, SE=0.08, p=5.2×10^{-6}) and attending college (r_g =0.30, SE=0.07, p=4.4×10^{-5}) were also positive and significant. Obsessive compulsive disorder GWAS data were unavailable to us but a previous analysis reported a positive r_g with anorexia nervosa of 0.53 (SE=0.11, SE=0.13, p=5.5×10^{-6}) (24).

Several significant negative genetic correlations emerged between anorexia nervosa and weight-related phenotypes, suggesting shared genetic loci underlying these phenotypes and opposing effects for relevant alleles. Extreme high body mass index (BMI) was significantly negatively correlated with anorexia nervosa (r_g =−0.29, SE=0.08, p=2.0×10^{-4}) as were obesity, BMI in the normal range, overweight, and hip circumference, with genetic correlations ranging from −0.2 to −0.3.

We also observed significant negative genetic correlations between anorexia nervosa and insulin and glucose related traits—e.g., exceeding those of BMI for both insulin resistance (HOMA-IR) (r_g =−0.50, SE=0.11, p=1.3×10^{-5}) and fasting insulin (r_g =−0.41, SE=0.09, p=5.2×10^{-6}); as well as a similar correlation with fasting glucose (r_g =−0.26, SE=0.07, p=3.0×10^{-4}). Although BMI corrected HOMA-IR GWAS statistics were not available genome-wide, additional analyses with the available BMI corrected GWAS results for related phenotypes suggest that this metabolic signal is at least partly independent of BMI with leptin levels (r_g = −0.24, SE=0.11, p=0.03). Regarding cholesterol and lipid measures, a distinction between different lipid fractions emerges when comparing high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) phenotypes. Genetic correlations between anorexia nervosa and HDL phenotypes were positive: e.g., total cholesterol in large HDL particles (r_g =0.39, SE=0.12, p=1.6×10^{-3}); free cholesterol in large HDL particles (r_g =0.37, SE=0.12, p=2.2×10^{-3}); and phospholipids in large HDL particles (r_g =0.30, SE=0.11, p=6.7×10^{-3}). In contrast, VLDL cholesterol phenotypes were negatively correlated with AN, albeit with nominal significance (i.e., uncorrected p<.05): e.g., total lipids in VLDL (r_g =−0.30, SE=0.12, p=0.01); phospholipids in VLDL (r_g =−0.33, SE=0.13, p=4.4×10^{-3}); and LDL cholesterol (r_g =−0.20, SE=0.08, p=0.011).

Discussion

To our knowledge, this is the first report of a genome-wide significant association for anorexia nervosa. As is typical of many GWAS loci for complex disorders, the region implicated is broad, with a modest odds ratio of 1.2 but at a common allele ($MAF_{controls}$=0.44) (25). Our genome-wide h^2_{SNP} estimate of 20% for anorexia nervosa supports a substantial role for common genetic variation. As we now expect (26), the h^2_{SNP} estimate reported here indicates that common variants account for a sizeable portion of twin-based heritability (h^2_{Twin} 48–74%)[6]. Further, these results fit with the expectation that h^2_{Twin} should exceed h^2_{SNP}, because the former captures the effects of all types of genetic variation (common and rare, as well as variation not captured with current methods).

The observed pattern of genetic correlations with psychiatric, personality, educational, and metabolic phenotypes provides grounds for broadening our conceptualization of the disorder. First, the strong positive genetic correlations of anorexia nervosa with obsessive-compulsive disorder and neuroticism reinforce clinical and epidemiological observations. AN is commonly comorbid with OCD and twin studies have reported high twin-based genetic correlations (27). High neuroticism in adolescence predicts subsequent onset of AN (1). In addition, anorexia nervosa is commonly comorbid with multiple anxiety phenotypes, which often pre-date the onset of anorexia nervosa (28).

Second, the positive genetic correlations seen with schizophrenia and the cross psychiatric disorder phenotype firmly anchor anorexia nervosa with other psychiatric disorders and reflect the substantial evidence for partially shared genetic risk across many psychiatric disorders (29). Third, congruent with our results, positive associations been anorexia nervosa and educational attainment have been reported (30) and have been conjectured to reflect greater internal and external demands for academic success in highly educated families. Our results, in contrast, suggest that genetic factors may partially account for these reported associations.

Fourth, the identification of significant negative correlations between anorexia nervosa and BMI-related and anthropometric measures could potentially serve as an important first step toward gaining a better understanding of the shared biology underlying extremes of weight dysregulation (i.e., obesity vs. anorexia nervosa). This is of critical importance as adequate explanations for how individuals with anorexia nervosa reach, sustain, and revert to exceedingly low BMIs have been elusive. Clinically, one of the most perplexing features of anorexia nervosa, is how patients' bodies seem to revert rapidly to a "low set point" after renourishment, which may represent the biological inverse of the reversion to high set points commonly seen in the unsuccessful treatment of obesity (31, 32). As noted by Bulik-Sullivan et al. (23) and Hinney et al. (33), these observations extend our understanding that the same genetic factors that influence normal variation in BMI, body shape, and body composition may also influence extreme dysregulation of these weight-related features in anorexia nervosa. This pattern of observations complements prior strong evidence for the involvement of neural mechanisms in obesity (34). Finally, positive correlations with "favorable" metabolic phenotypes (i.e., HDL and lipid measures) and negative correlations

with “unfavorable” metabolic phenotypes (i.e., fasting insulin, fasting glucose, HOMA-IR) encourage additional exploration of the role metabolic factors may play in extreme dysregulation of appetite and weight in anorexia nervosa.

The genome-wide significant locus we identify to be associated with anorexia nervosa is broad and multigenic (chr12:56,372,585-56,482,185). Mechanistic explanations about the role of the associated variant require additional functional data; nevertheless, we note the possible role for genes at this locus in the pathophysiology of anorexia nervosa. *PA2G4* is involved in growth regulation and acts as a corepressor of the androgen receptor (35). *ESYT1* [extended synaptotagmin-1 which binds and transports lipids (36)] is enriched in the postsynaptic density, which is implicated in the etiology of schizophrenia (37). Perhaps more convincing is that the sentinel marker for this locus, rs4622308, is in high LD with a known GWAS hit for type 1 diabetes (20), and rheumatoid arthritis (21), and the region around it harbors multiple other autoimmune associations. Multiple reports of shared effects between anorexia nervosa and immune phenotypes fit into a broader pattern of above-chance comorbidity across psychiatric and immune phenotypes (38, 39). Evidence suggests that this shared risk is at least partly genetic in origin (23, 39). A negative genetic correlation between anorexia nervosa and rheumatoid arthritis was previously reported (23), and our LDSC estimate—though only nominally significant—is in the negative direction as well (see Supplementary Table S5).

The primary strength of this investigation is to have extended prior work by increasing sample size via collaboration. Importantly, our combined sample size remains modest given contemporary understanding of complex trait genetics. Moreover, since our collection represents all of the currently GWAS genotyped anorexia nervosa samples in the world, no known genotyped replication samples exist. As such, we expect this to be the beginning of genomic discovery in eating disorders (25). Future work with additional and better-powered anorexia nervosa GWAS will clarify the magnitude of genetic relationships among metabolic and psychiatric phenotypes and methods such as that proposed by Pickrell et al. (40) will provide clues about the direction of causal relationships.

In summary, we identified the first robust genome-wide significant locus for anorexia nervosa, which is also a previously reported type 1 diabetes and general autoimmune disorder locus. Perhaps of greater importance, is that we find anorexia nervosa is a complex heritable phenotype with intriguingly large and significant genetic correlations not only with psychiatric disorders but also multiple metabolic traits. This encourages a reconceptualization of this frequently lethal disorder as both psychiatric and metabolic. Just as obesity is increasingly considered to be both a metabolic/endocrine and psychiatric disorder, approaching anorexia nervosa as both a psychiatric and metabolic condition could ignite interest in developing or repositioning pharmacologic agents for its treatment where currently none exist.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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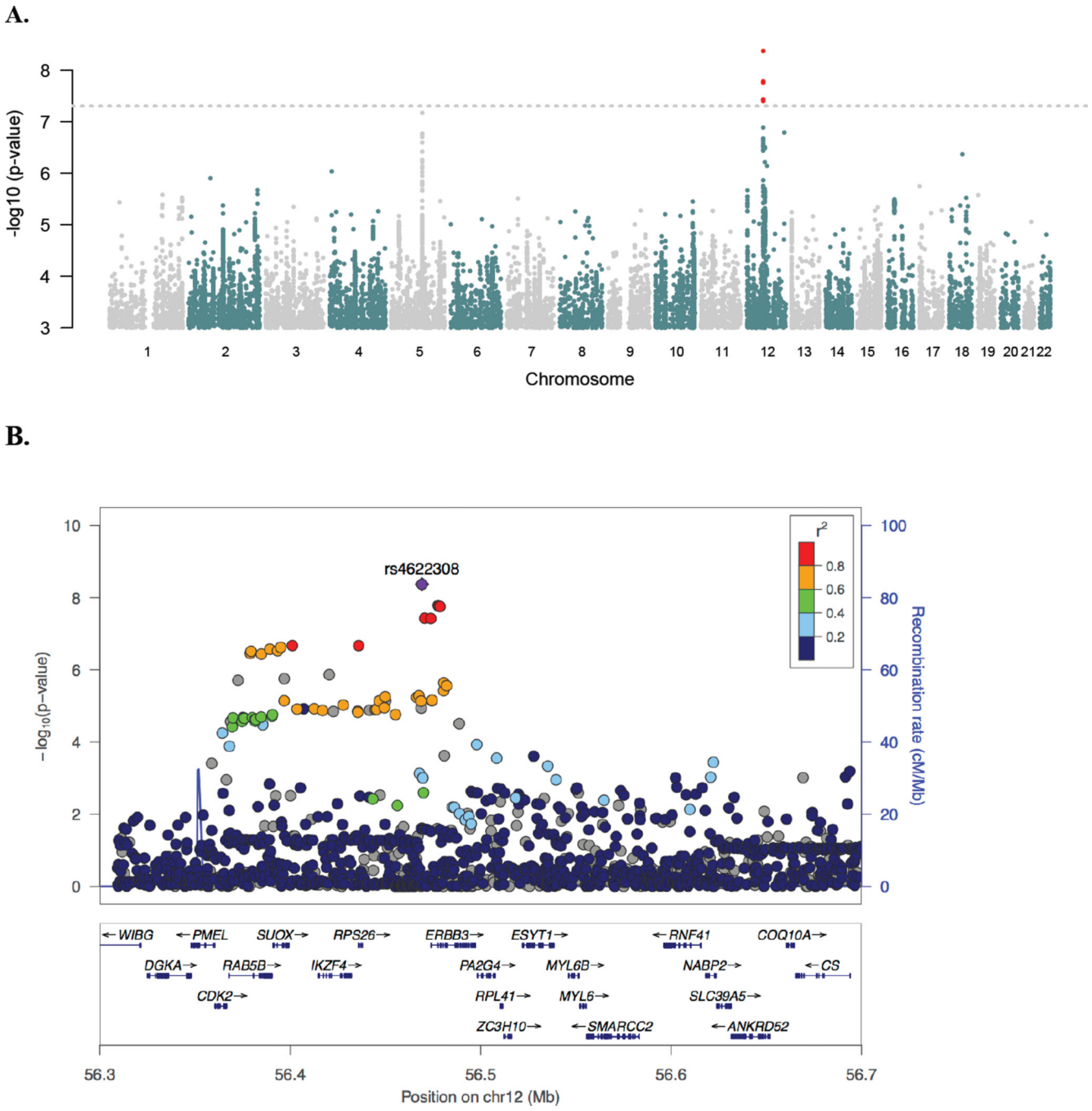

Figure 1. Manhattan and regional plot of the genome-wide significant locus for anorexia nervosa

A. Manhattan plot depicts a genome-wide significant locus on chromosome 12. The threshold for significance (see y-axis) is 7.3, which is $-\log_{10}(5\times10^{-8})$. B. Regional LOCUSZOOM plot of the top locus reveals numerous genes in the region. Results depicted here reflect the full meta-analysis. Per text, see Supplementary Figure 1 for area plot with phenotypic associations. The right axis gives recombination rate, depicted with a light blue line.

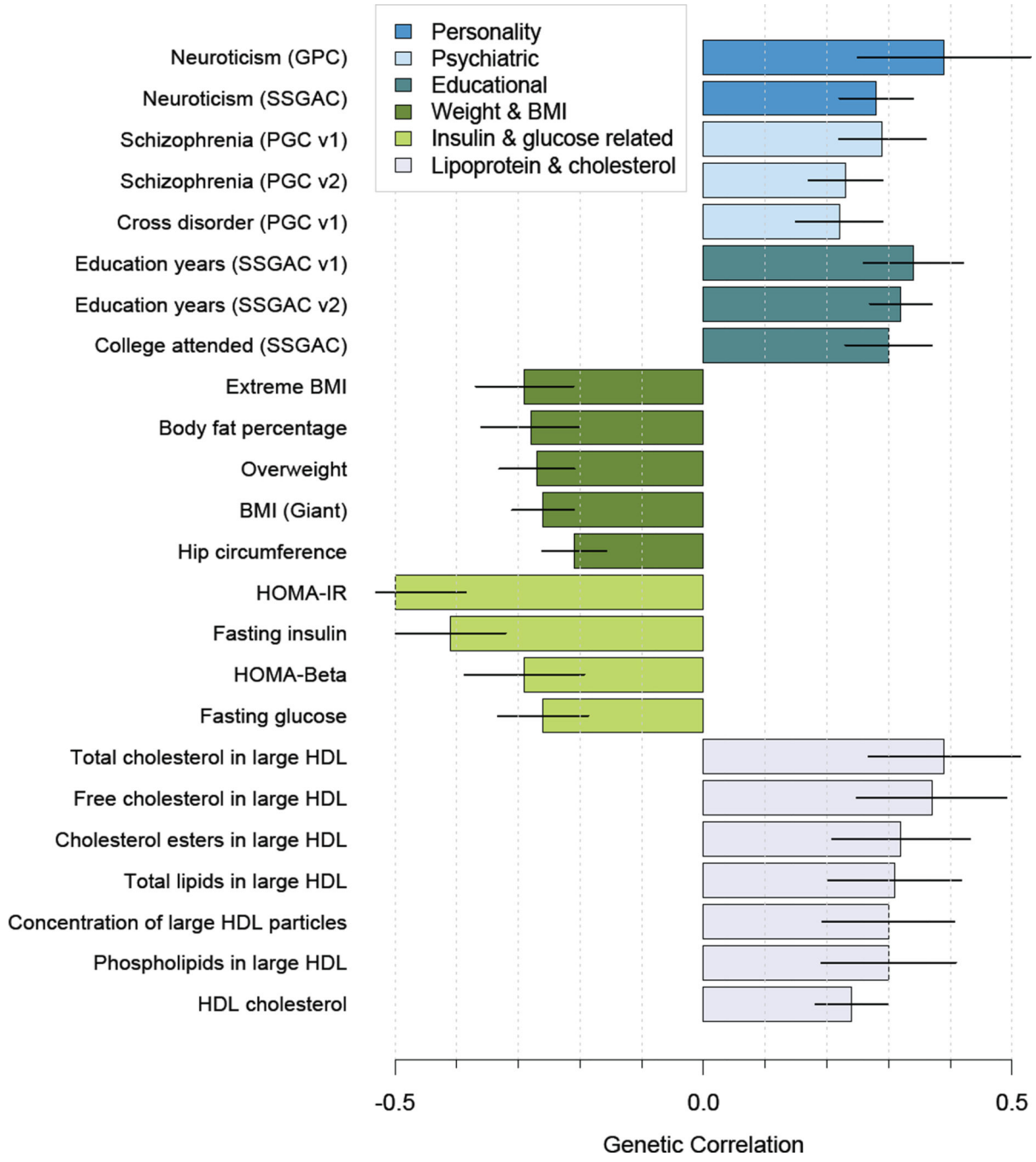

Figure 2. Genetic correlations between anorexia nervosa and diverse phenotypes reveal overlap across psychiatric, educational, weight, insulin, lipoprotein, and cholesterol phenotypes

The 24 correlations depicted here (of 159 phenotypes tested) have FDR<0.05. Bars are ± standard error.