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Genome-wide Association Study Identifies Eight Risk Loci and Implicates Metabo-Psychiatric Origins for Anorexia Nervosa

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Genome-wide Association Study Identifies Eight Risk Loci and Implicates Metabo-Psychiatric Origins for Anorexia Nervosa

Characterized primarily by low BMI, anorexia nervosa is a complex and serious illness[1], affecting 0.9-4% of women and 0.3% of men[2-4], with twin-based heritability estimates of 50-60%[5]. Mortality rates are higher than other psychiatric disorders[6], and outcomes are unacceptably poor[7]. Combining data from the Anorexia Nervosa Genetics Initiative (ANGI)[8,9] and the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED), we conducted a genome-wide association study (GWAS) of 16,992 anorexia nervosa cases and 55,525 controls, identifying eight significant loci. The genetic architecture of anorexia nervosa mirrors its clinical presentation showing significant genetic correlations with psychiatric disorders, physical activity, metabolic (including glycemic), lipid, and anthropometric traits, independent of the effects of common variants associated with BMI. Results further encourage a reconceptualization of anorexia nervosa as a metabo-psychiatric disorder. Explicating the metabolic component is a critical direction, and attention to both psychiatric and metabolic components may be key to improving outcomes.

The first PGC-ED GWAS (3,495 cases, 10,982 controls) estimated the common genetic variant-based heritability of anorexia nervosa as ~20%, identified the first genome-wide significant locus, and reported significant genetic correlations (r_g) between anorexia nervosa and psychiatric and metabolic/anthropometric phenotypes[10]. These r_g pointed toward metabolic etiological factors, as they are robust to reverse causation although they could be mediated associations[11] or reflect confounding processes[12]. To advance genomic discovery in anorexia

nervosa and further explore genetic correlations, we combined samples from ANGI[8,9], the Genetic Consortium for Anorexia Nervosa (GCAN)/Wellcome Trust Case Control Consortium-3 (WTCCC-3)[13], and the UK Biobank[14], quadrupling our sample size.

Our GWAS meta-analysis included 33 datasets comprising 16,992 cases and 55,525 controls of European ancestry from 17 countries (**Supplementary Tables 1-4**). We had 80% power to detect an odds ratio (OR) of 1.09-1.19 (additive model, 0.9% lifetime risk, $\alpha = 5 \times 10^{-8}$, MAF 0.05–0.5). Typical of complex trait GWAS, we observed test statistic inflation ($\lambda = 1.22$) consistent with polygenicity, with no evidence of significant population stratification according to the LD intercept and attenuation ratio (**Supplementary Results; Supplementary Fig. 1**). Meta-analysis results were completed for autosomes and the X chromosome. We identified eight loci exceeding genome-wide significance ($P < 5 \times 10^{-8}$; **Table 1** for loci; **Fig. 1** for the Manhattan plot; **Supplementary Figs. 2a-h** and **3a-h** for the forest and region plots). Many were near the threshold for significance, and no significant heterogeneity of SNP associations across cohorts was detected ($P = 0.15$-0.64; **Supplementary Figs 2a-h**). Conditional and joint analysis (GCTA-COJO)[15] confirmed independence of the lead SNPs within the significant loci (**Supplementary Table 5**). The eight loci were annotated to identify known protein-coding genes (**Supplementary Table 6; Supplementary Table 7** reports a gene look-up restricted to the single-gene loci). The previously reported PGC-ED genome-wide significant variant (rs4622308)[10] on 12q13.2 did not reach genome-wide significance ($P = 7.02 \times 10^{-5}$); however, between-cohort heterogeneity was apparent ($I^2 = 53.7$; **Supplementary Fig. 4** and **Supplementary Results**). The OR was in the same direction in 22 (67%) of the cohorts ($z = 2.00$, $P = 0.05$, 2-tailed).

Although GWAS findings are informative genome-wide, identifying strong hypotheses about their connections to specific genes is not straightforward. We evaluated three ways to "connect" anorexia nervosa GWAS loci to genes: regulatory chromatin interactions; relationship to brain expression QTLs (eQTLs; using a superset of CommonMind[16] and GTEx[17]) and the standard approach of gene location within a GWAS locus. The significant anorexia nervosa loci implicated 121 brain-expressed genes, 74% by location, 55% by adult brain eQTL, 93% by regulatory chromatin interaction, and 58 genes by all three methods. **Supplementary Figs. 5a-h** show the eight GWAS loci, GENCODE gene models, adult brain regulatory chromatin interactions, brain eQTLs, and functional genomic annotations.

Four single-gene loci were confirmed by eQTL, chromatin interaction, or both. These were the locus-intersecting genes *CADM1* (locus 2 chr11:114.9-115.4 Mb, **Supplementary Fig. 5b**), *MGMT* (locus 4, chr10:131.2-131.4 Mb, **Supplementary Fig. 5d**), *FOXP1* (locus 5, chr3:70.6-71.0 Mb, **Supplementary Fig. 5e**) and *PTBP2* (locus 6, chr1:96.6-97.2 Mb, **Supplementary Fig. 5f**). For locus 5, eQTL data implicated a distal gene, *GPR27*. One intergenic locus (locus 7, chr5:24.9-25.3 Mb, **Supplementary Fig. 5g**) had no eQTL or chromatin interactions whereas the other intergenic locus (locus 8, chr3:93.9-95.0 Mb, **Supplementary Fig. 5h**) had eQTL connections to *PROS1* and *ARL13B*. Two complex multigenic loci had many brain-expressed genes and dense chromatin and eQTL interactions that precluded identification of any single gene (locus 1, chr3:47.5-51.3 Mb; locus 3, chr2:53.8-54.3 Mb, **Supplementary Figs. 5a** and **5c**). The clearest evidence and connections were for the single-gene loci intersecting *CADM1*, *MGMT*, *FOXP1,* and *PTBP2* and we conclude these genes may play a role in anorexia nervosa etiology (**Supplementary Results**).

Supplementary Table 8 presents multi-trait analysis (GCTA-mtCOJO[18] conditioning our genome-wide significant SNPs on associated variants in GWAS of BMI, type 2 diabetes, education years, HDL cholesterol, neuroticism, and schizophrenia. Seven loci appear to be independent. Locus 2 on chr11 may not be unique to anorexia nervosa and may be driven by genetic variation also associated with type 2 diabetes.

Liability-scale SNP heritability (SNP-h^2) was estimated with LD score regression (LDSC)[19,20]. Assuming a lifetime prevalence of 0.9-4%[2-4], SNP-h^2 was 11-17% (s.e. = 1%), supporting the polygenic nature of anorexia nervosa. Polygenic risk score (PRS) analyses using a leave-one-out approach indicated that the PRS captures ~1.7% of the phenotypic variance on the liability scale for discovery $P = 0.5$. We did not observe differences in polygenic architecture between anorexia nervosa subtypes with binge eating (2,381 cases, 10,249 controls) or without (2,262 cases, 10,254 controls) or between males (447 cases, 20,347 controls) and females (14,898 cases, 27,545 controls) (**Methods**, **Supplementary Results**, **Supplementary Fig. 6, Supplementary Table 9**). Similar to females, males in the highest PRS decile had 4.13 (95% CI: 2.58-6.62) times the odds of anorexia nervosa than those in the lowest decile. Confirmation of these results requires larger samples.

We tested SNP-based genetic correlations (SNP-r_g) with external traits using bivariate LDSC[19,20]. Bonferroni-significant SNP-r_g assorted into five trait categories: psychiatric and personality; physical activity; anthropometric; metabolic; and educational attainment (**Supplementary Table 10**). **Fig. 2** presents Bonferroni-corrected positive SNP-r_g with OCD (SNP-$r_g \pm$ s.e. = 0.45 ± 0.08; $P = 4.97 \times 10^{-9}$), MDD (0.28 ± 0.07; $P = 8.95 \times 10^{-5}$), anxiety disorders (0.25 ± 0.05; $P = 8.90 \times 10^{-8}$), and schizophrenia (0.25 ± 0.03; $P = 4.61 \times 10^{-18}$). This pattern reflects observed comorbidities in clinical and epidemiological studies[21,22]. The newly-

identified positive SNP-r_g with physical activity (0.17 ± 0.05; $P = 1.00 \times 10^{-4}$) encourages further exploration of the refractory symptom of pathologically elevated activity in anorexia nervosa[23]. We note that the significant SNP-r_g of anorexia nervosa with educational attainment (0.25 ± 0.03; $P = 1.69 \times 10^{-15}$) and related constructs was not seen for IQ[24].

Expanding our previous observations[10], we present a palette of metabolic and anthropometric r_g with anorexia nervosa more pronounced than in other psychiatric disorders. We observed significant negative SNP-r_g with fat mass (-0.33 ± 0.03; $P = 7.23 \times 10^{-25}$), fat-free mass (-0.12 ± 0.03; $P = 4.65 \times 10^{-5}$), BMI (-0.32 ± 0.03; $P = 8.93 \times 10^{-25}$), obesity (-0.22 ± 0.03; $P = 2.96 \times 10^{-11}$), type 2 diabetes (-0.22 ± 0.05; $P = 3.82 \times 10^{-5}$), fasting insulin (-0.24 ± 0.06; $P = 2.31 \times 10^{-5}$), insulin resistance (-0.29 ± 0.07; $P = 2.83 \times 10^{-5}$), and leptin (-0.26 ± 0.06; $P = 4.98 \times 10^{-5}$), and a significant positive SNP-r_g with HDL cholesterol (0.21 ± 0.04; $P = 3.08 \times 10^{-7}$).

Systems biology analyses of our results revealed preliminarily interesting results (**Methods, Supplementary Tables 11-13, Supplementary Figs. 7-15**). Gene-wise analysis with MAGMA prioritized 79 Bonferroni-significant genes, most within the multigenic locus on chr3 (**Supplementary Table 11**). MAGMA indicated an association with *NCAM1* **(Supplementary Table 11)** the expression of which increases in response to food restriction in a rodent activity-based anorexia nervosa model[25]. Partitioned heritability analysis showed, as with other GWAS[26], considerable enrichment of SNP-h^2 in conserved regions (fold enrichment = 24.97, s.e. = 3.29, $P = 3.32 \times 10^{-11}$; **Supplementary Fig. 7)**[27]. Cell type group-specific annotations revealed that the overall SNP-h^2 is significantly enriched for CNS tissue (**Supplementary Fig. 8**). One biological pathway was significant: GO:positive_regulation_of_embryonic_development (32 genes, $P = 1.39 \times 10^{-7}$; **Supplementary Table 12**), which contains two Bonferroni-significant genes on

chr3, *CTNNB1* and *DAG1*. *CTNNB1* encodes catenin beta-1, which is part of adherens junctions, and *DAG1* encodes dystroglycan, a receptor which binds extracellular matrix proteins[28]. *DAG1* falls within locus 1 (47.5-51.3 Mb). This pathway points to a potential role of developmental processes in the etiology of this complex phenotype (although this is currently speculative). Genes associated with anorexia nervosa were enriched for expression in most brain tissues, particularly the cerebellum, which has a notably high proportion of neurons[29] (**Supplementary Fig. 9**). Among 24 brain cell types from mouse brain, significant enrichment was found for medium spiny neurons and pyramidal neurons from hippocampal CA1 (**Supplementary Fig. 10**). Both medium spiny and pyramidal neurons are linked to feeding behaviors including food motivation and reward[30,31] (**Supplementary Results**). Using PrediXcan (**Supplementary Methods)**, 36 genes were predicted to be differentially expressed in GTEx tissues or blood (**Supplementary Table 13**) with the expression of *MGMT* predicted to be downregulated in the caudate. We cautiously note that these results represent the first indications of specific pathways, tissues, and cell types that may mediate genetic risk for anorexia nervosa.

Because low BMI is pathognomonic of anorexia nervosa, we investigated the extent to which genetic variants associated with BMI accounted for genetic correlations with metabolic and anthropometric traits. First, covarying for the genetic associations of BMI (**Methods**) led to a mild but statistically non-significant attenuation of the SNP-r_g between anorexia nervosa and fasting insulin, leptin, insulin resistance, type 2 diabetes, and HDL cholesterol (**Supplementary Tables 14-15**), suggesting that anorexia nervosa shares genetic variation with these metabolic phenotypes that may be independent of BMI. Second, we investigated bidirectional causality using generalized summary data-based Mendelian randomization[18]. GSMR analyses indicate a significant bidirectional causal relationship such that anorexia nervosa risk-increasing alleles

may increase risk for low BMI and BMI-lowering alleles may increase the risk of anorexia nervosa (**Supplementary Table 16**). It is important to note that having only eight genome-wide significant loci for anorexia nervosa render this analysis marginally powered in the direction of anorexia nervosa to BMI, although this analysis is well powered in the direction of BMI to anorexia nervosa.

Replication is challenging with GWAS of low prevalence conditions like anorexia nervosa, as replication samples must be sufficiently powered to detect the initial findings. We included all available samples in our analysis to maximize chances of reaching the GWAS inflection point, after which there might be a linear increase in "hits"[32]. The PRS leave-one-out analyses provide evidence of replication by demonstrating a higher burden of anorexia nervosa common risk variants in cases, compared with controls, across all the cohorts (**Supplementary Fig. 16**).

In conclusion, we report multiple genetic loci alongside promising clinical and functional analyses and enrichments. The increased sample size in the present GWAS has allowed us to characterize more fully the metabolic contribution to anorexia nervosa than our previous report[10] by revealing significant r_g with metabolism related phenotypes including glycemic and anthropometric traits and by demonstrating that the effect is robust to correction for the effects of common variants significantly associated with BMI. Low BMI has traditionally been viewed as a consequence of the psychological features of anorexia nervosa (i.e., drive for thinness and body dissatisfaction). This perspective has failed to yield interventions that reliably lead to sustained weight gain and psychological recovery[7]. Fundamental metabolic dysregulation may contribute to the exceptional difficulty that individuals with anorexia nervosa have in maintaining a healthy BMI (even after therapeutic renourishment). Our results encourage consideration of both

metabolic and psychological drivers of anorexia nervosa when exploring new avenues for treating this frequently lethal illness.

URLs. GCTA, http://cnsgenomics.com/software/gcta; GSMR, http://cnsgenomics.com/software/gsmr; LDSC, https://github.com/bulik/ldsc; MAGMA, http://ctg.cncr.nl/software/magma.

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Author contributions

C.M.B. and P.F.S. conceived and designed the study. L.T., C.M.B., and G.B. performed overall study coordination. C.M.B. was lead PI of ANGI. P.F.S. was Co-Investigator of ANGI. N.G.M., M.L., and P.B.M. were site PIs of ANGI. H.J.W., Z.Y., J.R.I.C., C.H., J.B., H.A.G., S.Y., V.M.L., M.M., P.G-R. and S.E.M. performed the statistical analyses. H.J.W., Z.Y., C.H., J.R.I.C., H.A.G., J.B., A.H., P.G-R., P.F.S., G.B. and C.M.B. comprised the writing group. C.M.B. and G.B. were PGC-ED co-chairs. S.R. provided statistical consultation. A.H. assisted with data interpretation. A.W.B., C.M.B., J.J., M.K., K.M.K., P.L., G.M., C.N., R.P., L.T., and T.D.W. collected and managed the ANGI samples at sites and assisted with site-specific study co-ordination. A.W.B., J.M.B., H.B., S.C., K.A.H., L.J.H., C.J., A.S.K., W.K., J.M., C.M.O., J.F.P., N.L.P., M.S., T.W., D.C.W., and D.B.W. provided ANGI controls and extra samples. L.E.D provided data expertise. S.G., J.G., A.K.H., A.J., K.M.K., J.T.L., R.P., and L.P. contributed to the ANGI study. S.G., J.G., K.K., J.T.L., M.M., S.M., and L.P. were ANGI site

analysts. K.B.H. and K.L.P. provided additional analysis for some secondary analyses. G.W.M., T.D.W., A.B., P.L., and C.N. were ANGI investigators. J.J. and M.K. assisted with ANGI recruitment in NZ. C.M.B., G.B., and P.F.S. supervised the study. H.J.W., C.M.B., Z.Y., C.H., G.B., J.R.I.C., H.A.G., S.Y., J.B., P.F.S., and P.G. wrote the manuscript. PGC-ED members and other individuals contributed to sample acquisition and made individual data from subjects available: R.A.H.A., L.A. T.A., O.A.A., J.H.B., A.W.B., W.H.B., A.B., I.B., C.B., J.M.B., H.B., G.B., K. B., C.M.B., R.B., M.C., S.C., M.C., J.R.I.C., R.D.C., P.C., S.C., S.C., J.C., U.N.D., O.S.P.D, M.D, G.D., D.D., J.E.D., D.M.D., D.D., C.D., M.D., E.D.M., K.E., S.E., G.E., T.E., X.E., A.F., A.F., F.F., M.M.F., K.F., M.F., L.F., A.J.F., M.F., S.G., I.G., J.G., F.G., S.G., P.G., M.G.M., J.G., S.G., K.A.H., K.H., J.H., J.H., S.G.H., A.K.H., S.H., B.H., W.H., A.H., L.J.H., J.I.H., H.I., H.I., V.J., S.J., C.J., J.J., A.J., A.J., G.K., D.K., A.S.K., J.K,. L.K., A.K., M.J.H.K., W.K., J.L.K., M.K., A.K., K.K., Y.K., L.K., G.S.K., M.C.L, M.L., S.L., R.D.L., P.L., L.L., B.L., J.L., J.L., P.M., M.M., K.M., S.M., C.M., N.G.M., M.M., S.M., P.M., A.M., I.M., N.M., J.M., A.M.M., P.M., P.M., M.A.M., B.N., M.N., C.N., I.N., C.M.O., J.K.O., R.A.O., L.P., A.P., J.P., H.P., N.L.P., J.F.P., D.P., R.R., A.R., N.R., T.R., V.R., S.R., F.R., M.R., A.R., D.R., F.R., P.S., S.W.S., U.S., A.S., J.S., L.S., P.E.S., M.C.T.S.L., A.S., S.S., M.S., P.F.S., B.Ś., J.P.S., I.T., E.T., A.T., F.T., J.T., A.T., M.T., K.T., A.A.V, E.F.V., T.D.W., G.W., E.W., H.J.W., T.W., D.C.W., E.W., D.B.W., G.S., S.Z., and S.Z. All authors critically reviewed the manuscript.

Competing interests

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C.M.B. is a grant recipient from Shire Pharmaceuticals and served on Shire Scientific Advisory Board; she receives author royalties from Pearson. D.D. served as a speaker and on advisory boards, and has received consultancy fees for participation in research from various pharmaceutical industry companies including: AstraZeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Genesis Pharma, GlaxoSmithKline, Janssen, Lundbeck, Organon, Sanofi, UniPharma, and Wyeth; he has received unrestricted grants from Lilly and AstraZeneca as director of the Sleep Research Unit of Eginition Hospital (National and Kapodistrian University of Athens, Greece). J.I.H. has received grant support from Shire and Sunovion, and has received consulting fees from DiaMentis, Shire, and Sunovion. A.S.K. is a member of the Shire Canadian BED Advisory Board and is on the steering committee for the Shire B/educated Educational Symposium: June 15-16, 2018. J.L.K. served as an unpaid member of the scientific advisory board of AssurexHealth Inc. M.L. declares that, over the past 36 months, he has received lecture honoraria from Lundbeck and served as scientific consultant for EPID Research Oy. No other equity ownership, profit-sharing agreements, royalties, or patent. P.F.S. is on the Lundbeck advisory committee and is a Lundbeck grant recipient; he has served on the scientific advisory board for Pfizer, has received a consultation fee from Element Genomics, and a speaker reimbursement fee from Roche. J.T. has received an honorarium for participation in an EAP meeting and has received royalties from several books from Routledge, Wiley, and Oxford University press. T.W. has acted as a lecturer and scientific advisor to H. Lundbeck A/S. All other authors have no conflicts of interest to disclose.

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References

1. Schaumberg, K. *et al.* The science behind the Academy for Eating Disorders' nine truths about eating disorders. *Eur. Eat. Disord. Rev.* **25**, 432-450 (2017).
2. Keski-Rahkonen, A. & Mustelin, L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. *Curr. Opin. Psychiatry* **29**, 340-345 (2016).
3. Hudson, J.I., Hiripi, E., Pope, H.G. & Kessler, R.C. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol. Psychiatry* **61**, 348-358 (2007).
4. Micali, N. *et al.* Lifetime and 12-month prevalence of eating disorders amongst women in mid-life: a population-based study of diagnoses and risk factors. *BMC Med.* **15**, 12 (2017).
5. Yilmaz, Z., Hardaway, J.A. & Bulik, C.M. Genetics and epigenetics of eating disorders. *Adv. Genomics Genet.* **5**, 131-150 (2015).
6. Arcelus, J., Mitchell, A.J., Wales, J. & Nielsen, S. Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. *Arch. Gen. Psychiatry* **68**, 724-731 (2011).
7. Watson, H. & Bulik, C. Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines and emerging interventions. *Psychol. Med.* **43**, 2477-2500 (2013).

8. Kirk, K.M. *et al.* The Anorexia Nervosa Genetics Initiative: study description and sample characteristics of the Australian and New Zealand arm. *Aust. N. Z. J. Psychiatry* **51**, 583-594 (2017).

9. Thornton, L., Munn-Chernoff, M., Baker, J., Juréus, A. & al., e. The Anorexia Nervosa Genetics Initiative (ANGI): Overview and methods. *Contemp. Clin. Trials* **74**, 61-69 (2018).

10. Duncan, L. *et al.* Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. *Am. J. Psychiatry* **173**, 850-858 (2017).

11. Pickrell, J.K. *et al.* Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* **48**, 709-717 (2016).

12. Martin, J., Taylor, M.J. & Lichtenstein, P. Assessing the evidence for shared genetic risks across psychiatric disorders and traits. *Psychol. Med.* **48**, 1759-1774 (2018).

13. Boraska, V. *et al.* A genome-wide association study of anorexia nervosa. *Mol. Psychiatry* **19**, 1085-1094 (2014).

14. Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).

15. Yang, J. *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369-375 (2012).

16. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* **19**, 1442-1453 (2016).

17. GTEx Consortium. Genetic effects on gene expression across human tissues. *Nature* **550**, 204-213 (2017).

18. Zhu, Z. *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun.* **9**, 224 (2018).

19. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291-295 (2015).

20. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236-1241 (2015).

21. Cederlöf, M. *et al.* Etiological overlap between obsessive-compulsive disorder and anorexia nervosa: a longitudinal cohort, multigenerational family and twin study. *World Psychiatry* **14**, 333-338 (2015).

22. Kaye, W.H., Bulik, C.M., Thornton, L., Barbarich, N. & Masters, K. Comorbidity of anxiety disorders with anorexia and bulimia nervosa. *Am. J. Psychiatry* **161**, 2215-2221 (2004).

23. Dalle Grave, R., Calugi, S. & Marchesini, G. Compulsive exercise to control shape or weight in eating disorders: prevalence, associated features, and treatment outcome. *Compr. Psychiatry* **49**, 346-352 (2008).

24. Savage, J.E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat. Genet.* **50**, 912-919 (2018).

25. Ho, E.V., Klenotich, S.J., McMurray, M.S. & Dulawa, S.C. Activity-based anorexia alters the expression of BDNF transcripts in the mesocorticolimbic reward circuit. *PLoS One* **11**, e0166756 (2016).

26. Finucane, H.K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228-1235 (2015).

27. Lindblad-Toh, K. *et al.* A high-resolution map of human evolutionary constraint using 29 mammals. *Nature* **478**, 476 (2011).

28. Bello, V. *et al.* The dystroglycan: nestled in an adhesome during embryonic development. *Dev. Biol.* **401**, 132-142 (2015).

29. Azevedo, F.A.C. *et al.* Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J. Comp. Neurol.* **513**, 532-541 (2009).

30. O'Connor, E.C. *et al.* Accumbal D1R neurons projecting to lateral hypothalamus authorize feeding. *Neuron* **88**, 553-564 (2015).

31. Kim, J., Zhang, X., Muralidhar, S., LeBlanc, S.A. & Tonegawa, S. Basolateral to central amygdala neural circuits for appetitive behaviors. *Neuron* **93**, 1464-1479.e5 (2017).

32. Levinson, D.F. *et al.* Genetic studies of major depressive disorder: why are there no genome-wide association study findings and what can we do about it? *Biol. Psychiatry* **76**, 510-512 (2014).

Figure Titles and Captions

Figure 1. **The Manhattan plot for the primary genome-wide association meta-analysis of anorexia nervosa with 33 case-control samples (16,992 cases and 55,525 controls of European descent).** The -$\log_{10}(P)$ values for the association tests (two-tailed) are shown on the y-axis and the chromosomes are ordered on the x-axis. Eight genetic loci surpassed genome-wide significance (-$\log_{10}(P) > 7.3$). The lead variant is indicated by a diamond and green circles show the variants in linkage-disequilibrium. The blue and red colors differentiate adjacent chromosomes.

Figure. 2. Bonferroni-significant genetic correlations (SNP-r_gs) and standard errors (error bars) between anorexia nervosa and other phenotypes as estimated by LD score regression. Only traits with significant *P* values following Bonferroni correction are shown. Correlations with 447 phenotypes were tested (Bonferroni-corrected significance threshold $P > 1.11 \times 10^{-4}$). Complete results are shown in Table S10. PGC = Psychiatric Genomics Consortium, UKB = UK Biobank, HOMA-IR = Homeostatic model assessment - insulin resistance.

Table 1. Newly associated genome-wide significant loci for anorexia nervosa

Locus	Chr	Basepair region		Lead SNP	BP	*P*	A1/A2	OR	s.e.	Freq	Type	Number of genes	Nearest gene
		range left	range right										
1	3	47588253	51368253	rs9821797	48718253	6.99E-15	A/T	1.17	0.02	0.12	multigenic	111	*NCKIPSD*
2	11	114997256	115424956	rs6589488	115096956	6.31E-11	A/T	1.14	0.02	0.13	single-gene	1	*CADM1*
3	2	53881813	54362813	rs2287348	54039813	5.62E-09	T/C	1.11	0.02	0.16	multigenic	13	*ASB3, ERLEC1*
4	10	131269764	131463964	rs2008387	131448764	1.73E-08	A/G	1.08	0.01	0.33	single-gene	2	*MGMT*
5	3	70670750	71074150	rs9874207	71019750	2.05E-08	C/T	1.08	0.01	0.49	single-gene	2	*FOXP1*
6	1	96699455	97284455	rs10747478	96901455	3.13E-08	T/G	1.08	0.01	0.41	single-gene	2	*PTBP2*
7	5	24945845	25372845	rs370838138	25081845	3.17E-08	G/C	1.08	0.01	0.56	intergenic	0	*CDH10*
8	3	93968107	95059107	rs13100344	94605107	4.21E-08	T/A	1.08	0.01	0.54	intergenic	2	*NSUN3*

Note. Shown are the results of the GWAS meta-analysis of anorexia nervosa (16,992 cases and 55,552 controls) which detected eight genome-wide significant loci. All of the eight loci are novel. Chr (chromosome) and Region (hg19) are shown for SNPs with $P < 1e\text{-}05$ and linkage-disequilibrium (LD) $r^2 > 0.1$ with the most associated "lead" SNP, the location of which is given in BP (basepair). A1/A2 refers to Allele 1/Allele 2 and OR and s.e. are the odds ratio and standard error for the association between A1 and the phenotype. Freq is the frequency of A1 in controls. Number of genes was determined by genomic location, adult brain eQTL, regulatory chromatin interactions, and MAGMA gene-wise analysis (see Methods). Nearest gene is the nearest gene within the region of LD "friends" of the lead variant (LD-$r^2 > 0.6$ +/- 500 Kb). The meta-analysis was restricted to variants with minor allele frequency (MAF) ≥ 0.01 and information quality (INFO) score ≥ 0.70. All loci were confirmed via forest plots based on consistent direction of effect in the majority of cohorts and via region plots whereby neighboring LD "friends" were required to show a similar effect. Chromosome X was analyzed but had no loci that reached genome-wide significance. Note that although lead variants are annotated to the nearest gene, this does not mean that the gene listed is a causal gene.

Methods

Samples and study design. Thirty-three datasets with 16,992 anorexia nervosa cases and 55,525 controls were included in the primary GWAS. We included individuals from the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) Freeze 1[10]; newly collected samples from the Anorexia Nervosa Genetics Initiative (ANGI)[8,9]; archived samples from the Genetic Consortium for Anorexia Nervosa (GCAN)/Wellcome Trust Case Control Consortium-3 (WTCCC3)[13]; anorexia nervosa samples from UK Biobank[14]; and additional controls from Poland. Case definitions established a lifetime diagnosis of anorexia nervosa via hospital or register records, structured clinical interviews, or on-line questionnaires based on standardized criteria (DSM-III-R, DSM-IV, ICD-8, ICD-9, or ICD-10), whereas in the UK Biobank cases self-reported a diagnosis of anorexia nervosa. Controls were carefully matched for ancestry, and some, but not all control cohorts were screened for lifetime eating and/or some or all psychiatric disorders. Given the relative rarity of anorexia nervosa, large unscreened control cohorts were deemed appropriate for inclusion[33].

The cohorts are detailed in the Supplement. Ethical approvals and consent forms were reviewed and archived for all participating cohorts (see Supplementary Methods ANGI-DK for Danish methods). Summary details about ascertainment (Supplementary Table 2), the genotyping platforms used (Supplementary Table 3), and genotype availability (Supplementary Table 4) can be accessed in the Supplement.

Statistical analysis. Data processing and analysis were done on the Lisa Compute Cluster hosted by SURFsara (http://www.surfsara.nl) and the GenomeDK high-performance computing cluster (http://genome.au.dk).

Meta-analysis of genome-wide association data. Quality control (QC), imputation, GWAS, and meta-analysis followed the standardized pipeline of the PGC, Ricopili (Rapid Imputation Consortium Pipeline). Ricopili versions used were 2017_Oct_11.002 and 2017_Nov_30.003. QC included SNP and sample QC, population stratification and ancestry outliers, and familial and cryptic relatedness. Further information about the Ricopili pipeline is available from the website (https://sites.google.com/a/broadinstitute.org/ricopili) and GitHub repository (https://github.com/Nealelab/ricopili/tree/master/rp_bin). Further details of the QC procedures can be found in the Supplementary Methods.

Imputation. Imputation of SNPs and insertions-deletions was based on the 1000 Genomes Phase 3 (http://www.internationalgenome.org) data[34].

GWAS. GWASs were conducted separately for each cohort using imputed variant dosages and an additive model. Covariates nominally associated with the phenotype in univariate analysis ($P < 0.05$) and five ancestry PCs were included in GWAS (Supplementary Table 18). These analyses used the tests and methods programmed in the Ricopili pipeline. Genomic inflation factors (λ) of the final datasets indicated no evidence of inflation of the test statistics due to population stratification or other sources (Supplementary Table 1). The 33 cohorts were meta-analyzed with the Ricopili pipeline which uses an inverse-variance weighted fixed-effect model. We filtered our GWAS results with minor allele frequency (MAF) ≥ 0.01 and INFO score ≥ 0.70 (indicating "high-quality").

Analysis of chrX. Several cohorts in the primary GWAS did not have X chromosome variant data, specifically, some GCAN-based cohorts (*fre1*, *ukd1*, *usa1*, *gns2*) and were excluded. Imputation was performed separately from the autosome[35]. ChrX variants in the pseudoautosomal regions were excluded prior to imputation. SNPs exceeding MAF and INFO score thresholds of 0.01 and 0.70 were retained and analysis was performed with PLINK v1.9 (https://www.cog-genomics.org/plink2) and Ricopili.

Female-only GWAS. A supplementary GWAS analysis was conducted on females only to determine the similarity of the results to the primary GWAS analysis which included both females and males. The cohorts that did not have chrX variants to verify sex could not be included (*fre1*, *ukd1*, *usa1*, *gns2*).

Distance- and LD-based clumping. The GWAS results implicate genomic regions ("loci"). To define a locus, (1) SNPs that met the genome-wide significant threshold of $P < 5 \times 10^{-8}$ were identified; (2) clumping was used to convert significant SNPs to regions. The SNP with the smallest *P* value in a genomic window was kept as the index SNP and SNPs in high linkage disequilibrium (LD) with the index SNP defined the left and right end of the region (SNPs with $P < 0.0001$ and $r^2 > 0.1$ within 3 Mb windows); (3) partially or wholly overlapping clumps within 50 Kb were identified and merged into one region; (4) only loci with additional evidence of association from variants in high LD as depicted by regional plots were retained; further, forest plots needed to confirm the associations based on the majority of cohorts; and (5) conditional analyses were conducted to identify SNPs with associations independent of the top SNP within the genomic chunk of interest.

Annotation. Genome-wide significant loci were annotated with RegionAnnotator (https://github.com/ivankosmos/RegionAnnotator) to identify known protein-coding genes within loci (Supplementary Table 6).

Conditional and joint analysis. Conditional and joint analysis was conducted using GCTA-COJO[15]. GCTA-COJO investigates every locus with a joint combination of independent markers via a genome-wide SNP selection procedure. It takes into account the LD correlations between SNPs and runs a conditional and joint analysis on the basis of conditional *P* values. After a model optimizing process, the joint effects of all selected SNPs are calculated. The largest subsample from our GWAS (*sedk*) was used to approximate the underlying LD structure of the investigated lead SNPs. The conditional regression was performed in a stepwise manner using the GCTA software[36]. We analyzed SNPs that had a $P < 5 \times 10^{-8}$ (Supplementary Table 5).

Multi-trait-based conditional and joint analysis. To separate marginal effects from conditional effects (i.e., the effect of a risk factor on an outcome controlling for the effect of another risk factor), we performed a multi-trait-based conditional and joint analysis (GCTA-mtCOJO)[18] using an extension of the GCTA software[36] (Supplementary Table 8). This method uses summary-level data to perform the conditional analysis. We conditioned the results of our anorexia nervosa GWAS on GWAS results for education years[37], type 2 diabetes[38], HDL cholesterol[39], BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), schizophrenia[40], and neuroticism[41]. We again used the individual-level genotype data from our largest cohort (*sedk*) to approximate the underlying LD structure. As a first step, the method performs a

generalized summary data-based Mendelian randomization (GSMR) analysis to test for causal association between the outcome (i.e., anorexia nervosa) and the risk factor (e.g., schizophrenia). We removed potentially pleiotropic SNPs from this analysis by the heterogeneity in dependent instruments (HEIDI) outlier method[18]. Pleiotropy is the phenomenon when a single locus directly affects several phenotypes. The power of the HEIDI-outlier method is dependent on sample size of the GWAS. Pleiotropic SNPs are defined as the SNPs that show an effect on the outcome that significantly diverges from that expected under a causal model. Second, the GCTA-mtCOJO method calculates the genetic correlation between the exposure and the outcome using linkage disequilibrium score regression (LDSC) to adjust for genetic overlap[19,20]. It also uses the intercept of the bivariate LDSC to account for potential sample overlap[19,20]. As a result, GCTA-mtCOJO calculates conditional betas, conditional standard errors, and conditional *P* values. Subsequently, we clumped the conditional GWAS results using the standard PLINK v1.9[42] algorithm (SNPs with $P < 0.0001$ and $r^2 > 0.1$ within 3 Mb windows) to investigate if any of the genome-wide significant loci showed dependency on genetic variation associated with other phenotypes. As stated in Zhu et al.[18], the GCTA-mtCOJO analysis requires the estimates of b_{xy} of the covariate risk factors on the target risk factor and disease, r_g of the covariate risk factors, heritability (h^2_{snp}) for the covariate risk factors, and the sampling covariance between SNP effects estimated from potentially overlapping samples.

eQTL and Hi-C interactions. Although GWAS findings are informative genome-wide, identifying strong hypotheses about their connections to specific genes is not straightforward. The lack of direct connections to genes constrains subsequent experimental modeling and efforts to develop improved therapeutics. Genomic location is often used to connect significant SNPs to

genes, but this is problematic because GWAS loci usually contain many correlated and highly significant SNP associations over hundreds of Kb. Moreover, the three-dimensional (3D) arrangement of chromosomes in cell nuclei enables regulatory interactions between genomic regions located far apart[43]. Chromosome conformation capture methods like Hi-C enable identification of 3D interactions *in vivo*[44,45] and can clarify GWAS findings. For example, an intergenic region associated with multiple cancers was shown to be an enhancer for *MYC* via a long-range chromatin loop[46,47], and intronic *FTO* variants are robustly associated with body mass but influence expression of distal genes via long-range interactions[48]. The *Nature* paper of Won et al.[49] used Hi-C to assess the 3D chromatin interactome in fetal brain, and asserted connections of some schizophrenia associations to specific genes.

To gain further understanding of 3D chromatin organization of the brain and to evaluate disease relevance, we applied "easy Hi-C"[50] to postmortem samples ($N = 3$ adult temporal cortex). Library quality and yield from eHi-C are comparable to conventional Hi-C but requires much less starting material. Please refer to the following pre-print for details on methodology, data processing, quality control and statistical models used for these analyses[51]. We generated sufficient reads to enable a kilobase resolution map of the chromatin interactome from adult human brain. To our knowledge, these are the deepest Hi-C data on any human tissue (excluding cell lines) as they generated 22.5X as many *cis*-contacts as for the next largest datasets (DLPFC and hippocampus). We generated tissue RNA-seq, total-stranded RNA-seq, ChIP-seq (H3K27ac, H3K4me3, and CTCF), and open chromatin data (ATAC-seq) for adult brain to help interpret the eHi-C results. We also integrated brain expression and eQTL data from GTEx to aid these analyses. The Hi-C analysis is unbiased in that all chromatin interactions that pass a confidence

threshold are considered when evaluating the associations between SNPs and genes (i.e., it is not a capture experiment where only "candidate" SNP-to-gene associations are evaluated).

Similar to the work by Won *et al*.[49], we used Hi-C data generated from human adult brain to identify genes implicated by three-dimensional functional interactomics (Supplementary Figs. 5 a-h). These Hi-C data ($N = 3$, anterior temporal cortex) contain more than 103K high-confidence, regulatory chromatin interactions[51]. These interactions capture the physical proximity of two regions of the genome in brain nuclei ("anchors", 10 Kb resolution) although they are separated by 20 Kb to 2 Mb in genomic distance. We focused on the regulatory subset of E-P or P-P (E = enhancer, P = promoter) chromatin interactions (with P defined by location of an open chromatin anchor near the transcription start site of an adult brain-expressed transcript and E defined by overlap with open chromatin in adult brain plus either H3K27ac or H3K4me3 histone marks). The presence of a regulatory chromatin interaction from a GWAS locus to a gene provides a strong hypothesis about SNP-to-gene regulatory functional interactions.

SNP-based heritability estimation. LDSC software (https://github.com/bulik/ldsc**)** and method were used to estimate SNP-based heritabilities for each cohort and overall[19,20]. We used precomputed LD scores based on the 1000 Genomes Project European ancestry samples[34] directly downloaded from https://github.com/bulik/ldsc. The liability scale estimate assumed a population prevalence of 0.9%-4% for anorexia nervosa[2,3].

Within-trait prediction: polygenic risk scoring. Polygenic leave-one-dataset-out analysis, using PRSice v2.1.3[52]**,** was conducted in the first instance to identify any extreme outlying datasets. In addition, it enabled the evaluation of the association between anorexia nervosa polygenic risk

score (PRS) and anorexia nervosa risk in an independent cohort as a means of replication of the GWAS results. We derived a PRS for anorexia nervosa from the meta-analysis of all datasets except for the target cohort, then applied the PRS to the target cohort to predict affected status (Supplementary Fig. 16). Logistic regression was performed, including as covariates the first five ancestry components and any other PCs significantly associated with the phenotype in the target cohort, and the target cohort was split into deciles based on anorexia nervosa PRS, with decile 1 comprised of those with the lowest anorexia nervosa PRS serving as the referent.

Anorexia nervosa subtype analysis. PRS analyses were conducted with anorexia nervosa subgroups to investigate prediction of case status across the subtypes. For this, we split the anorexia nervosa cases to two groups based on whether binge eating was present. First, GWAS meta-analyses were conducted for (a) anorexia nervosa with binge eating vs controls (2,381 cases and 10,249 controls; $k = 3$ datasets: *aunz*, *chop*, *usa2*) and (b) anorexia nervosa with no binge eating vs controls (2,262 cases and 10,254 controls; $k = 3$ datasets: *aunz*, *chop*, *usa2*). Controls were randomly split between analyses to maintain independence (Supplementary Fig. 6). Genetic correlation analysis using LDSC[19,20] was conducted to examine the potential genetic overlap of the two anorexia nervosa subtypes (Supplementary Table 9). Second, using PRSice[52], we calculated PRS for each anorexia nervosa subtype separately in the three target cohorts for which anorexia nervosa subtype data were available. Finally, mean PRS scores were estimated for each subtype by cohort after accounting for covariates in R. Subtype phenotyping is described in the Supplementary Methods.

Males. In order to assess whether sex-specific differences in anorexia nervosa genetic risk load exist, we calculated PRS, using PRSice[52], from a GWAS meta-analysis performed on females only (14,898 cases and 27,545 controls) and applied it to a male-only target cohort (447 cases and 20,347 controls) to predict affected status.

Cross-trait analysis: genetic correlations. Common variant-based genetic correlation (SNP-r_g) measures the extent to which two traits or disorders share common genetic variation. SNP-r_g between anorexia nervosa and 447 traits (422 from an internally curated dataset and 25 from LDHub[53]) were tested using GWAS summary statistics via an analytical extension of LDSC[19,20]. The sources of the summary statistics files (PMID, DOI, or unpublished results) used in the LDSC are provided in Supplementary Table 10. When there were multiple summary statistics files available for a trait, significant SNP-r_g reported in the main text were chosen based on the largest sample size and/or matching ancestry with our sample (i.e., European ancestry).

Genetic correlations with anorexia nervosa corrected for BMI were carried out to investigate whether the observed genetic correlations between anorexia nervosa and metabolic phenotypes were attributable to BMI or partially independent. We used GCTA-mtCOJO[18] to perform a GWAS analysis for anorexia nervosa conditioning on BMI using BMI summary data from our UK Biobank analysis (described in the next section) to derive anorexia nervosa GWAS summary statistics corrected for the common variants genetic component of BMI (Supplementary Tables 14 and 15).

GWAS of related traits in UK Biobank. Several GWAS analyses were carried out for traits in UK Biobank to allow us to investigate body composition genetics in healthy individuals without a

psychiatric disorder, a weight-altering disorder, or who were taking weight-altering medication. We also used UK Biobank to carry out GWAS of physical activity level, anxiety, and neuroticism. For details see the Supplementary Methods.

Generalized summary data-based Mendelian randomization (GSMR). We performed two bidirectional GSMR analyses[18] to test for the causal association between first, BMI and anorexia nervosa, and second, Type 2 diabetes and anorexia nervosa, using an extension of the GCTA software[36] (Supplementary Table 16). We used the individual-level genotype data from our largest cohort (*sedk*) to approximate the underlying LD structure. We removed potentially pleiotropic SNPs from this analysis by the HEIDI outlier method[18]. Pleiotropic SNPs are defined as the SNPs which show an effect on the outcome that significantly diverges from the one expected under a causal model. The method uses the intercept of the bivariate LD score regression to account for potential sample overlap[19,20]. As a rule of thumb GSMR requires GWAS to have at least ten genome-wide significant hits. We lowered the threshold for this requirement to eight SNPs in our analyses of anorexia nervosa as an exposure and BMI or Type 2 diabetes as an outcome. Results, therefore, should be interpreted cautiously. We, furthermore, investigated bidirectional conditional effects between BMI or Type 2 diabetes and anorexia nervosa. We used GCTA-mtCOJO to perform a GWAS analysis for anorexia nervosa conditioning on (1) BMI using summary data from our UK Biobank analysis and (2) Type 2 diabetes using summary data[38]. Our anorexia nervosa GWAS and the BMI and Type 2 diabetes GWASs are based on independent samples. For BMI, we also re-ran the GSMR analysis using the BMI-adjusted anorexia nervosa GWAS summary data from the GCTA-mtCOJO analysis.

Gene-wise analysis. MAGMA v1.06[54] was used to perform a gene-wise test of association with anorexia nervosa based on GWAS summary statistics. MAGMA generates gene-based *P* values by combining SNP-based *P* values within a gene while accounting for LD. In order to include regulatory regions, SNPs are mapped to genes within a 35 kb upstream and 10 kb downstream window, and the gene *P* value is obtained using the "multi=snp-wise" model, which aggregates mean and top SNP association models. We tested 19,846 ENSEMBL genes, including the X chromosome (Supplementary Table 11). As reference panel for the underlying LD structure we used 1000 Genomes European data phase 3[34].

Pathway analysis. MAGMA v1.06[54] was used to perform a competitive pathway analysis, testing whether genes associated with anorexia nervosa were more enriched in a given pathway than all other pathways. The analysis included chrX. Biological pathways were defined using gene ontology pathways and canonical pathways from MSigDB v6.1[55], and psychiatric pathways mined from the literature. A total 7,268 pathways were tested (Supplementary Table 12).

Partitioned heritability. Partitioned heritability was investigated using stratified LDSC[26] which estimates the per-SNP contribution to overall SNP-heritability (SNP-h^2) across various functional annotation categories of the genome (Supplementary Fig. 7). It accounts for linked markers and uses a 'full baseline model' of 24 annotations that are not specific to any cell type. We excluded the MHC region in our analysis. SNP-h^2 can be partitioned in two different ways: a non-cell type-specific and a cell type-specific manner. Partitioned heritability analysis was used to test for cell type-specific enrichment in the GWAS of anorexia nervosa among 10 cell type groups; adrenal and pancreas, cardiovascular, central nervous system (CNS), connective and

bone, gastrointestinal, immune and hematopoietic, kidney, liver, skeletal muscle, and other tissue, which includes adipose tissue (Supplementary Fig. 8).

Gene expression. We conducted a series of gene expression analyses as detailed in the Supplementary Methods.

Reporting summary

Further information on research design is available in the Life Science Reporting Summary linked to this article.

Data availability

The Psychiatric Genomics Consortium's (PGC) policy is to make genome-wide summary results public. Genome-wide summary statistics for the meta-analysis are freely downloadable from PGCs download website (http://www.med.unc.edu/pgc/results-and-downloads). Individual-level data are deposited in dbGaP (http://www.ncbi.nlm.nih.gov/gap) for ANGI-ANZ/SE/US (accession number phs001541.v1.p1) and CHOP/PFCG (accession number phs000679.v1.p1). ANGI-DK individual-level data are not available in dbGaP owing to Danish laws, but are available via collaboration with PIs. GCAN/WTCCC3 individual-level data are deposited in EGA (https://www.ebi.ac.uk/ega) (accession number EGAS00001000913) with the exception of Netherlands and US/Canada, which are available via collaboration with PIs. UK Biobank

individual-level data can be applied for on the UK Biobank website (http://www.ukbiobank.ac.uk/register-apply).

References

33. Moskvina, V., Holmans, P., Schmidt, K.M. & Craddock, N. Design of case-controls studies with unscreened controls. *Ann. Hum. Genet.* **69**, 566-576 (2005).

34. 1000 Genomes Project Consortium *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56-65 (2012).

35. Chang, D. *et al.* Accounting for eXentricities: analysis of the X chromosome in GWAS reveals X-linked genes implicated in autoimmune diseases. *PLoS One* **9**, e113684 (2014).

36. Yang, J., Lee, S.H., Goddard, M.E. & Visscher, P.M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76-82 (2011).

37. Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539-542 (2016).

38. Morris, A.P. *et al.* Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* **44**, 981-990 (2012).

39. Teslovich, T.M. *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707-713 (2010).

40. Schizophrenia Working Group of the Psychiatric Genomics Consortium *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421-427 (2014).

41. Hübel, C. *et al.* Genomics of body fat percentage may contribute to sex bias in anorexia nervosa. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **in press**.

42. Chang, C.C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).

43. Dekker, J. Mapping the 3D genome: aiming for consilience. *Nat. Rev. Mol. Cell Biol.* **17**, 741-742 (2016).

44. Dekker, J. Gene regulation in the third dimension. *Science* **319**, 1793-1794 (2008).

45. Ethier, S.D., Miura, H. & Dostie, J. Discovering genome regulation with 3C and 3C-related technologies. *Biochim. Biophys. Acta* **1819**, 401-410 (2012).

46. Pomerantz, M.M. *et al.* The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. *Nat. Genet.* **41**, 882-884 (2009).

47. Wright, J.B., Brown, S.J. & Cole, M.D. Upregulation of c-MYC in cis through a large chromatin loop linked to a cancer risk-associated single-nucleotide polymorphism in colorectal cancer cells. *Mol. Cell Biol.* **30**, 1411-1420 (2010).

48. Smemo, S. *et al.* Obesity-associated variants within FTO form long-range functional connections with IRX3. *Nature* **507**, 371-375 (2014).

49. Won, H. *et al.* Chromosome conformation elucidates regulatory relationships in developing human brain. *Nature* **538**, 523-527 (2016).

50. Lu, L., Liu, X., Peng, J., Li, Y. & Jin, F. Easy Hi-C: A simple efficient protocol for 3D genome mapping in small cell populations. *bioRxiv*, 245688 (2018).

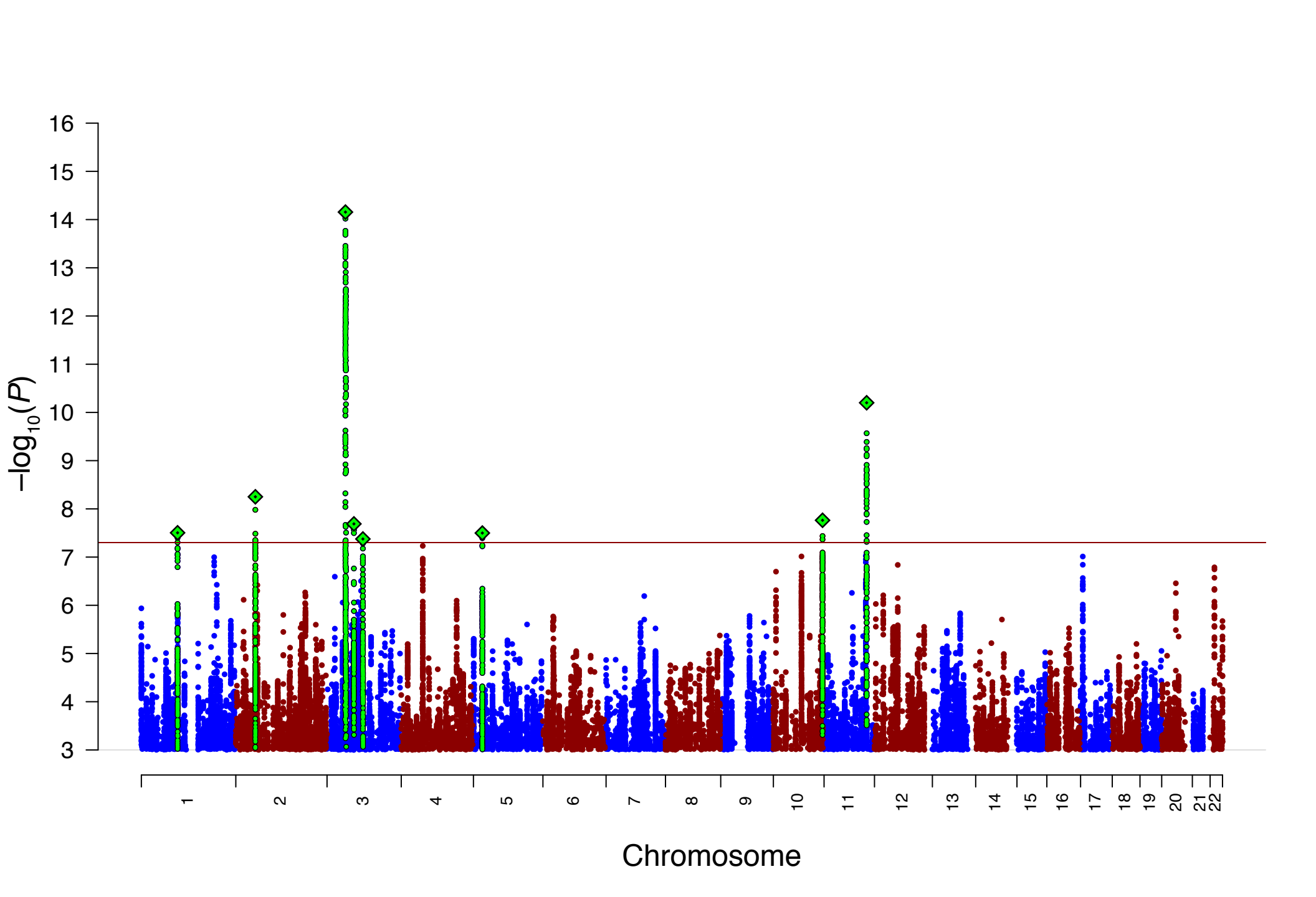
51. Giusti-Rodriguez, P.M. & Sullivan, P.F. Schizophrenia and a high-resolution map of the three-dimensional chromatin interactome of adult and fetal cortex. *bioRxiv*, 406330 (2018).

52. Euesden, J., Lewis, C.M. & O'Reilly, P.F. PRSice: Polygenic Risk Score software. *Bioinformatics* **31**, 1466-1468 (2015).

53. Zheng, J. *et al.* LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* **33**, 272-279 (2017).

54. de Leeuw, C.A., Mooij, J.M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).

55. Subramanian, A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 15545-15550 (2005).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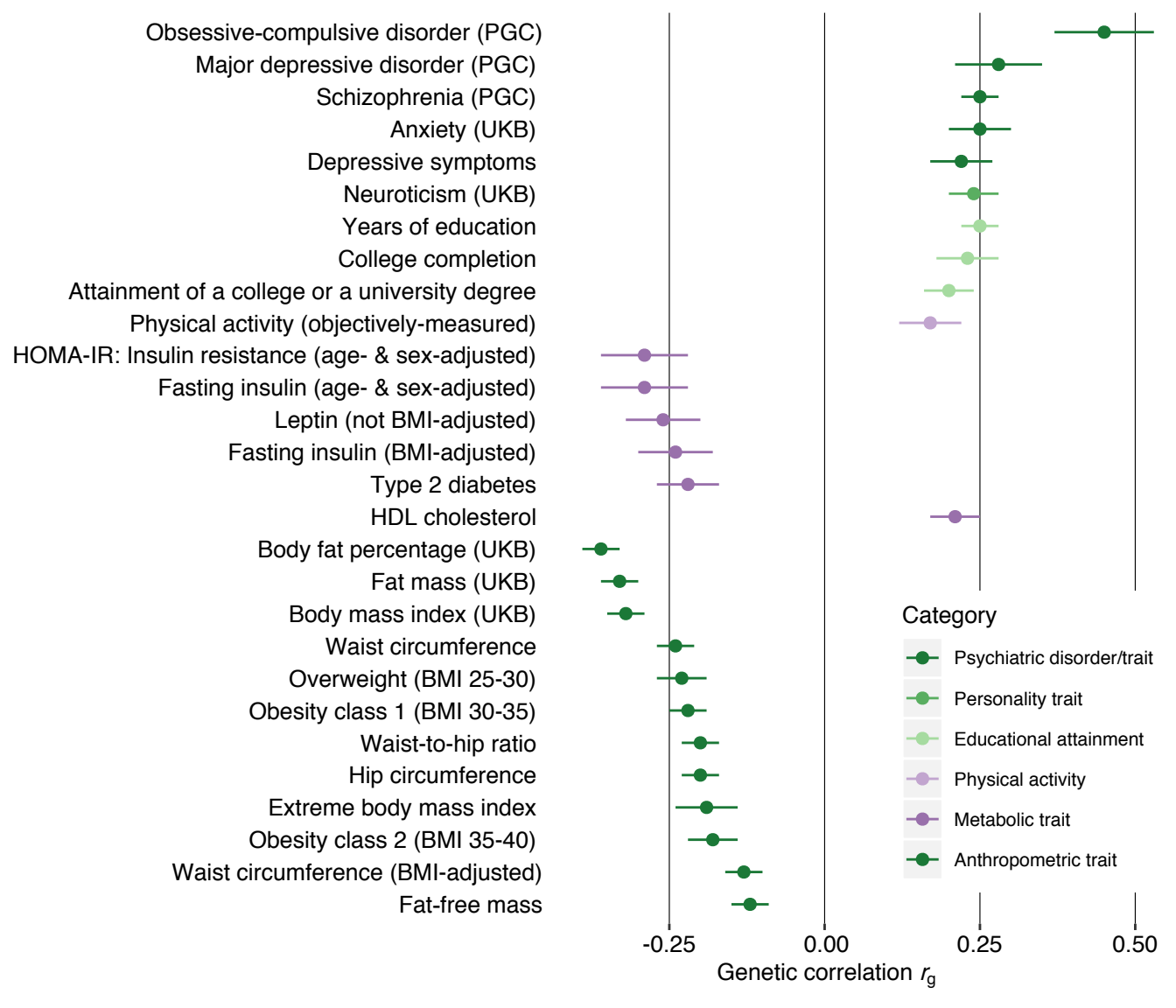
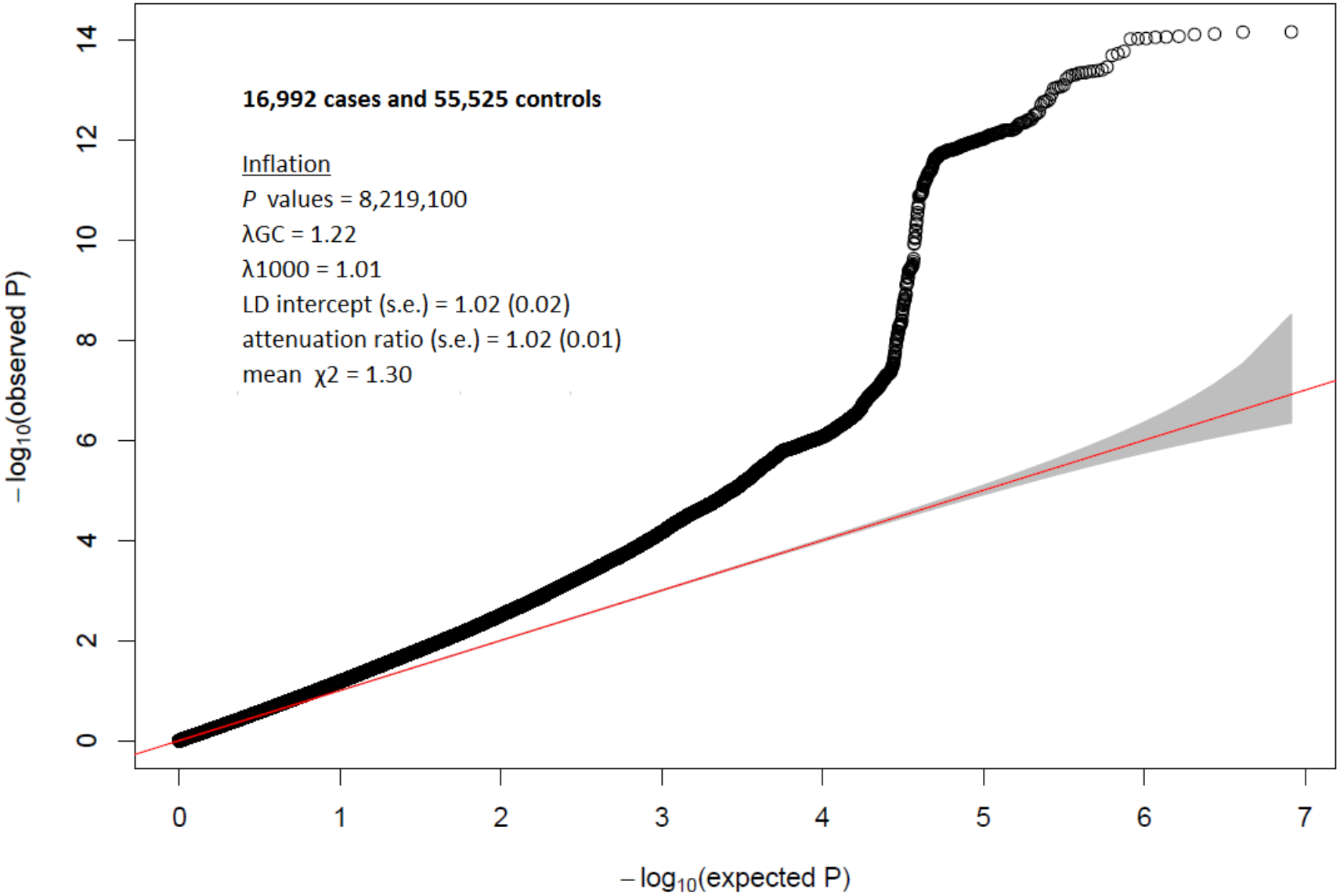
Chromosome

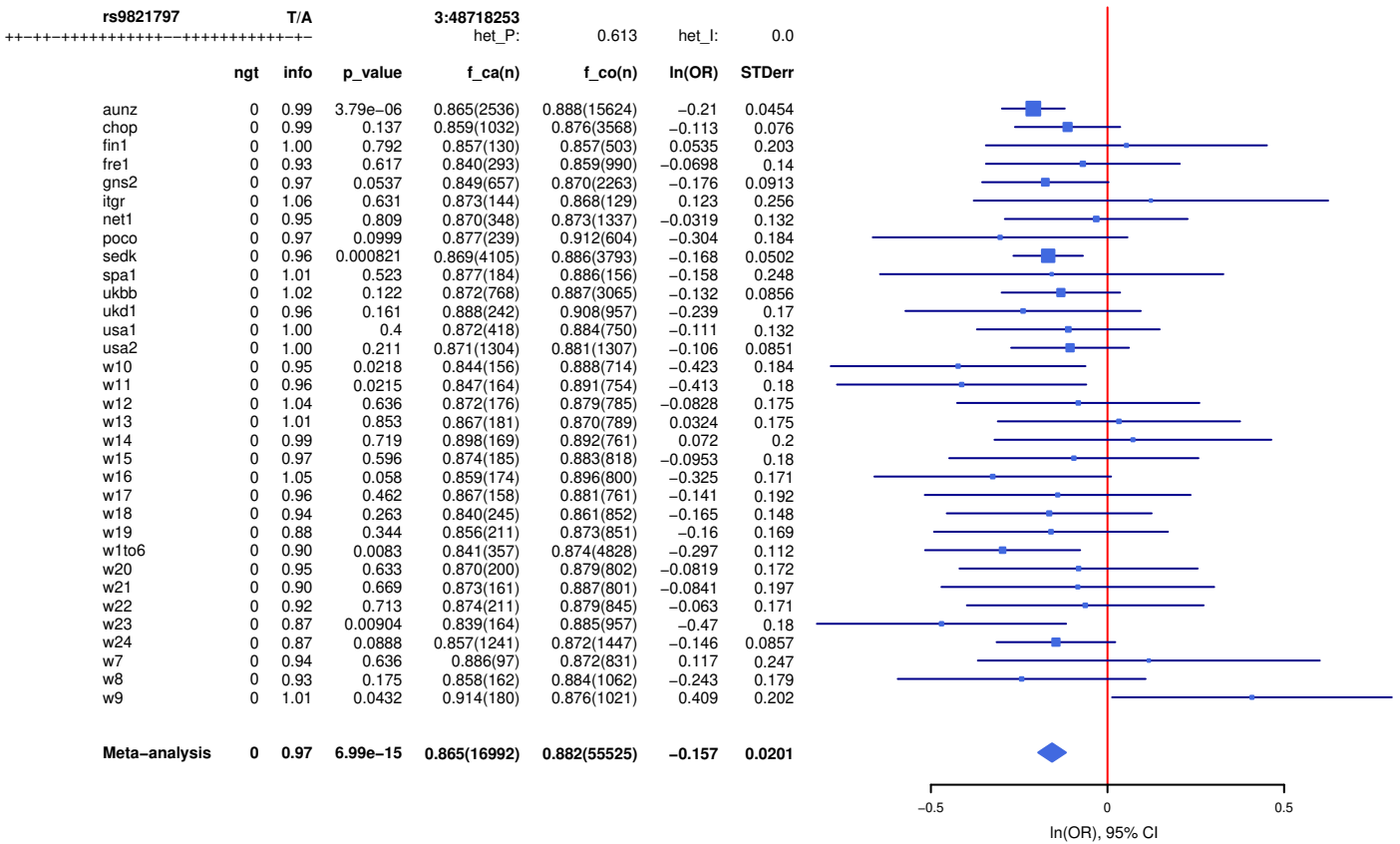

Obsessive-compulsive disorder (PGC)
Major depressive disorder (PGC)
Schizophrenia (PGC)
Anxiety (UKB)
Depressive symptoms
Neuroticism (UKB)
Years of education
College completion
Attainment of a college or a university degree
Physical activity (objectively-measured)
HOMA-IR: Insulin resistance (age- & sex-adjusted)
Fasting insulin (age- & sex-adjusted)
Leptin (not BMI-adjusted)
Fasting insulin (BMI-adjusted)
Type 2 diabetes
HDL cholesterol
Body fat percentage (UKB)
Fat mass (UKB)
Body mass index (UKB)
Waist circumference
Overweight (BMI 25-30)
Obesity class 1 (BMI 30-35)
Waist-to-hip ratio
Hip circumference
Extreme body mass index
Obesity class 2 (BMI 35-40)
Waist circumference (BMI-adjusted)
Fat-free mass
Category
Psychiatric disorder/trait
Personality trait
Educational attainment
Physical activity
Metabolic trait
Anthropometric trait
-0.25
0.00
0.25
0.50
Genetic correlation r_g

Supplementary Figure 1. Quantile-quantile (QQ) plot of association P values for the meta-analysis of anorexia nervosa (MAF ≥ 0.01 and INFO score ≥ 0.7). The red diagonal line shows the theoretical null distribution. The shading shows the 95% confidence interval bounds. MAF = minor allele frequency and INFO = imputation quality score.



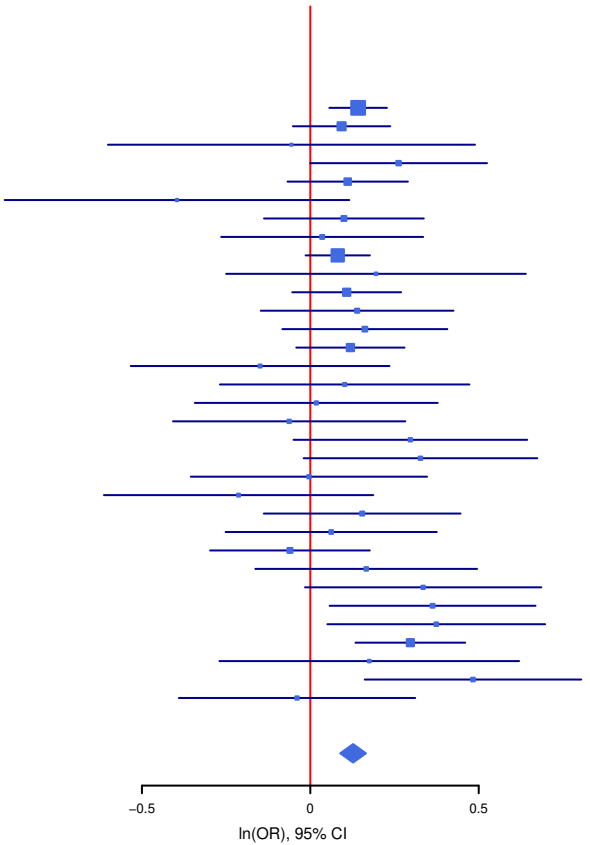
Supplementary Figure 2a-h legend. Forest plots of GWAS meta-analysis results for all genome-wide significant SNPs ($P < 5 \times 10^{-8}$). The overall sample size is 16,992 cases and 55,525 controls. For specific cohort sample sizes, see Supplementary Table 1. Two SNPs were located in regions that overlapped (index SNPs of rs9821797 and rs73088112), therefore we refer to only one of these (rs9821797) in the main manuscript. The red vertical line is the reference line of no effect. The center values are ln(OR) estimates from logistic regression association analyses and the error bars show the 95% confidence interval.

(a) chr3:rs9821797.



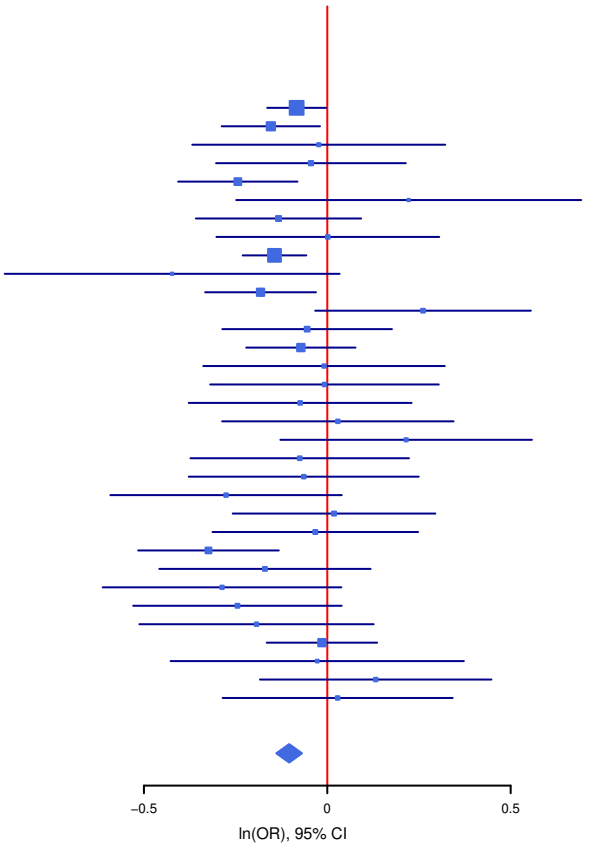
(b) chr11:6589488.

rs6589488		A/T		11:115096956			
				het_P:	0.339	het_I:	7.9
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.96	0.00117	0.152(2536)	0.135(15624)	0.142	0.0436
chop	0	0.94	0.208	0.158(1032)	0.148(3568)	0.0929	0.0738
fin1	0	0.92	0.84	0.076(130)	0.078(503)	−0.056	0.278
fre1	0	0.94	0.0509	0.180(293)	0.145(990)	0.262	0.134
gns2	0	0.92	0.223	0.157(657)	0.146(2263)	0.111	0.0912
itgr	0	0.87	0.13	0.140(144)	0.175(129)	−0.396	0.261
net1	0	0.98	0.41	0.157(348)	0.151(1337)	0.0997	0.121
poco	0	0.92	0.818	0.179(239)	0.173(604)	0.0352	0.153
sedk	0	0.98	0.0947	0.136(4105)	0.123(3793)	0.0814	0.0487
spa1	0	0.93	0.39	0.173(184)	0.148(156)	0.195	0.227
ukbb	0	0.97	0.19	0.148(768)	0.136(3065)	0.108	0.0824
ukd1	0	0.96	0.339	0.157(242)	0.139(957)	0.139	0.146
usa1	0	0.94	0.197	0.157(418)	0.140(750)	0.162	0.125
usa2	0	0.96	0.146	0.148(1304)	0.135(1307)	0.119	0.082
w10	0	0.90	0.449	0.132(156)	0.146(714)	−0.149	0.196
w11	0	0.91	0.589	0.135(164)	0.123(754)	0.102	0.189
w12	0	0.90	0.923	0.133(176)	0.132(785)	0.0178	0.184
w13	0	0.91	0.721	0.149(181)	0.148(789)	−0.0628	0.176
w14	0	0.95	0.0925	0.150(169)	0.118(761)	0.297	0.177
w15	0	0.93	0.0641	0.147(185)	0.112(818)	0.327	0.177
w16	0	0.91	0.982	0.144(174)	0.141(800)	−0.00411	0.179
w17	0	0.90	0.297	0.114(158)	0.140(761)	−0.213	0.204
w18	0	0.96	0.302	0.150(245)	0.132(852)	0.154	0.149
w19	0	0.94	0.698	0.150(211)	0.143(851)	0.062	0.16
w1to6	0	0.93	0.619	0.126(357)	0.133(4828)	−0.0605	0.121
w20	0	0.89	0.323	0.150(200)	0.133(802)	0.166	0.168
w21	0	0.92	0.0614	0.158(161)	0.120(801)	0.335	0.179
w22	0	0.96	0.0198	0.164(211)	0.121(845)	0.363	0.156
w23	0	0.95	0.0235	0.175(164)	0.131(957)	0.374	0.165
w24	0	0.92	0.000345	0.154(1241)	0.122(1447)	0.297	0.0831
w7	0	0.91	0.439	0.148(97)	0.124(831)	0.175	0.227
w8	0	0.93	0.00317	0.189(162)	0.129(1062)	0.483	0.164
w9	0	0.95	0.825	0.123(180)	0.127(1021)	−0.0395	0.179
Meta−analysis	**0**	**0.95**	**6.31e−11**	**0.148(16992)**	**0.134(55525)**	**0.127**	**0.0195**



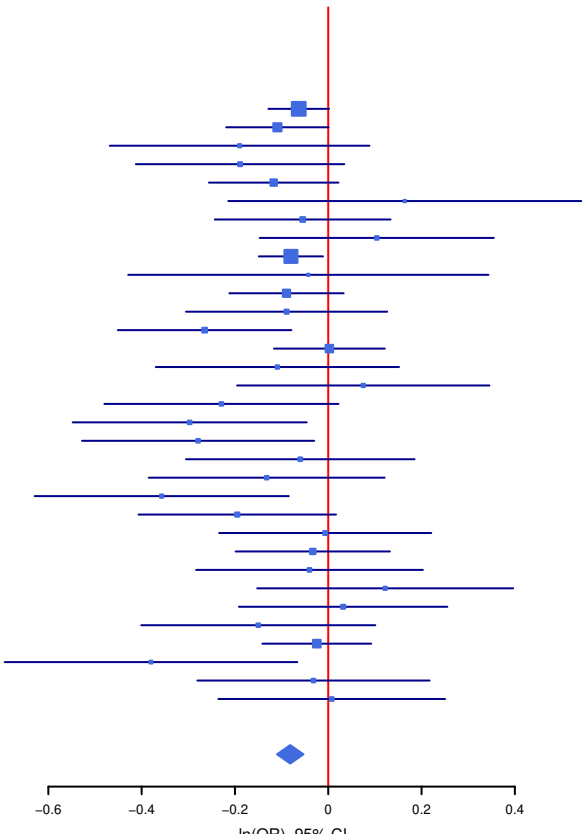
(c) chr2:2287348.

rs2287348		C/T		2:54039813			
				het_P:	0.309	het_I:	9.7
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.99	0.0412	0.830(2536)	0.843(15624)	−0.0836	0.041
chop	1	1.01	0.0244	0.822(1032)	0.845(3568)	−0.154	0.0684
fin1	1	1.01	0.894	0.796(130)	0.804(503)	−0.0233	0.176
fre1	0	0.99	0.735	0.834(293)	0.835(990)	−0.0446	0.132
gns2	0	0.98	0.00322	0.808(657)	0.845(2263)	−0.244	0.083
itgr	1	0.96	0.355	0.851(144)	0.818(129)	0.222	0.24
net1	1	0.97	0.247	0.816(348)	0.835(1337)	−0.133	0.115
poco	0	1.04	0.993	0.849(239)	0.839(604)	0.0014	0.155
sedk	0	0.99	0.00112	0.830(4105)	0.848(3793)	−0.144	0.0443
spa1	0	1.02	0.0693	0.824(184)	0.884(156)	−0.423	0.233
ukbb	1	1.00	0.0184	0.829(768)	0.853(3065)	−0.182	0.0771
ukd1	1	1.00	0.0823	0.872(242)	0.840(957)	0.261	0.15
usa1	1	0.99	0.64	0.830(418)	0.839(750)	−0.055	0.118
usa2	0	1.00	0.343	0.834(1304)	0.844(1307)	−0.0721	0.076
w10	0	1.02	0.958	0.833(156)	0.833(714)	−0.00894	0.168
w11	0	1.01	0.961	0.821(164)	0.823(754)	−0.00773	0.159
w12	0	1.02	0.634	0.826(176)	0.840(785)	−0.074	0.155
w13	0	1.02	0.858	0.845(181)	0.836(789)	0.0288	0.161
w14	0	1.05	0.219	0.873(169)	0.846(761)	0.215	0.175
w15	0	0.98	0.622	0.819(185)	0.825(818)	−0.0752	0.152
w16	0	1.00	0.688	0.828(174)	0.837(800)	−0.0642	0.16
w17	0	0.99	0.0858	0.791(158)	0.838(761)	−0.276	0.161
w18	0	0.99	0.896	0.841(245)	0.838(852)	0.0184	0.141
w19	0	1.01	0.819	0.822(211)	0.827(851)	−0.0327	0.143
w1to6	0	0.98	0.000925	0.792(357)	0.839(4828)	−0.324	0.0978
w20	0	1.05	0.247	0.828(200)	0.851(802)	−0.17	0.147
w21	0	0.99	0.0831	0.823(161)	0.856(801)	−0.287	0.166
w22	0	1.00	0.0899	0.820(211)	0.853(845)	−0.245	0.145
w23	0	0.95	0.237	0.821(164)	0.845(957)	−0.193	0.163
w24	0	0.97	0.85	0.843(1241)	0.845(1447)	−0.0146	0.0768
w7	0	1.00	0.893	0.825(97)	0.833(831)	−0.0274	0.204
w8	0	1.04	0.413	0.845(162)	0.825(1062)	0.132	0.161
w9	0	1.00	0.86	0.847(180)	0.844(1021)	0.0282	0.16
Meta−analysis	**7**	**0.99**	**5.62e−09**	**0.830(16992)**	**0.842(55525)**	**−0.104**	**0.0179**



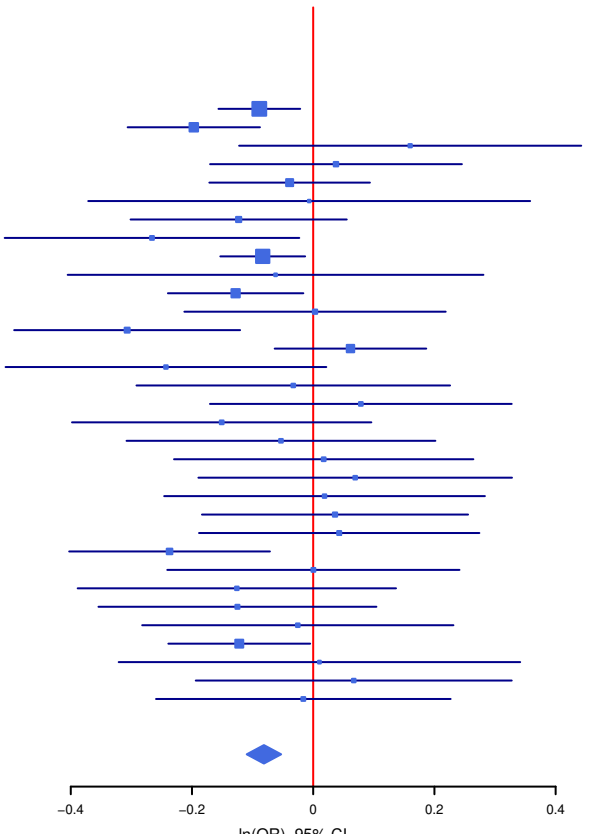
(d) chr10:rs2008387.

rs2008387		G/A		10:131448764			
				het_P:	0.358	het_I:	6.7
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.93	0.0565	0.650(2536)	0.663(15624)	−0.0633	0.0332
chop	0	0.93	0.0522	0.638(1032)	0.668(3568)	−0.109	0.056
fin1	0	1.01	0.182	0.556(130)	0.600(503)	−0.19	0.142
fre1	0	0.82	0.0967	0.653(293)	0.687(990)	−0.189	0.114
gns2	0	0.89	0.0999	0.653(657)	0.677(2263)	−0.117	0.0708
itgr	0	0.94	0.397	0.677(144)	0.642(129)	0.164	0.193
net1	0	0.93	0.569	0.680(348)	0.698(1337)	−0.0548	0.0961
poco	0	0.91	0.414	0.693(239)	0.661(604)	0.104	0.128
sedk	0	0.93	0.0226	0.645(4105)	0.661(3793)	−0.08	0.0351
spa1	0	0.77	0.829	0.677(184)	0.676(156)	−0.0427	0.197
ukbb	0	0.93	0.153	0.652(768)	0.670(3065)	−0.0895	0.0625
ukd1	0	0.97	0.416	0.653(242)	0.674(957)	−0.0893	0.11
usa1	0	0.93	0.0052	0.622(418)	0.674(750)	−0.265	0.0949
usa2	0	0.94	0.969	0.652(1304)	0.654(1307)	0.0024	0.0606
w10	0	0.99	0.413	0.643(156)	0.664(714)	−0.109	0.133
w11	0	0.92	0.586	0.692(164)	0.677(754)	0.0751	0.138
w12	0	0.95	0.0747	0.645(176)	0.696(785)	−0.229	0.128
w13	0	0.92	0.0199	0.620(181)	0.679(789)	−0.297	0.128
w14	0	0.99	0.0276	0.617(169)	0.681(761)	−0.279	0.127
w15	0	0.96	0.632	0.648(185)	0.665(818)	−0.06	0.125
w16	0	0.97	0.307	0.658(174)	0.681(800)	−0.132	0.129
w17	0	0.93	0.00996	0.635(158)	0.706(761)	−0.357	0.139
w18	0	0.99	0.0714	0.630(245)	0.675(852)	−0.195	0.108
w19	0	1.02	0.956	0.672(211)	0.671(851)	−0.00652	0.116
w1to6	0	0.95	0.693	0.666(357)	0.674(4828)	−0.0332	0.0844
w20	0	0.94	0.745	0.675(200)	0.683(802)	−0.0402	0.124
w21	0	0.93	0.383	0.706(161)	0.676(801)	0.122	0.14
w22	0	1.02	0.779	0.660(211)	0.653(845)	0.0319	0.114
w23	0	1.00	0.241	0.656(164)	0.685(957)	−0.15	0.128
w24	0	0.95	0.681	0.663(1241)	0.668(1447)	−0.0245	0.0595
w7	0	0.99	0.0175	0.598(97)	0.678(831)	−0.38	0.16
w8	0	1.02	0.803	0.682(162)	0.688(1062)	−0.0317	0.127
w9	0	0.98	0.952	0.667(180)	0.661(1021)	0.00747	0.124
Meta−analysis	**0**	**0.94**	**1.72e−08**	**0.651(16992)**	**0.670(55525)**	**−0.0815**	**0.0145**



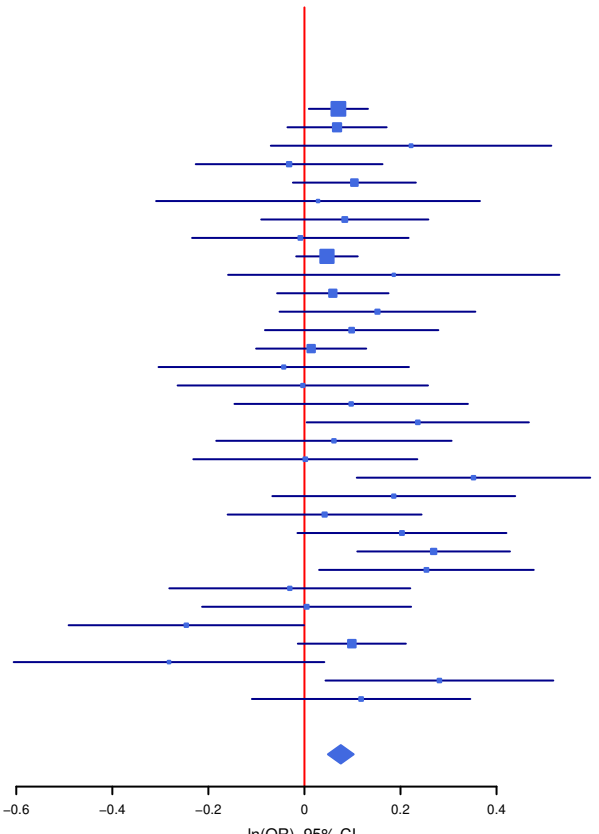
(e) chr3:rs9874207.

rs9874207		T/C		3:71019750			
				het_P:	0.212	het_I:	16.0
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.79	0.00971	0.483(2536)	0.500(15624)	−0.0889	0.0344
chop	0	0.87	0.0004	0.472(1032)	0.512(3568)	−0.197	0.0557
fin1	0	0.97	0.265	0.554(130)	0.522(503)	0.16	0.144
fre1	0	0.84	0.723	0.488(293)	0.485(990)	0.0376	0.106
gns2	0	0.88	0.564	0.486(657)	0.492(2263)	−0.0389	0.0676
itgr	0	0.89	0.972	0.469(144)	0.466(129)	−0.00662	0.186
net1	0	0.91	0.178	0.472(348)	0.500(1337)	−0.123	0.091
poco	0	0.86	0.0313	0.452(239)	0.497(604)	−0.266	0.124
sedk	0	0.82	0.0197	0.512(4105)	0.532(3793)	−0.0833	0.0357
spa1	0	0.85	0.723	0.470(184)	0.493(156)	−0.0621	0.175
ukbb	1	1.01	0.0246	0.467(768)	0.499(3065)	−0.128	0.057
ukd1	0	0.87	0.979	0.485(242)	0.486(957)	0.003	0.11
usa1	0	0.86	0.00122	0.450(418)	0.514(750)	−0.307	0.0951
usa2	0	0.77	0.335	0.488(1304)	0.477(1307)	0.0615	0.0638
w10	0	0.87	0.0727	0.460(156)	0.517(714)	−0.243	0.135
w11	0	0.86	0.804	0.485(164)	0.494(754)	−0.0329	0.132
w12	0	0.88	0.535	0.506(176)	0.491(785)	0.0786	0.127
w13	0	0.87	0.233	0.483(181)	0.520(789)	−0.151	0.126
w14	0	0.86	0.683	0.500(169)	0.512(761)	−0.0532	0.13
w15	0	0.87	0.891	0.519(185)	0.518(818)	0.0173	0.126
w16	0	0.83	0.599	0.542(174)	0.527(800)	0.0693	0.132
w17	0	0.88	0.889	0.528(158)	0.524(761)	0.0187	0.135
w18	0	0.86	0.748	0.522(245)	0.517(852)	0.036	0.112
w19	0	0.86	0.716	0.525(211)	0.514(851)	0.0429	0.118
w1to6	0	0.85	0.00504	0.460(357)	0.511(4828)	−0.237	0.0845
w20	0	0.83	0.998	0.538(200)	0.536(802)	0.0003	0.123
w21	0	0.85	0.346	0.500(161)	0.524(801)	−0.126	0.134
w22	0	0.88	0.285	0.489(211)	0.515(845)	−0.125	0.117
w23	0	0.85	0.846	0.513(164)	0.517(957)	−0.0254	0.131
w24	0	0.85	0.0416	0.495(1241)	0.520(1447)	−0.122	0.0597
w7	0	0.84	0.951	0.512(97)	0.507(831)	0.0103	0.169
w8	0	0.81	0.616	0.520(162)	0.510(1062)	0.0669	0.133
w9	0	0.86	0.895	0.512(180)	0.517(1021)	−0.0163	0.124
Meta−analysis	**1**	**0.84**	**2.05e−08**	**0.493(16992)**	**0.507(55525)**	**−0.0813**	**0.0145**



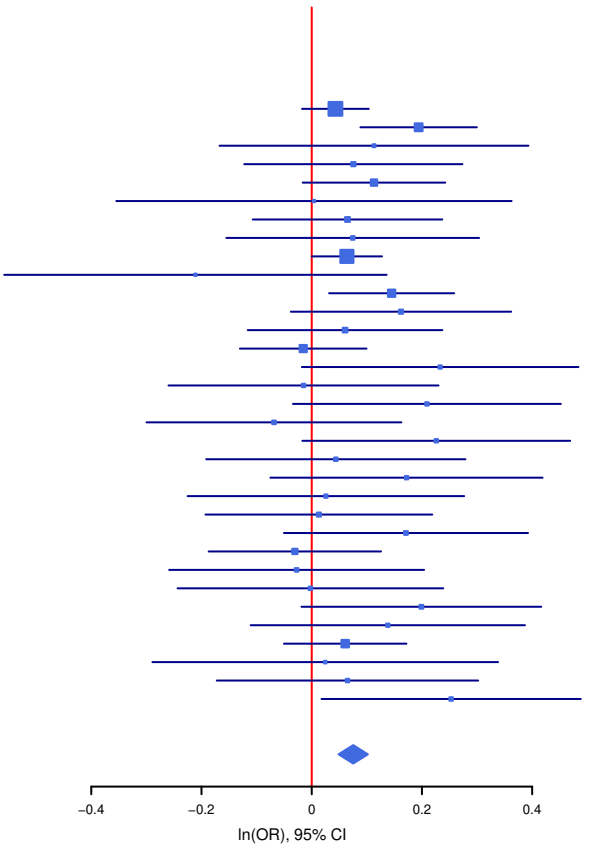
(f) chr1:rs10747478.

rs10747478		T/G		1:96901455			
				het_P:	0.149	het_I:	20.6
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.97	0.0241	0.421(2536)	0.401(15624)	0.0707	0.0314
chop	0	1.00	0.198	0.438(1032)	0.427(3568)	0.0679	0.0527
fin1	0	0.96	0.136	0.411(130)	0.366(503)	0.222	0.149
fre1	0	0.98	0.748	0.415(293)	0.427(990)	−0.0319	0.0992
gns2	0	0.96	0.111	0.455(657)	0.429(2263)	0.104	0.0653
itgr	0	1.04	0.87	0.513(144)	0.500(129)	0.0283	0.172
net1	0	0.96	0.344	0.437(348)	0.420(1337)	0.084	0.0888
poco	0	0.98	0.941	0.439(239)	0.447(604)	−0.00854	0.115
sedk	0	1.00	0.151	0.430(4105)	0.421(3793)	0.0469	0.0327
spa1	0	0.93	0.291	0.419(184)	0.387(156)	0.186	0.176
ukbb	0	0.96	0.318	0.419(768)	0.405(3065)	0.0591	0.0592
ukd1	0	1.01	0.146	0.417(242)	0.376(957)	0.152	0.104
usa1	0	0.93	0.286	0.434(418)	0.410(750)	0.0983	0.0921
usa2	0	0.94	0.811	0.421(1304)	0.419(1307)	0.014	0.0585
w10	0	0.94	0.746	0.418(156)	0.424(714)	−0.0431	0.133
w11	0	0.87	0.98	0.441(164)	0.440(754)	−0.00341	0.133
w12	0	0.94	0.435	0.438(176)	0.415(785)	0.0973	0.124
w13	0	1.02	0.0445	0.465(181)	0.408(789)	0.236	0.118
w14	0	0.96	0.624	0.440(169)	0.424(761)	0.0614	0.125
w15	0	0.99	0.988	0.439(185)	0.430(818)	0.0018	0.119
w16	0	0.96	0.00441	0.482(174)	0.404(800)	0.352	0.124
w17	0	0.98	0.149	0.443(158)	0.386(761)	0.186	0.129
w18	0	1.04	0.683	0.407(245)	0.397(852)	0.042	0.103
w19	0	0.99	0.0667	0.474(211)	0.424(851)	0.203	0.111
w1to6	0	0.93	0.000906	0.479(357)	0.420(4828)	0.269	0.0811
w20	0	0.99	0.0261	0.475(200)	0.411(802)	0.254	0.114
w21	0	0.95	0.812	0.416(161)	0.420(801)	−0.0305	0.128
w22	0	0.99	0.968	0.415(211)	0.412(845)	0.00449	0.111
w23	0	1.00	0.049	0.372(164)	0.427(957)	−0.246	0.125
w24	0	0.95	0.0856	0.421(1241)	0.399(1447)	0.0987	0.0574
w7	0	0.92	0.087	0.367(97)	0.430(831)	−0.282	0.165
w8	0	0.99	0.0203	0.473(162)	0.406(1062)	0.281	0.121
w9	0	1.00	0.308	0.449(180)	0.421(1021)	0.118	0.116
Meta−analysis	**0**	**0.97**	**3.13e−08**	**0.431(16992)**	**0.412(55525)**	**0.0757**	**0.0137**



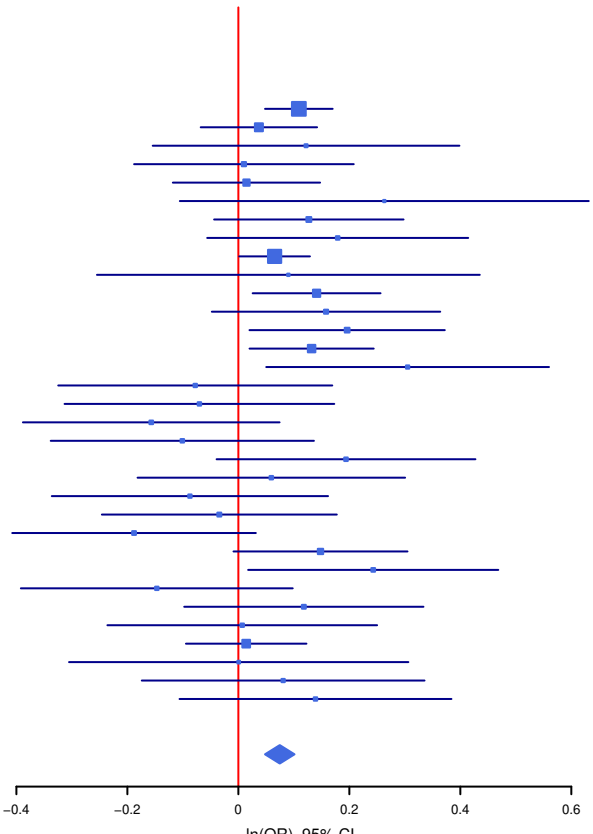
(g) chr5:rs370838138.

rs370838138		G/C		5:25081845			
				het_P:	0.637	het_I:	0.0
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.99	0.164	0.574(2536)	0.560(15624)	0.043	0.0309
chop	0	0.99	0.000315	0.607(1032)	0.563(3568)	0.194	0.0539
fin1	0	0.99	0.429	0.535(130)	0.504(503)	0.113	0.143
fre1	0	0.98	0.455	0.617(293)	0.589(990)	0.0755	0.101
gns2	0	0.95	0.0855	0.590(657)	0.563(2263)	0.113	0.066
itgr	0	0.97	0.982	0.625(144)	0.629(129)	0.00409	0.183
net1	0	1.02	0.46	0.597(348)	0.576(1337)	0.0649	0.0878
poco	0	0.92	0.527	0.546(239)	0.520(604)	0.0744	0.117
sedk	0	1.00	0.0499	0.563(4105)	0.548(3793)	0.0638	0.0325
spa1	0	0.93	0.233	0.609(184)	0.664(156)	−0.211	0.177
ukbb	0	1.01	0.0125	0.592(768)	0.555(3065)	0.145	0.0579
ukd1	0	1.04	0.11	0.578(242)	0.535(957)	0.162	0.102
usa1	0	0.96	0.502	0.588(418)	0.567(750)	0.0605	0.0901
usa2	0	0.95	0.793	0.586(1304)	0.592(1307)	−0.0154	0.0586
w10	0	1.03	0.0683	0.618(156)	0.559(714)	0.233	0.128
w11	0	0.98	0.905	0.568(164)	0.575(754)	−0.0149	0.125
w12	0	0.97	0.0919	0.614(176)	0.565(785)	0.209	0.124
w13	0	1.00	0.563	0.549(181)	0.567(789)	−0.0685	0.118
w14	0	1.02	0.0676	0.622(169)	0.570(761)	0.226	0.124
w15	0	0.95	0.716	0.572(185)	0.562(818)	0.0437	0.12
w16	0	0.96	0.174	0.614(174)	0.573(800)	0.172	0.126
w17	0	0.96	0.841	0.576(158)	0.559(761)	0.0257	0.128
w18	0	0.98	0.902	0.564(245)	0.563(852)	0.013	0.105
w19	0	0.99	0.131	0.614(211)	0.575(851)	0.171	0.113
w1to6	0	0.96	0.702	0.571(357)	0.579(4828)	−0.0306	0.0798
w20	0	0.93	0.816	0.586(200)	0.591(802)	−0.0274	0.118
w21	0	1.04	0.984	0.591(161)	0.590(801)	−0.0024	0.123
w22	0	1.03	0.0724	0.617(211)	0.569(845)	0.199	0.111
w23	0	0.93	0.278	0.595(164)	0.564(957)	0.138	0.127
w24	0	0.96	0.284	0.589(1241)	0.574(1447)	0.0607	0.0567
w7	0	0.93	0.879	0.555(97)	0.558(831)	0.0245	0.16
w8	0	1.00	0.592	0.577(162)	0.562(1062)	0.0649	0.121
w9	0	0.98	0.0358	0.633(180)	0.572(1021)	0.253	0.12
Meta−analysis	**0**	**0.98**	**3.17e−08**	**0.582(16992)**	**0.564(55525)**	**0.0753**	**0.0136**

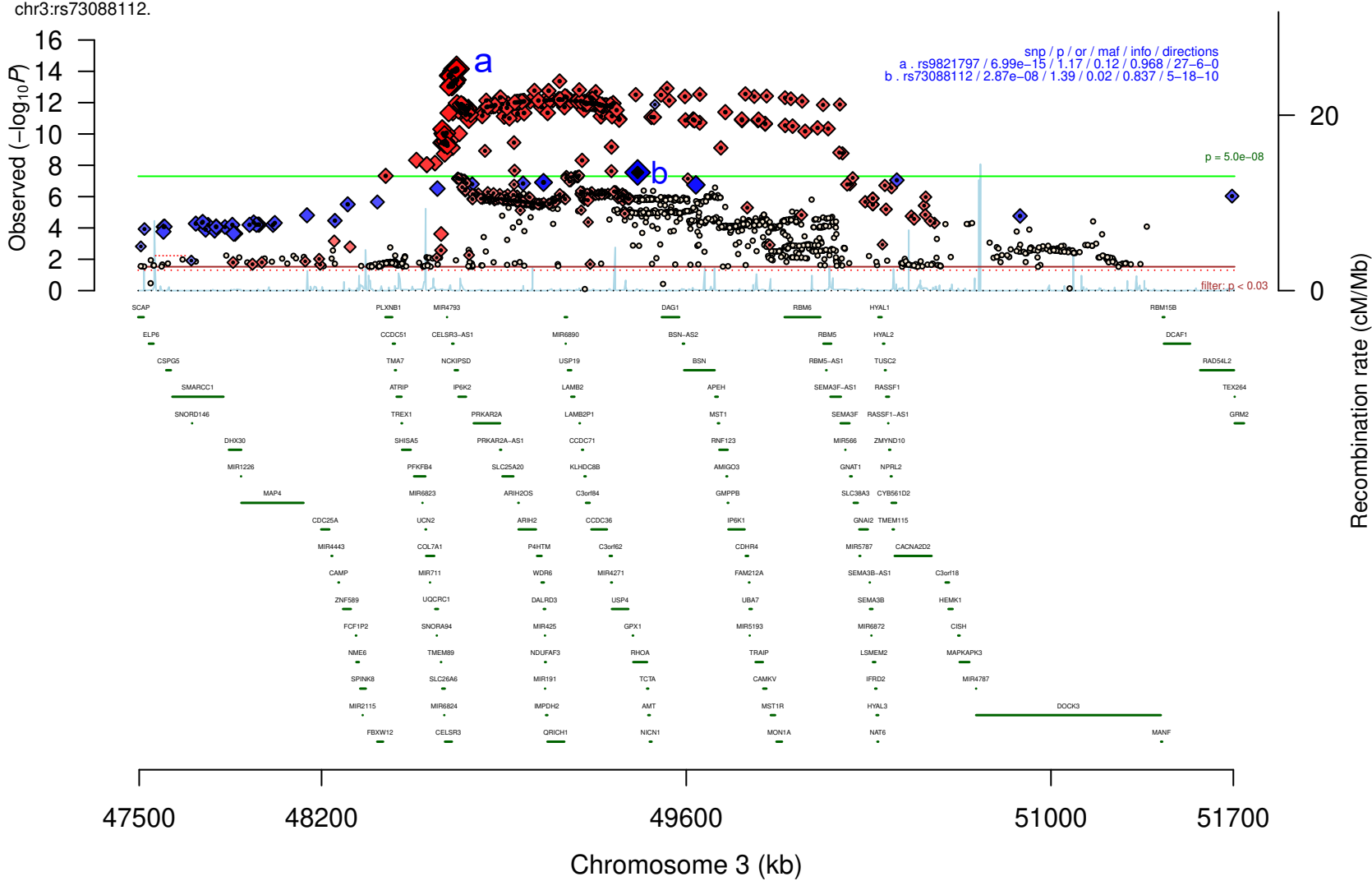


(h) chr3:rs13100344.

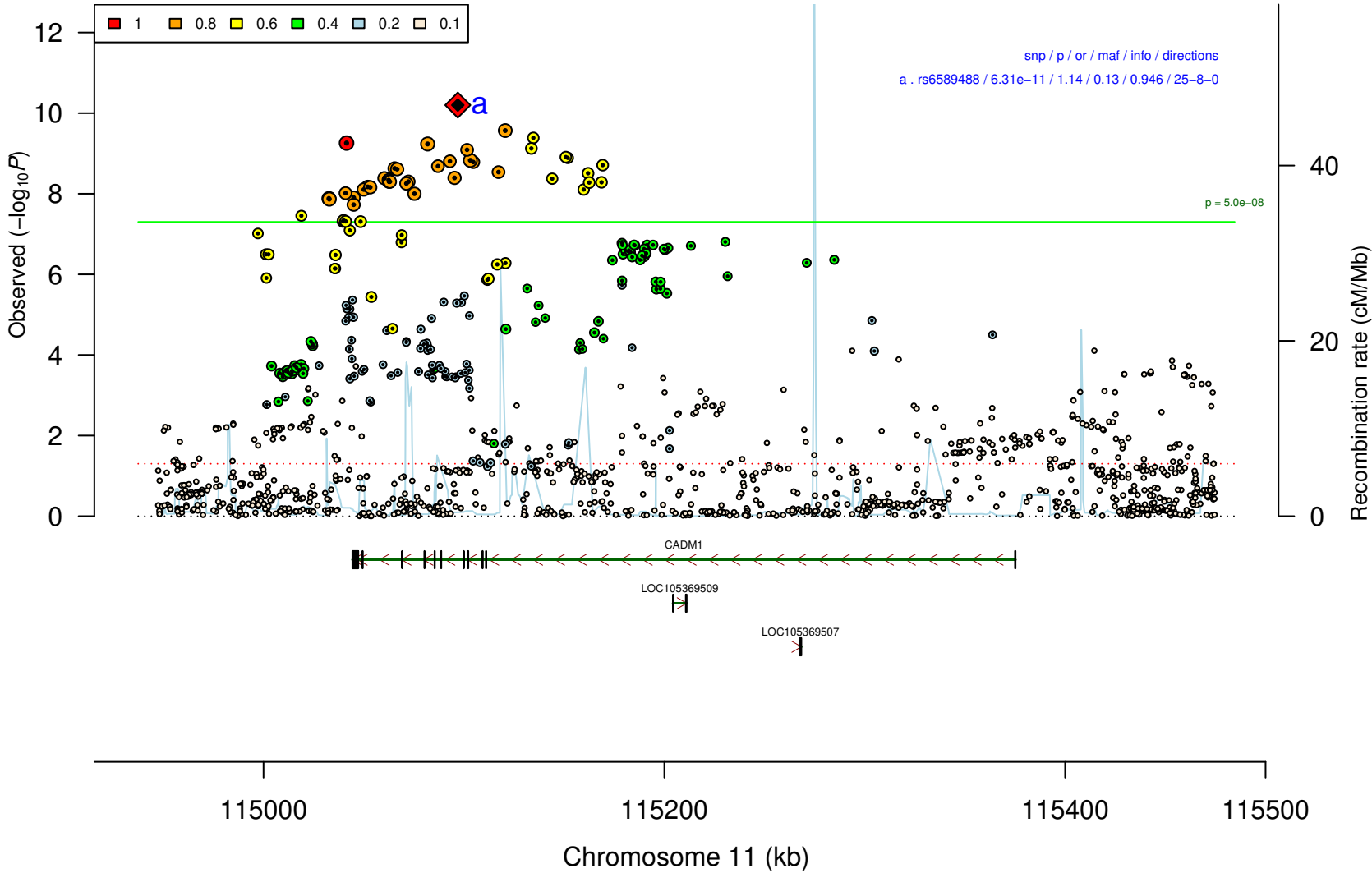
	rs13100344		T/A		3:94605107			
					het_P:	0.175	het_I:	18.6
		ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz		0	0.98	0.000439	0.564(2536)	0.536(15624)	0.109	0.0311
chop		0	0.95	0.489	0.545(1032)	0.541(3568)	0.037	0.0535
fin1		0	1.03	0.388	0.482(130)	0.448(503)	0.122	0.141
fre1		0	0.93	0.921	0.535(293)	0.524(990)	0.01	0.101
gns2		0	0.88	0.829	0.530(657)	0.526(2263)	0.0146	0.0677
itgr		0	0.94	0.162	0.626(144)	0.580(129)	0.263	0.188
net1		0	1.00	0.145	0.534(348)	0.505(1337)	0.127	0.0871
poco		0	0.91	0.135	0.581(239)	0.535(604)	0.179	0.12
sedk		0	0.99	0.0447	0.530(4105)	0.513(3793)	0.0653	0.0325
spa1		0	0.86	0.608	0.550(184)	0.541(156)	0.0901	0.176
ukbb		0	0.97	0.0162	0.581(768)	0.547(3065)	0.141	0.0588
ukd1		0	0.98	0.131	0.585(242)	0.549(957)	0.158	0.105
usa1		0	0.97	0.0291	0.580(418)	0.528(750)	0.196	0.0898
usa2		0	0.97	0.021	0.567(1304)	0.538(1307)	0.132	0.0571
w10		0	0.99	0.0194	0.617(156)	0.547(714)	0.305	0.13
w11		0	0.96	0.539	0.535(164)	0.554(754)	−0.0777	0.126
w12		0	0.92	0.57	0.517(176)	0.534(785)	−0.0702	0.124
w13		0	1.02	0.184	0.513(181)	0.553(789)	−0.157	0.118
w14		0	1.00	0.404	0.528(169)	0.552(761)	−0.101	0.121
w15		0	0.98	0.104	0.582(185)	0.535(818)	0.194	0.119
w16		0	0.97	0.63	0.572(174)	0.553(800)	0.0594	0.123
w17		0	0.98	0.49	0.521(158)	0.543(761)	−0.0873	0.127
w18		0	0.92	0.752	0.526(245)	0.532(852)	−0.0343	0.108
w19		0	0.97	0.0935	0.531(211)	0.571(851)	−0.188	0.112
w1to6		0	0.98	0.0646	0.586(357)	0.551(4828)	0.148	0.08
w20		0	0.98	0.0342	0.574(200)	0.514(802)	0.243	0.115
w21		0	0.98	0.24	0.521(161)	0.553(801)	−0.147	0.125
w22		0	1.00	0.284	0.561(211)	0.535(845)	0.118	0.11
w23		0	0.97	0.955	0.535(164)	0.541(957)	0.00698	0.124
w24		0	0.99	0.8	0.556(1241)	0.553(1447)	0.0141	0.0554
w7		0	0.99	0.997	0.557(97)	0.557(831)	0.0006	0.156
w8		0	0.86	0.534	0.555(162)	0.539(1062)	0.0807	0.13
w9		0	0.86	0.268	0.566(180)	0.536(1021)	0.139	0.125
Meta−analysis		**0**	**0.96**	**4.21e−08**	**0.551(16992)**	**0.537(55525)**	**0.0746**	**0.0136**



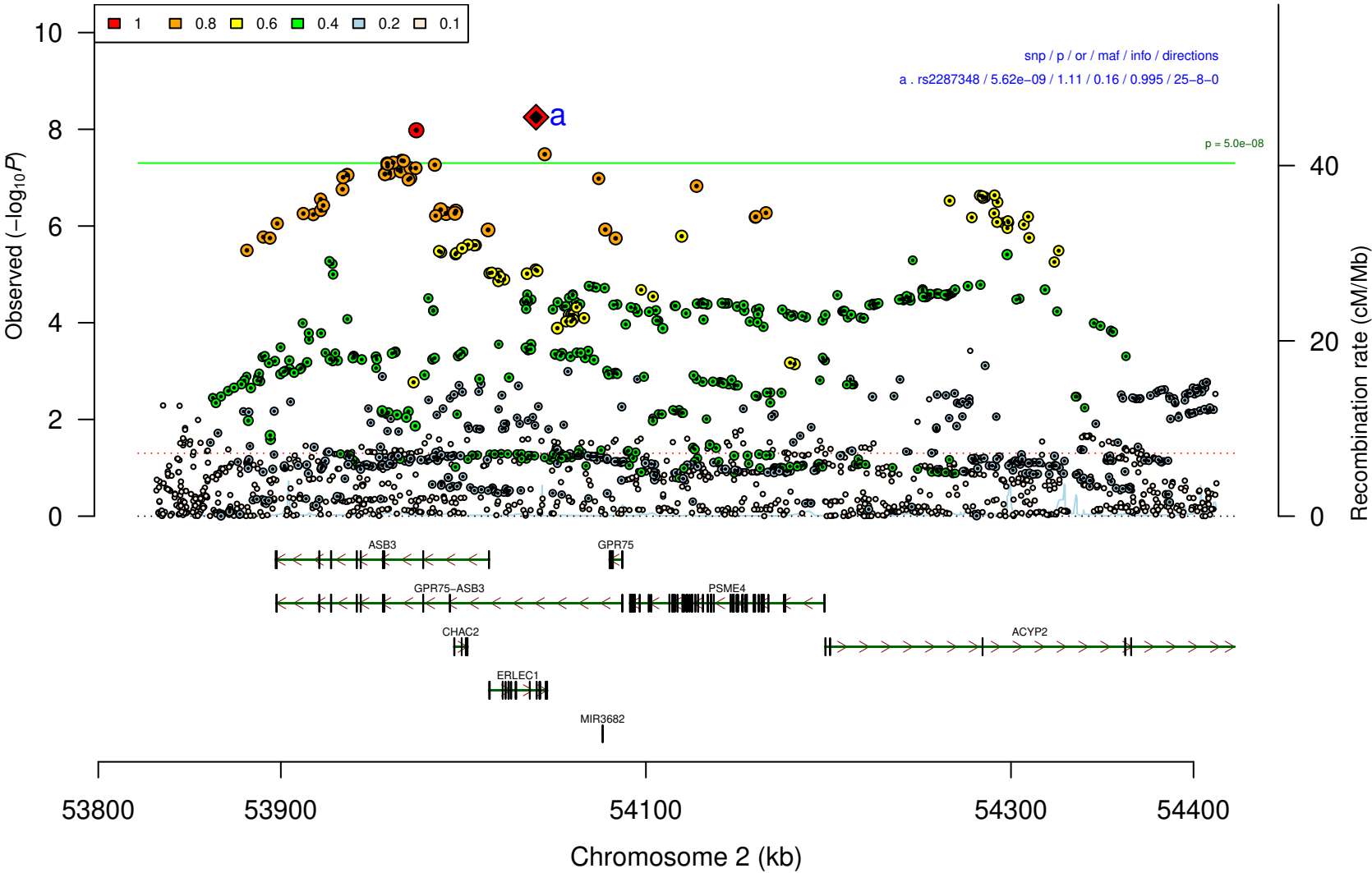
Supplementary Figure 3a-h legend. Regional plot of GWAS meta-analysis results for all genome-wide significant loci. The sample size is 16,992 cases and 55,525 controls. Two loci overlapped (index SNPs of rs9821797 and rs73088112), therefore we refer to only one of these (rs9821797) in the main manuscript. (a) chr3:rs9821797 and chr3:rs73088112.



(b) chr11:6589488.



(c) chr2:2287348.



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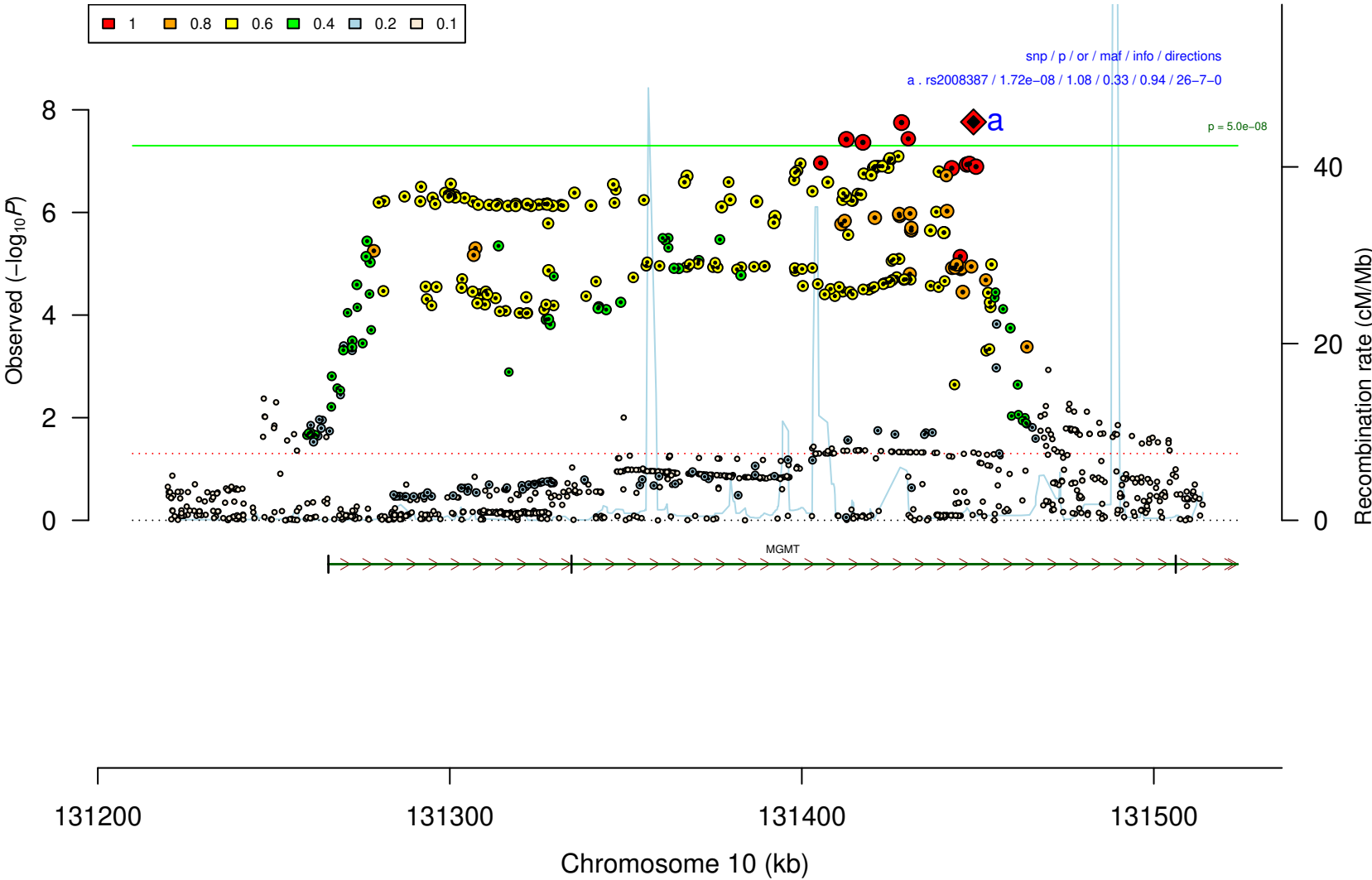
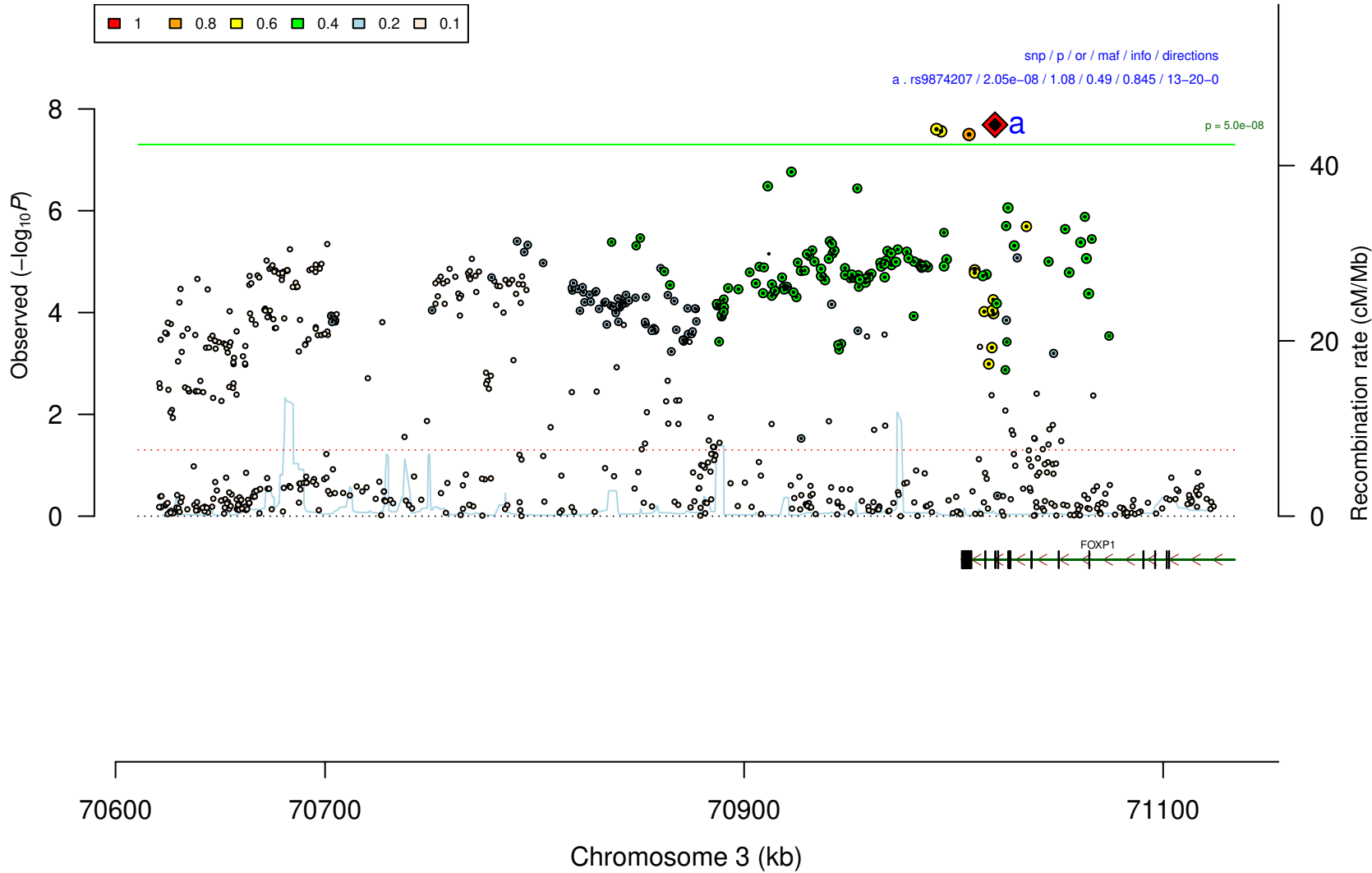
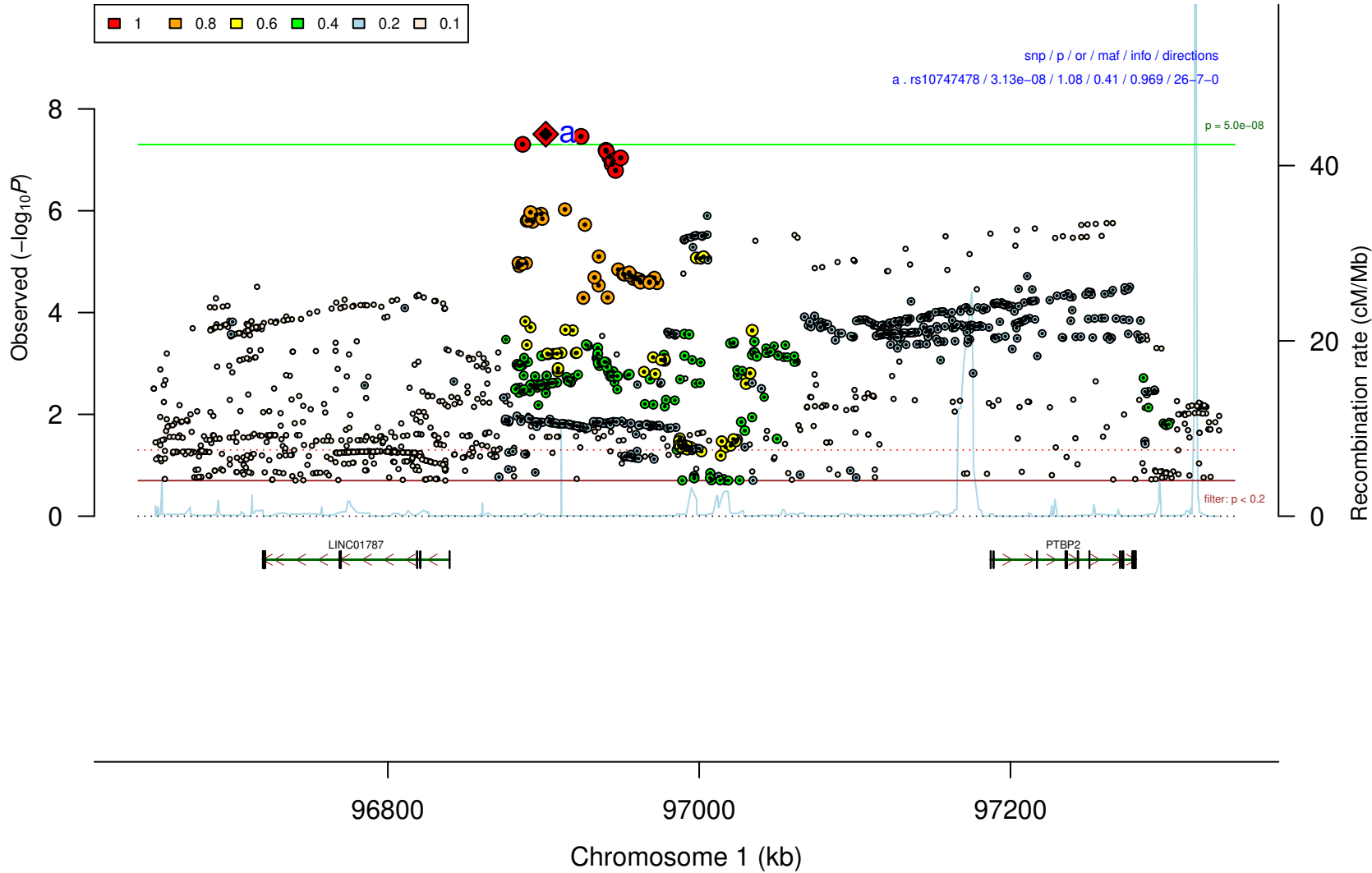


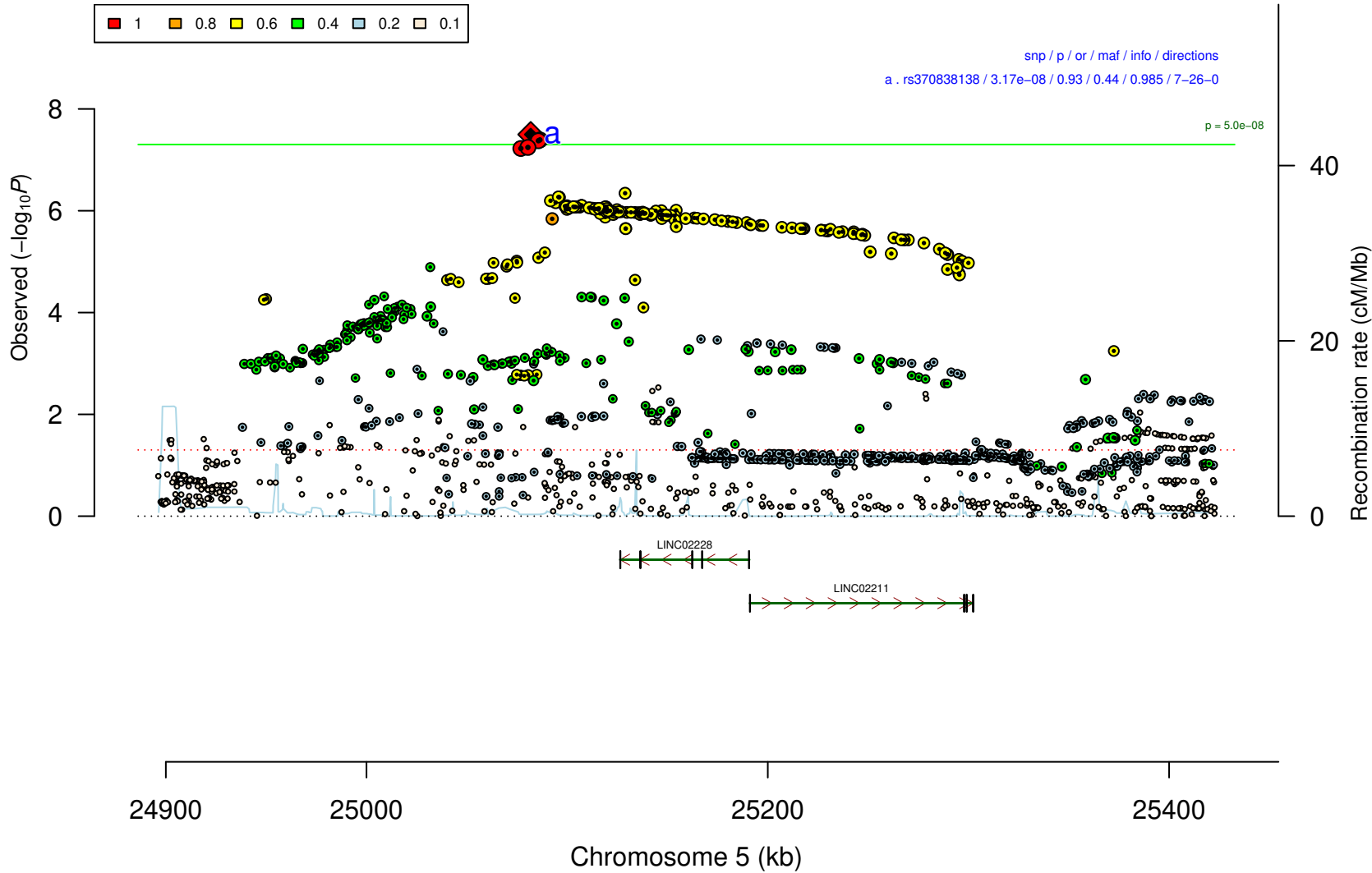
(e) chr3:rs9874207.



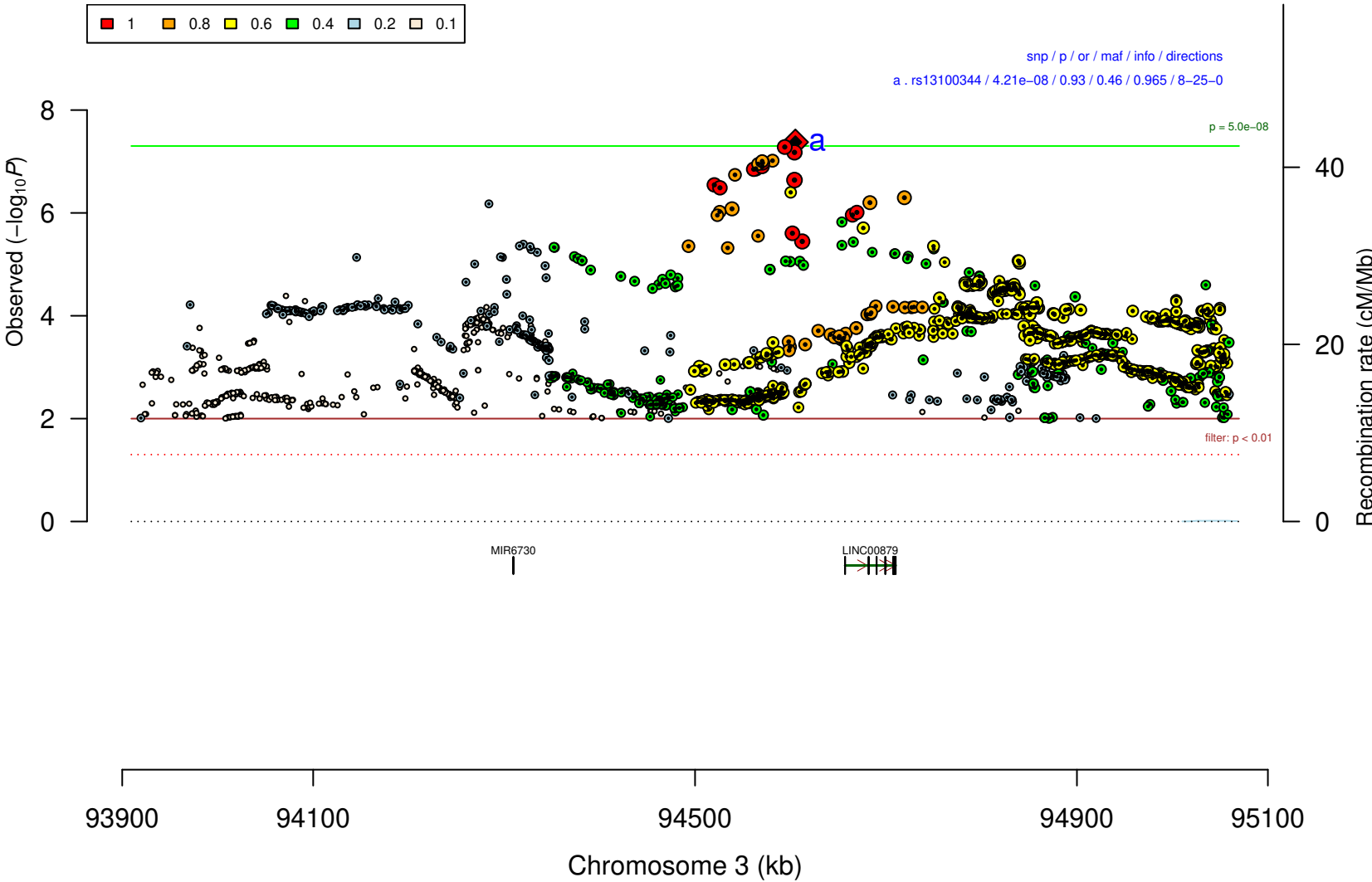
(f) chr1:rs10747478.



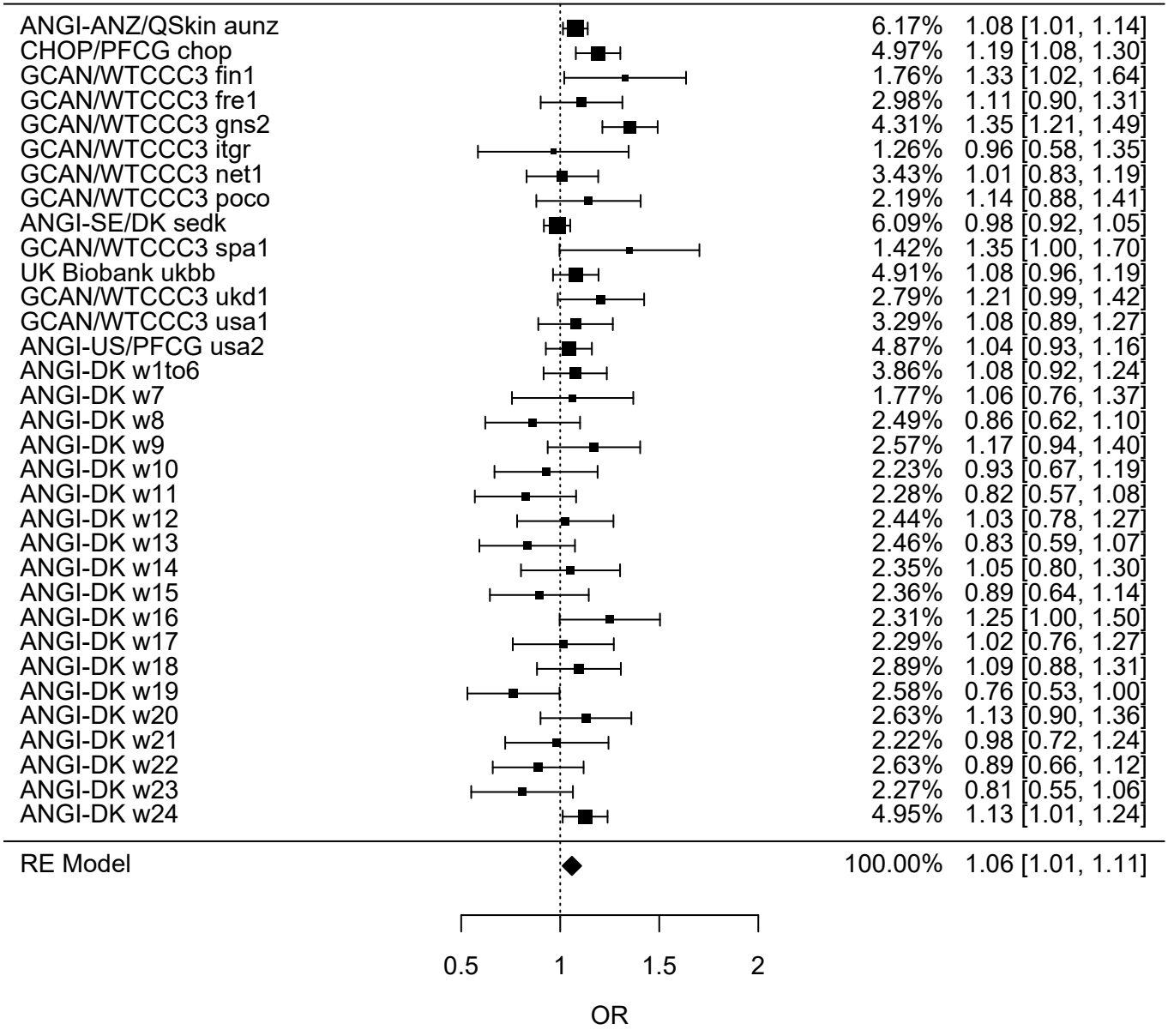
(g) chr5:rs370838138.



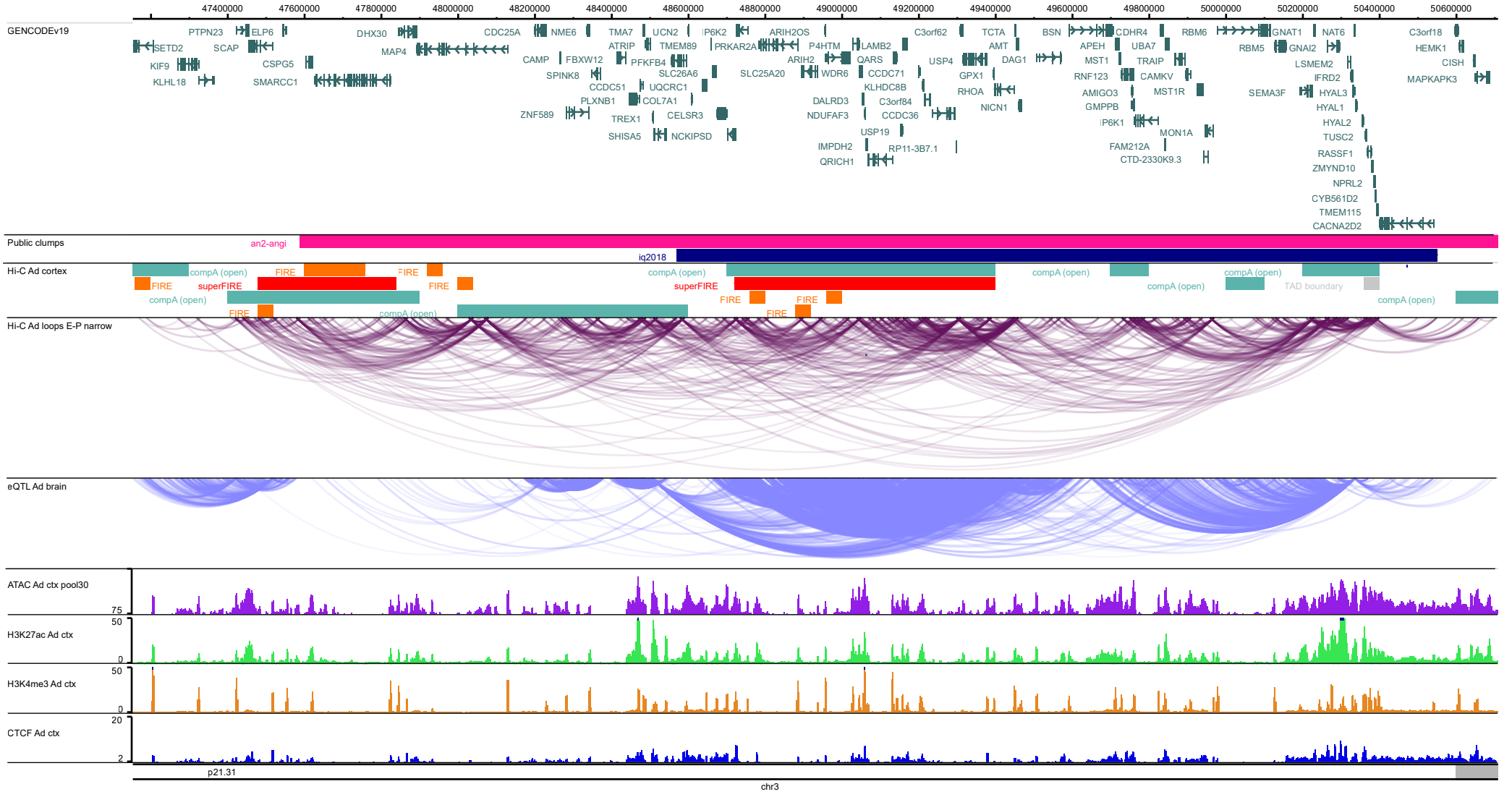
(h) chr3:rs13100344.



Supplementary Figure 4. A random-effects meta-analysis of the association between rs4622308 and anorexia nervosa. Previously, the first freeze of the PGC-ED revealed that this SNP was genome-wide significant (Duncan et al., 2017). In the present study, this SNP was not genome-wide significant in the primary GWAS meta-analysis using a fixed-effects model, and in a subsequent random effects meta-analysis as shown in this figure was also non-significant and showed evidence of heterogeneity (odds ratio [OR] = 1.06, 95% CI = 1.01-1.11, $P_{\text{two-tailed}} = 0.0002$, $I^2 = 53.76$). The percentages refer to the weight assigned to each cohort. The figures on the right are the percentage weight assigned to each cohort, the center values are the OR, and the error bar is the 95% confidence interval. The vertical line is the reference line of no effect. The sample size is 16,992 cases and 55,525 controls.


ANGI-ANZ/QSkin aunz 6.17% 1.08 [1.01, 1.14]
CHOP/PFCG chop 4.97% 1.19 [1.08, 1.30]
GCAN/WTCCC3 fin1 1.76% 1.33 [1.02, 1.64]
GCAN/WTCCC3 fre1 2.98% 1.11 [0.90, 1.31]
GCAN/WTCCC3 gns2 4.31% 1.35 [1.21, 1.49]
GCAN/WTCCC3 itgr 1.26% 0.96 [0.58, 1.35]
GCAN/WTCCC3 net1 3.43% 1.01 [0.83, 1.19]
GCAN/WTCCC3 poco 2.19% 1.14 [0.88, 1.41]
ANGI-SE/DK sedk 6.09% 0.98 [0.92, 1.05]
GCAN/WTCCC3 spa1 1.42% 1.35 [1.00, 1.70]
UK Biobank ukbb 4.91% 1.08 [0.96, 1.19]
GCAN/WTCCC3 ukd1 2.79% 1.21 [0.99, 1.42]
GCAN/WTCCC3 usa1 3.29% 1.08 [0.89, 1.27]
ANGI-US/PFCG usa2 4.87% 1.04 [0.93, 1.16]
ANGI-DK w1to6 3.86% 1.08 [0.92, 1.24]
ANGI-DK w7 1.77% 1.06 [0.76, 1.37]
ANGI-DK w8 2.49% 0.86 [0.62, 1.10]
ANGI-DK w9 2.57% 1.17 [0.94, 1.40]
ANGI-DK w10 2.23% 0.93 [0.67, 1.19]
ANGI-DK w11 2.28% 0.82 [0.57, 1.08]
ANGI-DK w12 2.44% 1.03 [0.78, 1.27]
ANGI-DK w13 2.46% 0.83 [0.59, 1.07]
ANGI-DK w14 2.35% 1.05 [0.80, 1.30]
ANGI-DK w15 2.36% 0.89 [0.64, 1.14]
ANGI-DK w16 2.31% 1.25 [1.00, 1.50]
ANGI-DK w17 2.29% 1.02 [0.76, 1.27]
ANGI-DK w18 2.89% 1.09 [0.88, 1.31]
ANGI-DK w19 2.58% 0.76 [0.53, 1.00]
ANGI-DK w20 2.63% 1.13 [0.90, 1.36]
ANGI-DK w21 2.22% 0.98 [0.72, 1.24]
ANGI-DK w22 2.63% 0.89 [0.66, 1.12]
ANGI-DK w23 2.27% 0.81 [0.55, 1.06]
ANGI-DK w24 4.95% 1.13 [1.01, 1.24]
RE Model 100.00% 1.06 [1.01, 1.11]
0.5
1
1.5
2
OR

Supplementary Figure 5a-h legend. Hi-C and eQTL analyses. These figures were generated using the WashU EpiGenome browser (http://epigenomegateway.wustl.edu/browser). Yellow shaded regions show the “clumps” associated with AN. The top track shows GENCODE v19 gene models. The "public clumps" track shows psychiatric GWA regions including AN GWAS. The "Hi-C Ad cortex" track shows "compartment A/B", "FIRES" (frequently interacting regions), "superFIRES" (local aggregates of FIREs), and topologically associated domain boundaries (TADs). The "Hi-C Ad loops E-P narrow" contains arcs that show the positions of high confidence chromatin interactions in adult brain (10 Kb resolution) between enhancers and/or promoters (according to ChIP-seq and brain-expressed TSS data) with a Bonferroni $P < 0.001$. The "eQTL Ad brain" track shows cis eQTL information from GTEx for all available brain tissues. The "ATAC Ad ctx pool30" track shows open chromatin data for 30 adult controls. The next three tracks show brain epigenomic marks from ChIP-seq in adult brain cortex (H3K27ac, H3K4me3, and CTCF). We selected eQTL SNP-gene pairs from CommonMind frontal cortex, GTEx in any brain region ($q < 0.05$), or in fetal cortex. Significant eQTL connections were identified by nominal $P < 0.05$ as supplied by CMC and GTEx and significant chromatin interactions were identified with a stringent Bonferroni correction for multiple testing, and only considered 10 Kb bin pairs with P value $< 2.31 \times 10^{-11}$ (0.001/43,222,677 tests). The chromatin interaction tests came from Fit-Hi-C with default parameters applied and FastHiC. All tests were two-tailed.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KLHL18
SMARCC1
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MAP4
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NPRL2
CYB561D2
TMEM115
CACNA2D2
C3orf18
HEMK1
CISH
MAPKAPK3
Public clumps
an2-angi
iq2018
Hi-C Ad cortex
compA (open)
FIRE
superFIRE
TAD boundary
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
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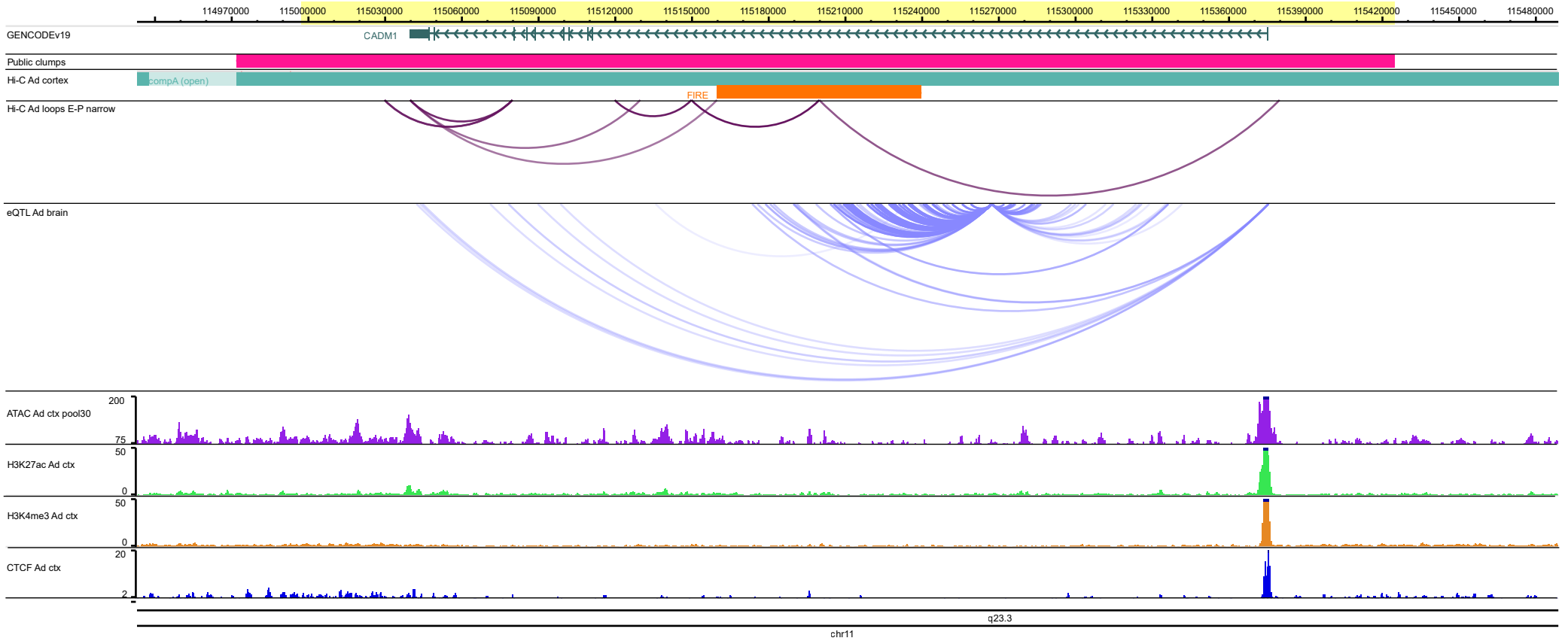
chr3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CADM1
Public clumps
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compA (open)
FIRE
Hi-C Ad loops E-P narrow
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0
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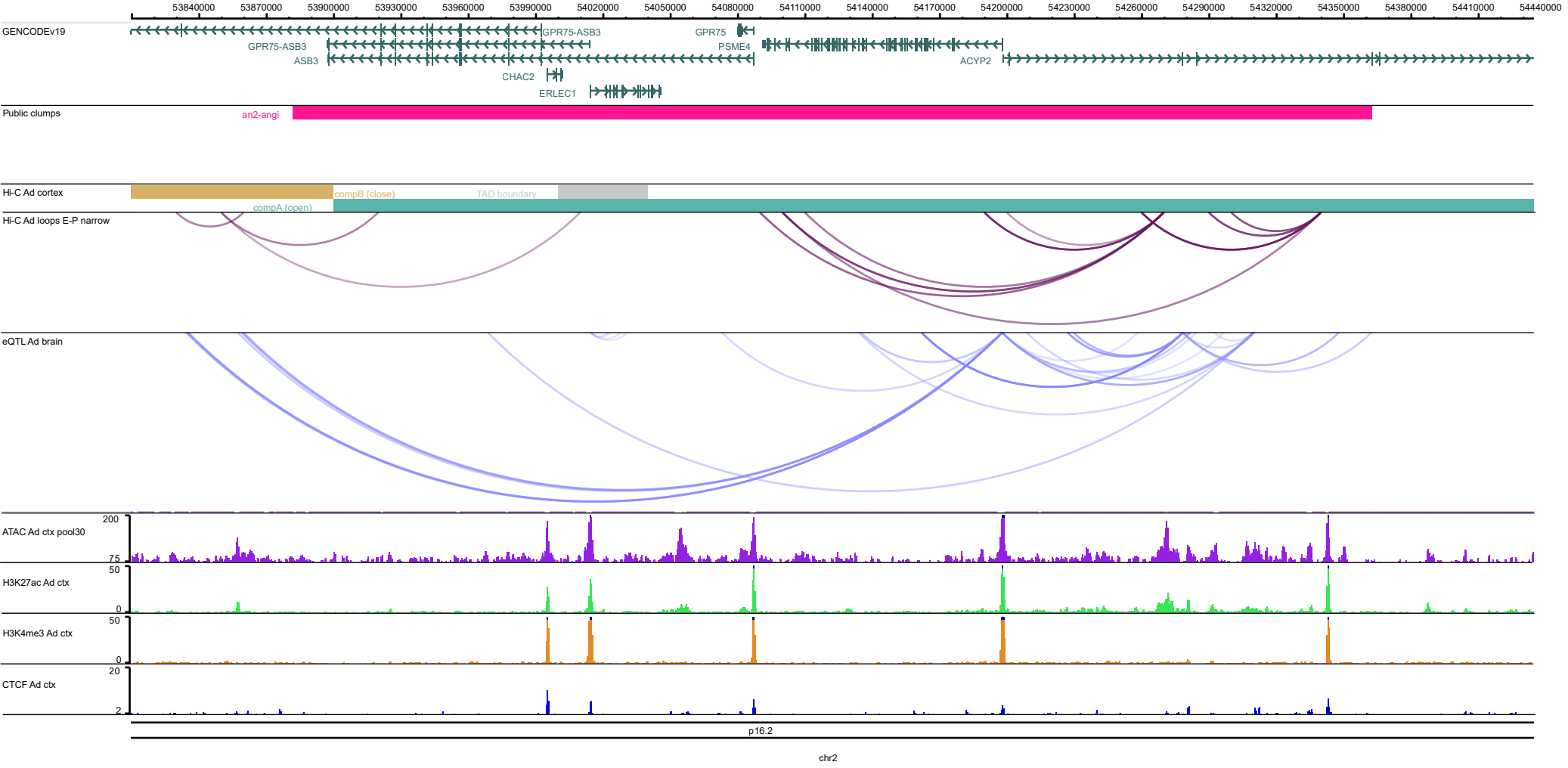
chr11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ASB3
CHAC2
ERLEC1
GPR75
PSME4
ACYP2
Public clumps
an2-angi
Hi-C Ad cortex
compB (close)
TAD boundary
compA (open)
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
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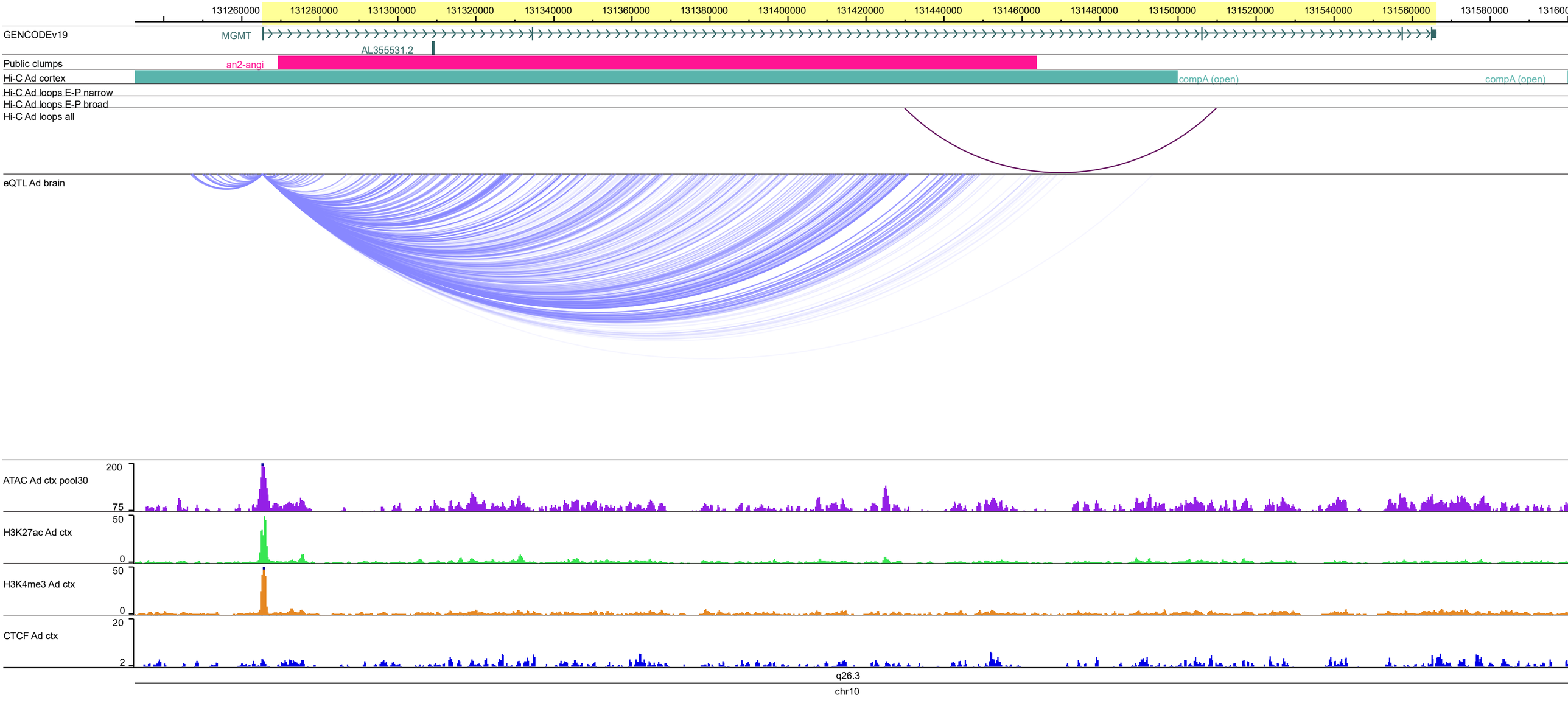
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GENCODEv19
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Public clumps
an2-angi
Hi-C Ad cortex
compA (open)
compA (open)
Hi-C Ad loops E-P narrow
Hi-C Ad loops E-P broad
Hi-C Ad loops all
eQTL Ad brain
ATAC Ad ctx pool30
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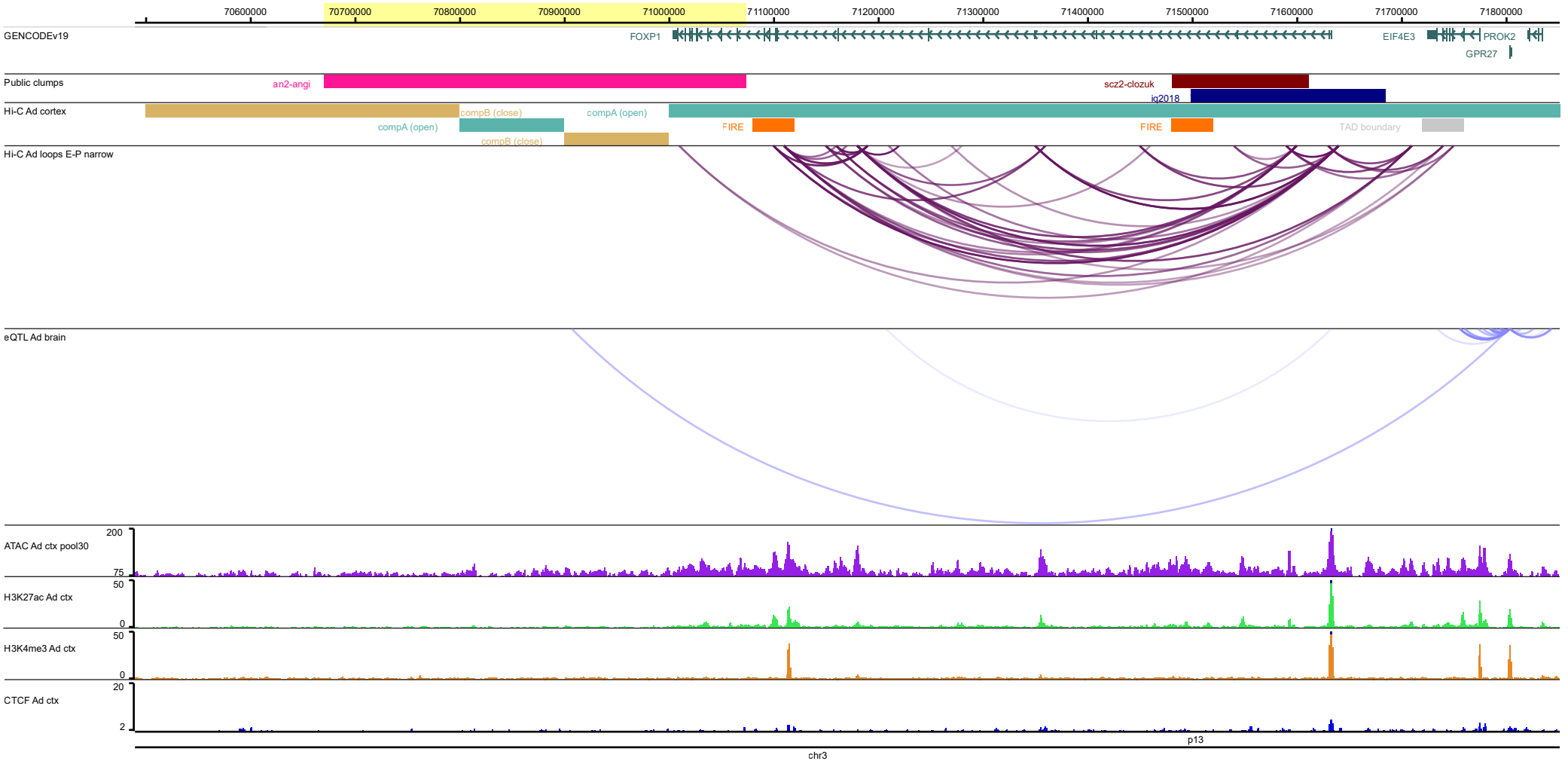
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Hi-C Ad cortex
compB (close)
compA (open)
compA (open)
compB (close)
FIRE
FIRE
TAD boundary
Hi-C Ad loops E-P narrow
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ATAC Ad ctx pool30
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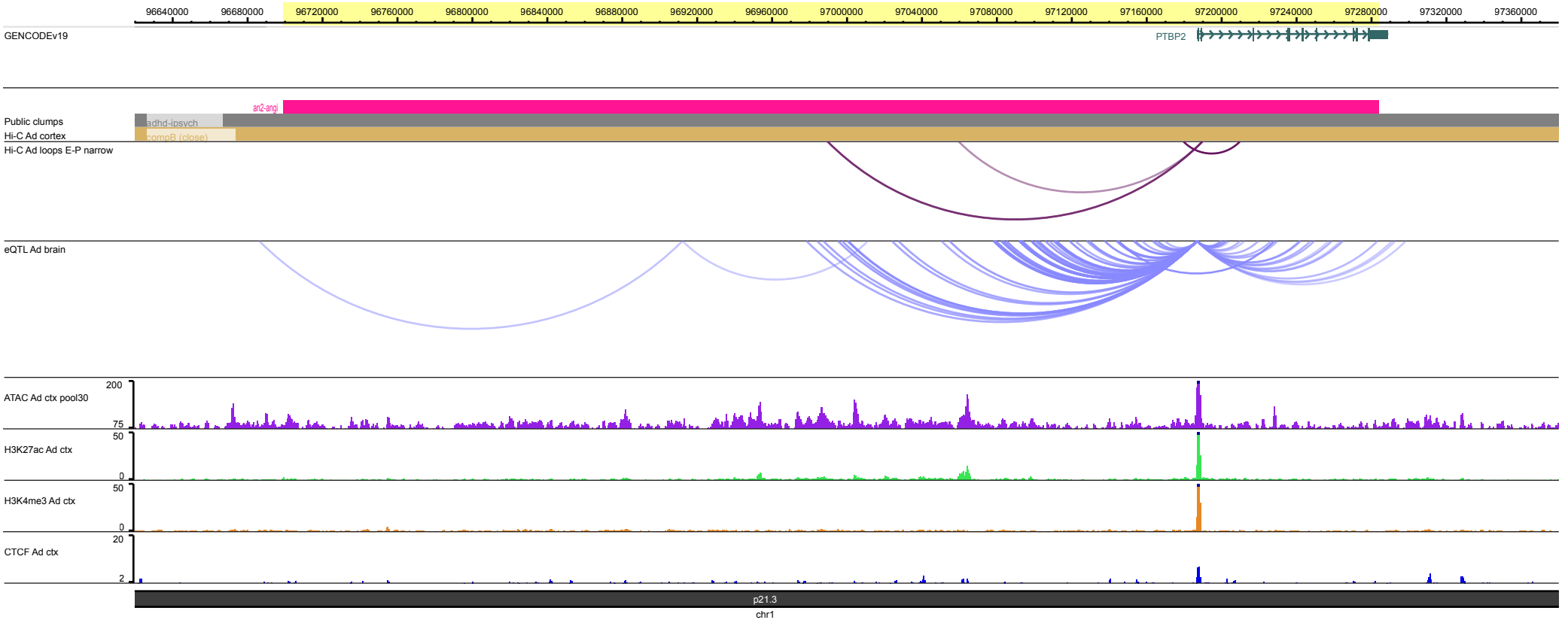
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Hi-C Ad cortex
compB (close)
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
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0
CTCF Ad ctx
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p21.3
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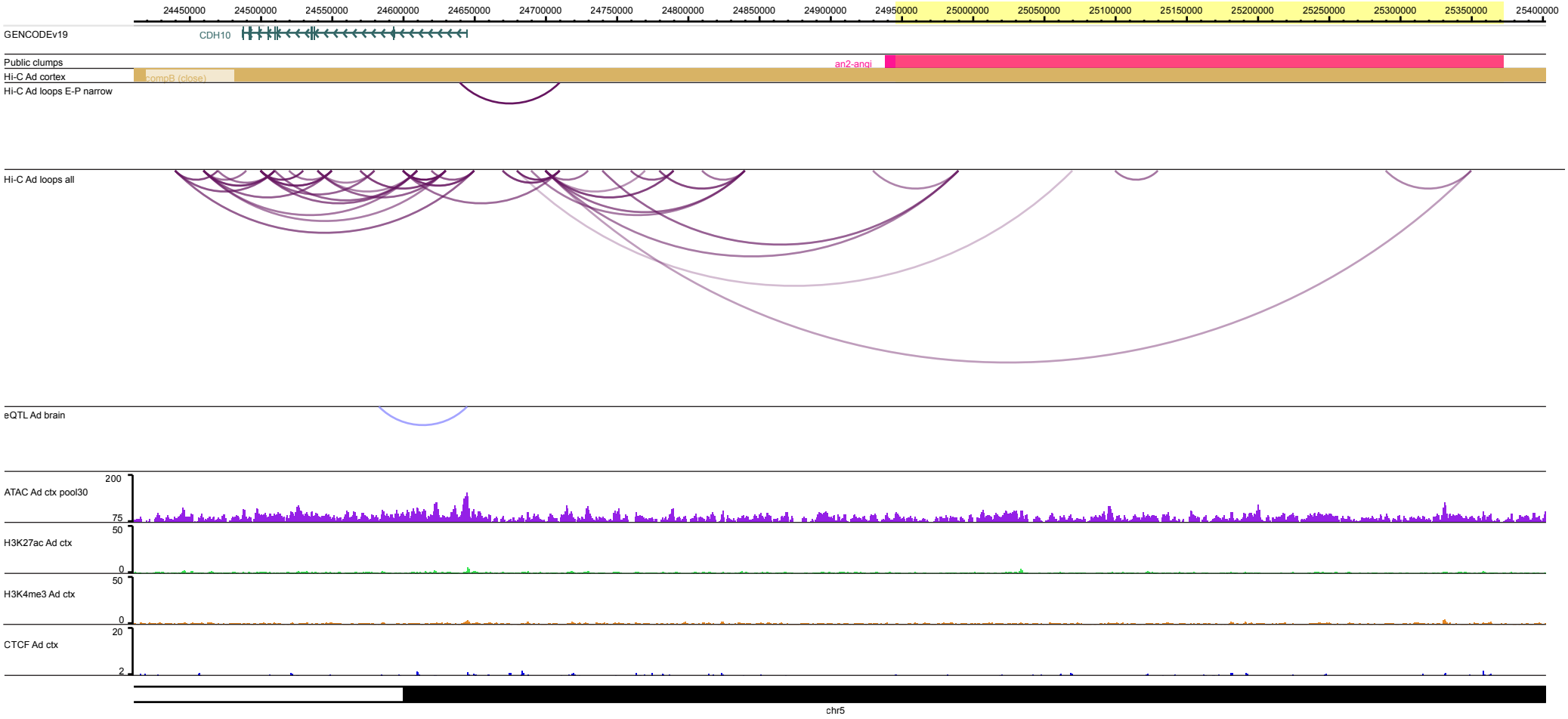
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CDH10
Public clumps
an2-angi
Hi-C Ad cortex
compB (close)
Hi-C Ad loops E-P narrow
Hi-C Ad loops all
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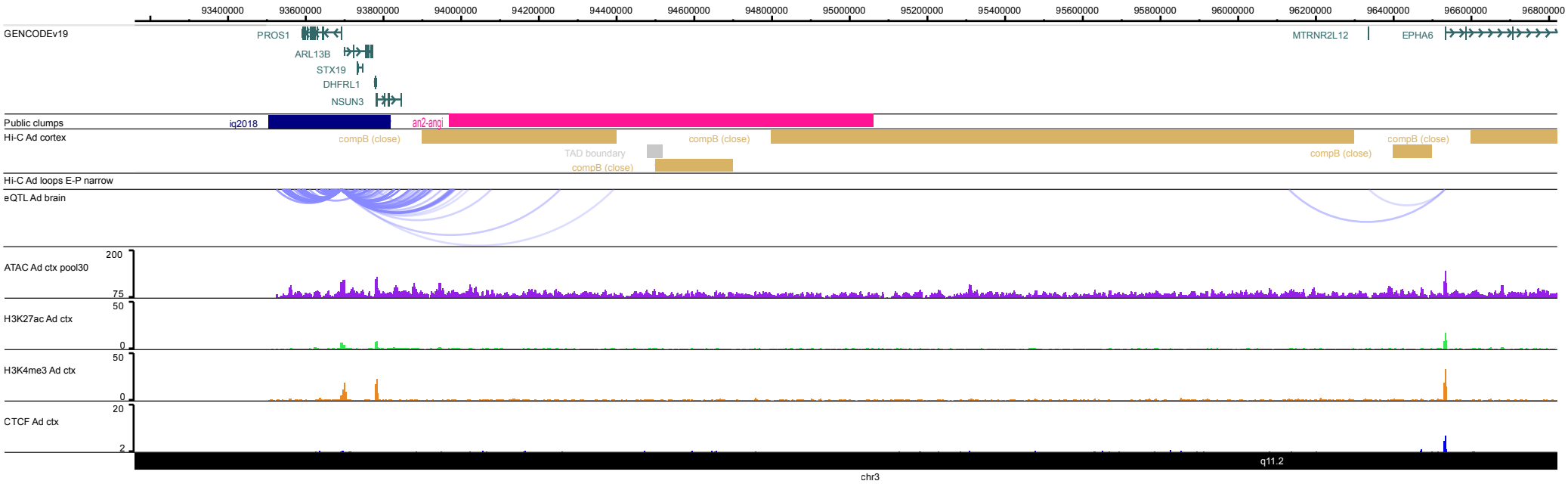
20
2
chr5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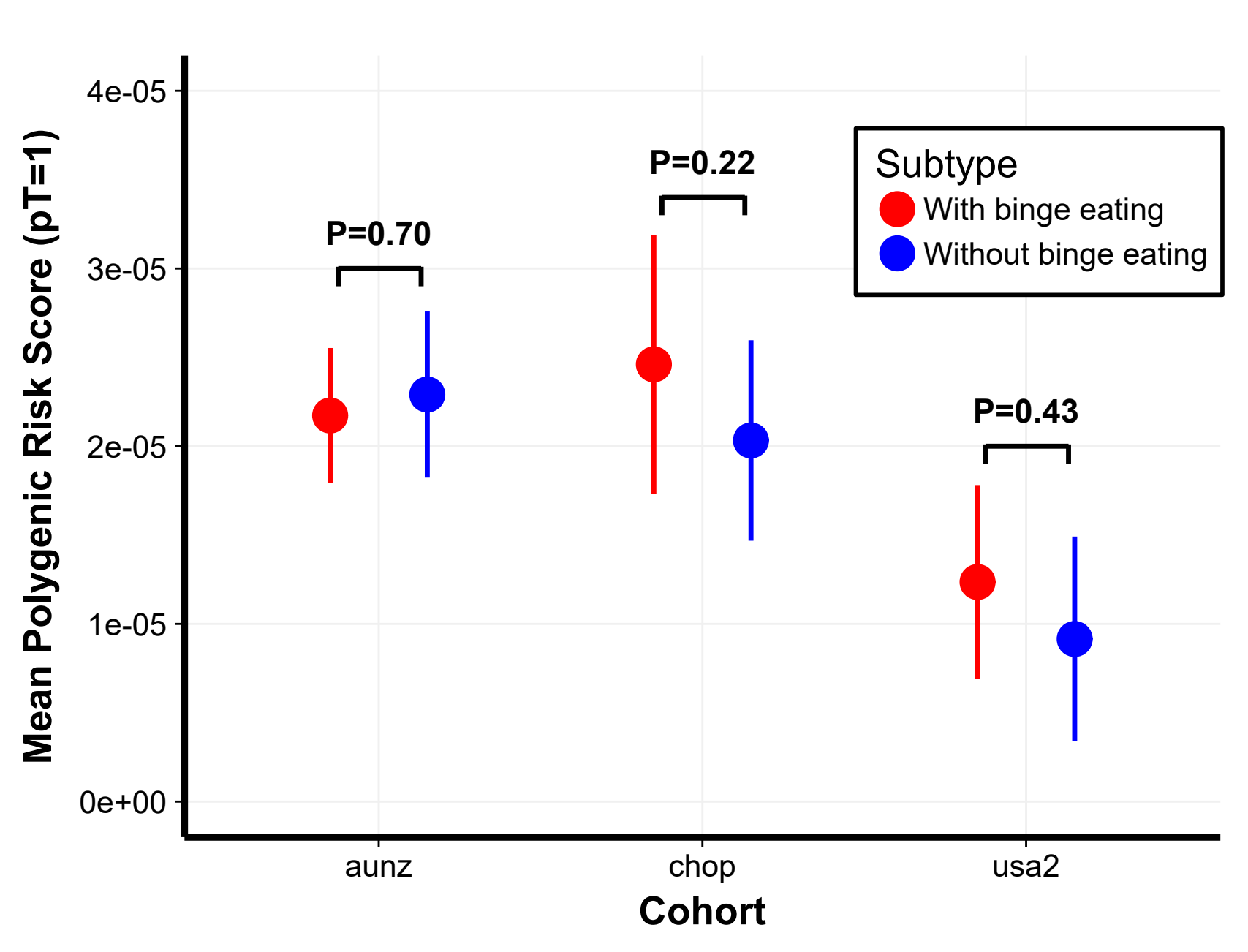
NSUN3
MTRNR2L12
EPHA6
Public clumps
iq2018
an2-angi
Hi-C Ad cortex
compB (close)
compB (close)
compB (close)
TAD boundary
compB (close)
compB (close)
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
200
75
H3K27ac Ad ctx
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
q11.2
chr3

Supplementary Figure 6. Mean polygenic risk scores (PRS) according to anorexia nervosa subtype (+/- binge eating). In the datasets with available subtype data—aunz (1,417 cases with binge eating, 997 cases without binge eating), chop (358 cases with binge eating, 634 cases without binge eating), and usa2 (606 cases with binge eating, 631 cases without binge eating)— AN PRS was computed for each individual. AN PRS was derived from the primary GWAS meta-analysis summary statistics and adjusted for the principal components used in the main GWAS. Individual PRS were then aggregated into subtype group means. The center values show mean PRS and the error bars show the 95% confidence interval. Two-tailed *T* tests testing for significant differences in PRS scores by subtype were conducted for each cohort using a Bonferroni-corrected *P* threshold of < 0.017.


Mean Polygenic Risk Score (pT=1)
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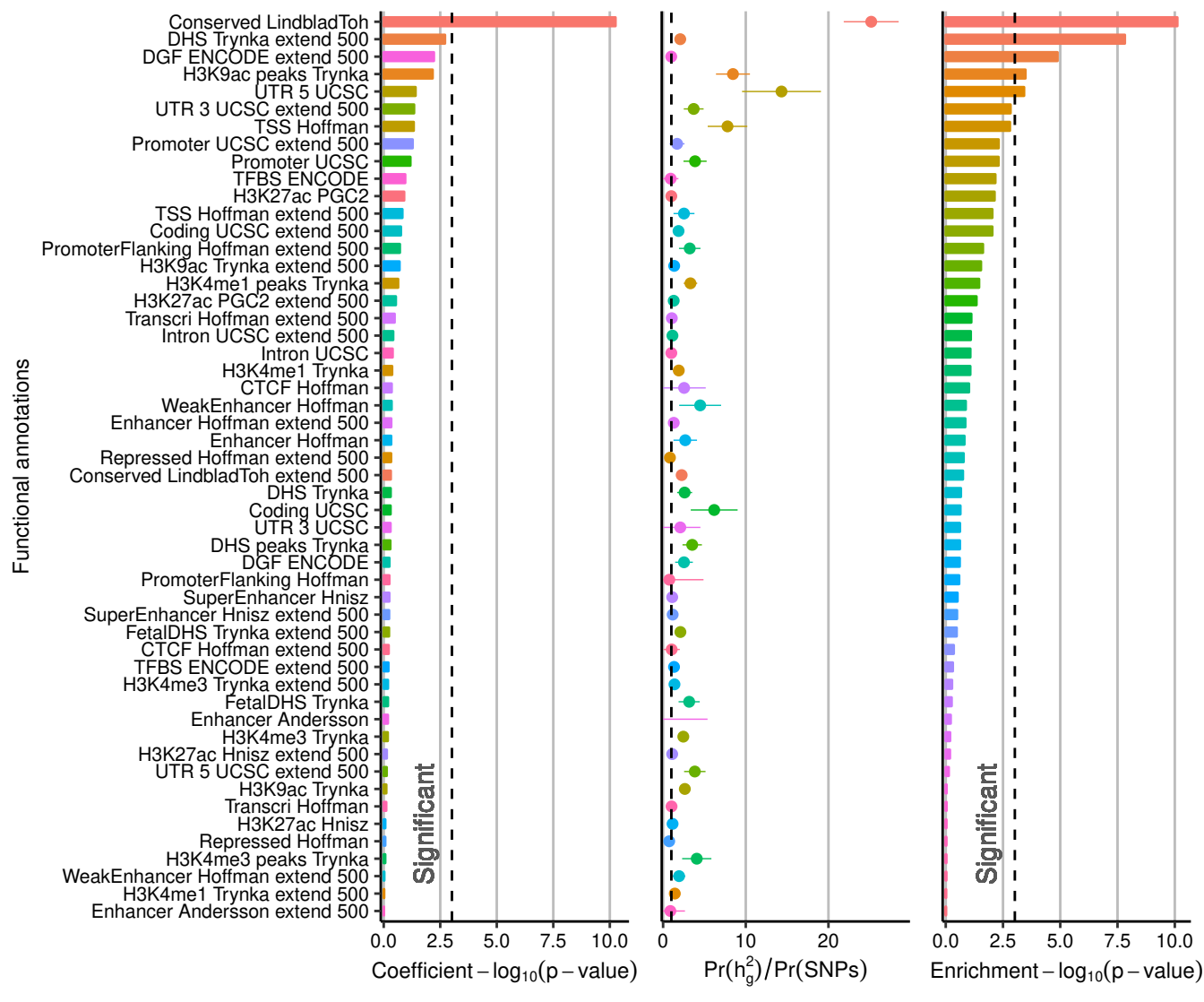
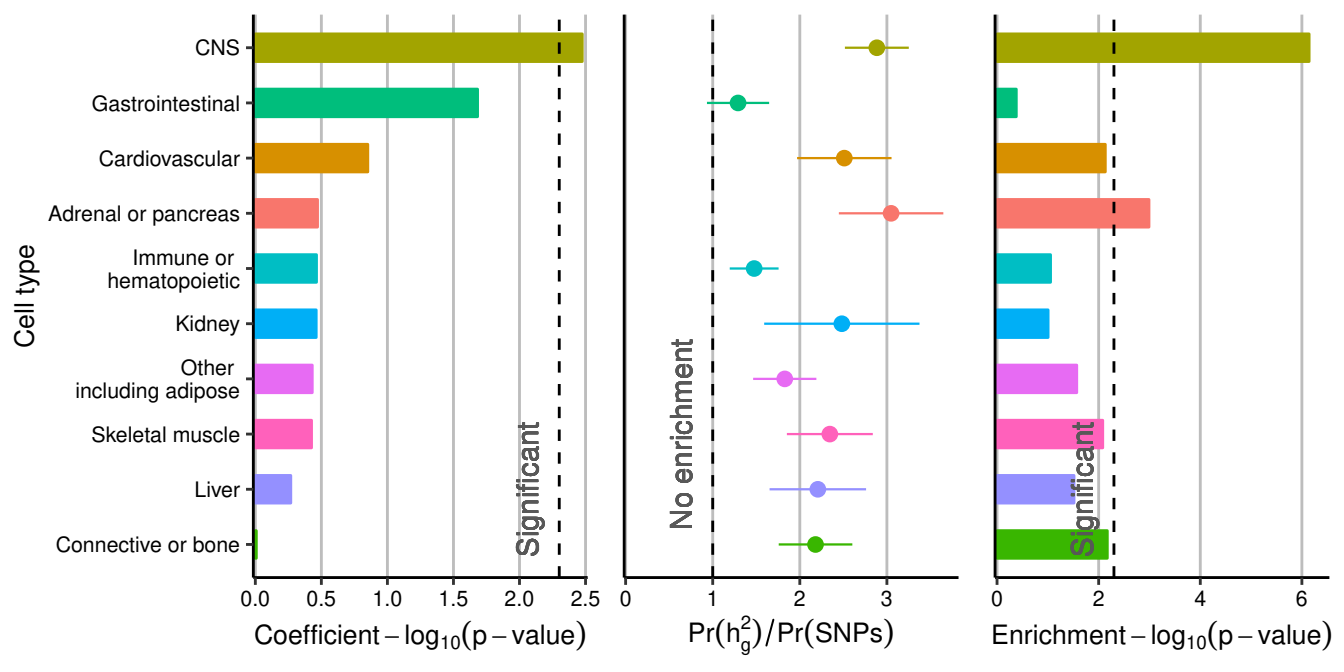
2e-05
1e-05
0e+00
P=0.70
P=0.22
P=0.43
Subtype
With binge eating
Without binge eating
aunz
chop
usa2
Cohort

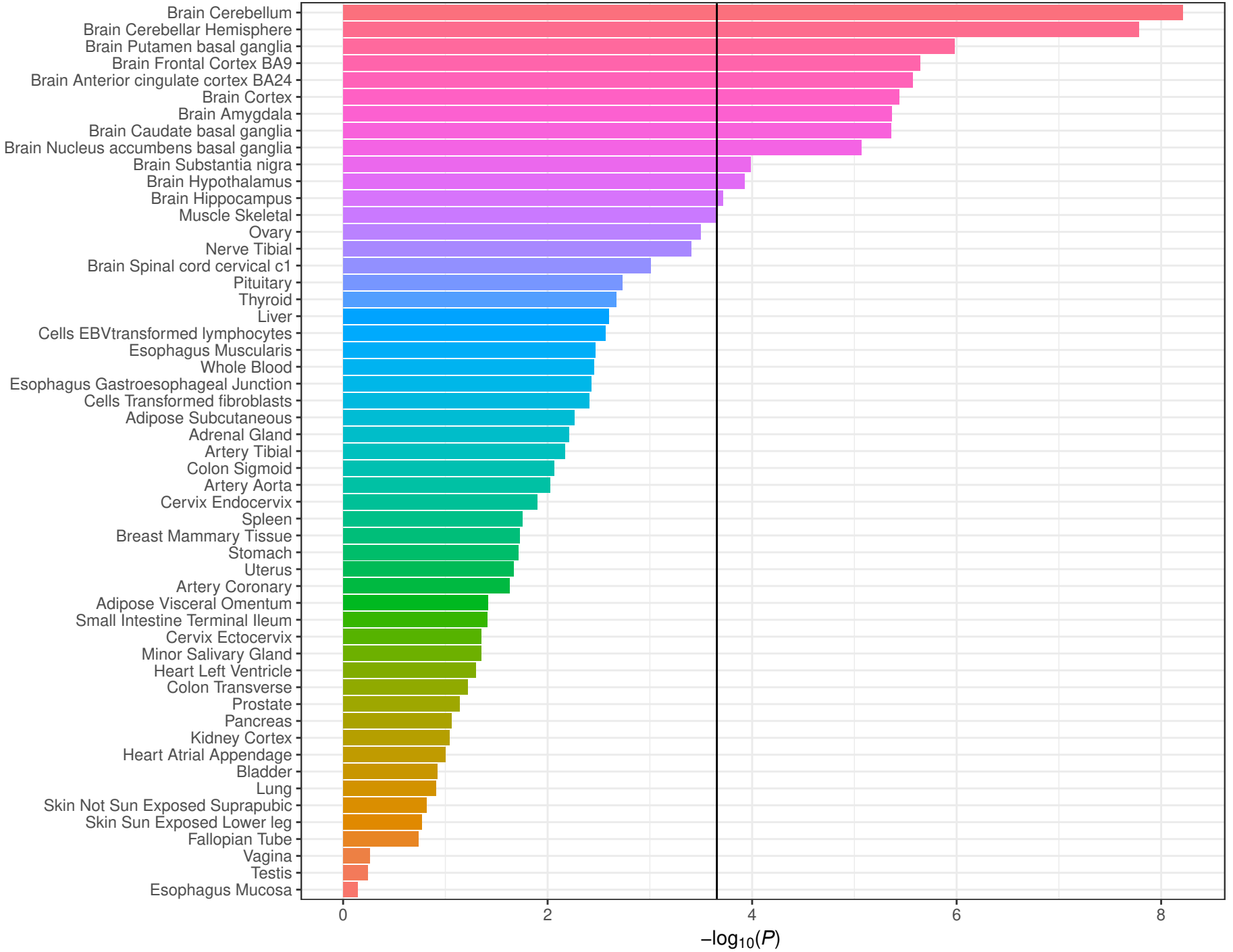
Supplementary Figure 7. Partitioned heritability analysis. The sample size is 16,992 cases and 55,525 controls. The coefficient *P* value (lefthand) tests for enrichment of heritability within each functional element, controlling for all other functional elements to address overlap. The enrichment *P* value (righthand) indicates whether this absolute enrichment is statistically significant. In each analysis, the Bonferroni-corrected threshold (vertical line) is $-\log_{10}(P) > 3.0$. The enrichment (middle) scales the heritability captured by each functional element according to the number of variants in the element (vertical line = 1, that is no enrichment). The error bar is the standard error.


Functional annotations
Conserved LindbladToh
DHS Trynka extend 500
DGF ENCODE extend 500
H3K9ac peaks Trynka
UTR 5 UCSC
UTR 3 UCSC extend 500
TSS Hoffman
Promoter UCSC extend 500
Promoter UCSC
TFBS ENCODE
H3K27ac PGC2
TSS Hoffman extend 500
Coding UCSC extend 500
PromoterFlanking Hoffman extend 500
H3K9ac Trynka extend 500
H3K4me1 peaks Trynka
H3K27ac PGC2 extend 500
Transcri Hoffman extend 500
Intron UCSC extend 500
Intron UCSC
H3K4me1 Trynka
CTCF Hoffman
WeakEnhancer Hoffman
Enhancer Hoffman extend 500
Enhancer Hoffman
Repressed Hoffman extend 500
Conserved LindbladToh extend 500
DHS Trynka
Coding UCSC
UTR 3 UCSC
DHS peaks Trynka
DGF ENCODE
PromoterFlanking Hoffman
SuperEnhancer Hnisz
SuperEnhancer Hnisz extend 500
FetalDHS Trynka extend 500
CTCF Hoffman extend 500
TFBS ENCODE extend 500
H3K4me3 Trynka extend 500
FetalDHS Trynka
Enhancer Andersson
H3K4me3 Trynka
H3K27ac Hnisz extend 500
UTR 5 UCSC extend 500
H3K9ac Trynka
Transcri Hoffman
H3K27ac Hnisz
Repressed Hoffman
H3K4me3 peaks Trynka
WeakEnhancer Hoffman extend 500
H3K4me1 Trynka extend 500
Enhancer Andersson extend 500
Significant
0.0
2.5
5.0
7.5
10.0
Coefficient − log10(p − value)
0
10
20
Pr(h2g)/Pr(SNPs)
Significant
0.0
2.5
5.0
7.5
10.0
Enrichment − log10(p − value)

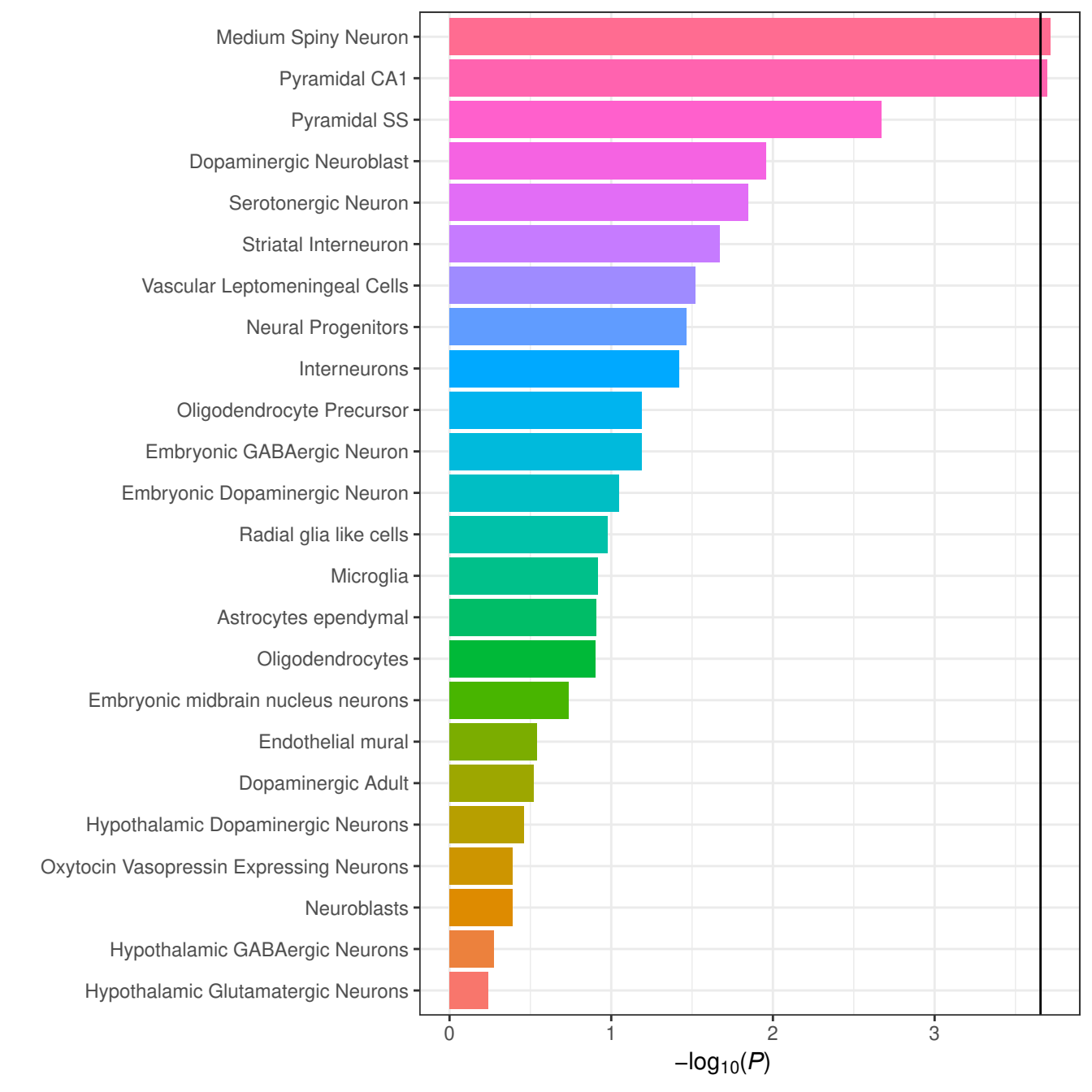
Supplementary Figure 8. Cell type group specific partitioned heritability analysis. The sample size is 16,992 cases and 55,525 controls. The coefficient *P* value (lefthand) tests for enrichment of heritability within each cell group, controlling for all other cell groups to address overlap. The enrichment *P* value (righthand) indicates whether this absolute enrichment is statistically significant. In each analysis, the Bonferroni-corrected threshold (vertical line) is $-\log_{10}(P) > 2.3$ (i.e., 0.05/10 tests). The enrichment (middle) scales the heritability captured by each cell group according to the number of variants in the group (vertical line = 1, that is no enrichment). The error bar is the standard error.


Cell type
CNS
Gastrointestinal
Cardiovascular
Adrenal or pancreas
Immune or hematopoietic
Kidney
Other including adipose
Skeletal muscle
Liver
Connective or bone
Significant
No enrichment
Significant
0.0
0.5
1.0
1.5
2.0
2.5
Coefficient – log10(p – value)
0
1
2
3
Pr(h2g)/Pr(SNPs)
0
2
4
6
Enrichment – log10(p – value)

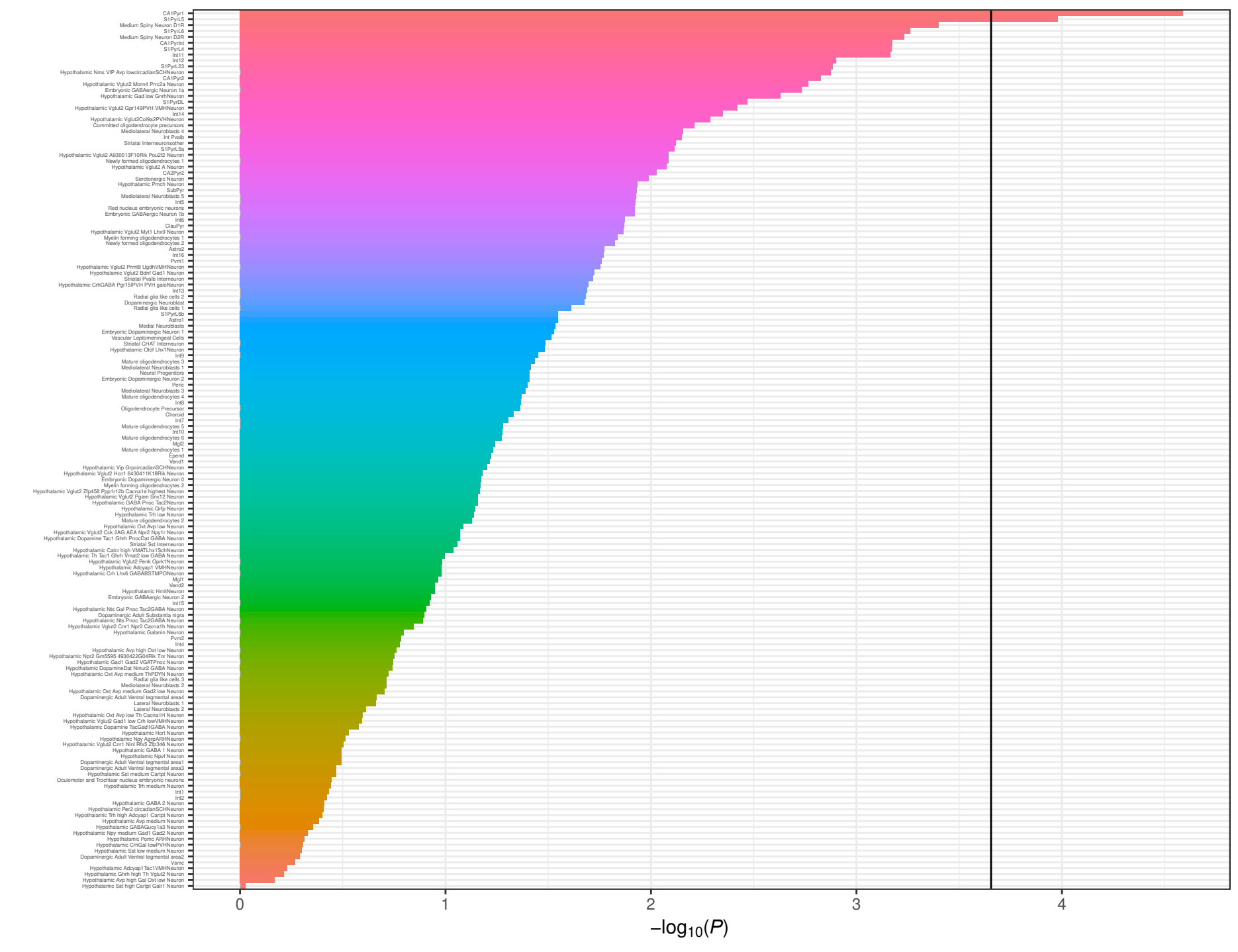
Supplementary Figure 9. *P* value of association between tissue specificity in GTEx and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Brain Cerebellum
Brain Cerebellar Hemisphere
Brain Putamen basal ganglia
Brain Frontal Cortex BA9
Brain Anterior cingulate cortex BA24
Brain Cortex
Brain Amygdala
Brain Caudate basal ganglia
Brain Nucleus accumbens basal ganglia
Brain Substantia nigra
Brain Hypothalamus
Brain Hippocampus
Muscle Skeletal
Ovary
Nerve Tibial
Brain Spinal cord cervical c1
Pituitary
Thyroid
Liver
Cells EBVtransformed lymphocytes
Esophagus Muscularis
Whole Blood
Esophagus Gastroesophageal Junction
Cells Transformed fibroblasts
Adipose Subcutaneous
Adrenal Gland
Artery Tibial
Colon Sigmoid
Artery Aorta
Cervix Endocervix
Spleen
Breast Mammary Tissue
Stomach
Uterus
Artery Coronary
Adipose Visceral Omentum
Small Intestine Terminal Ileum
Cervix Ectocervix
Minor Salivary Gland
Heart Left Ventricle
Colon Transverse
Prostate
Pancreas
Kidney Cortex
Heart Atrial Appendage
Bladder
Lung
Skin Not Sun Exposed Suprapubic
Skin Sun Exposed Lower leg
Fallopian Tube
Vagina
Testis
Esophagus Mucosa
0
2
4
6
8
$-\log_{10}(P)$

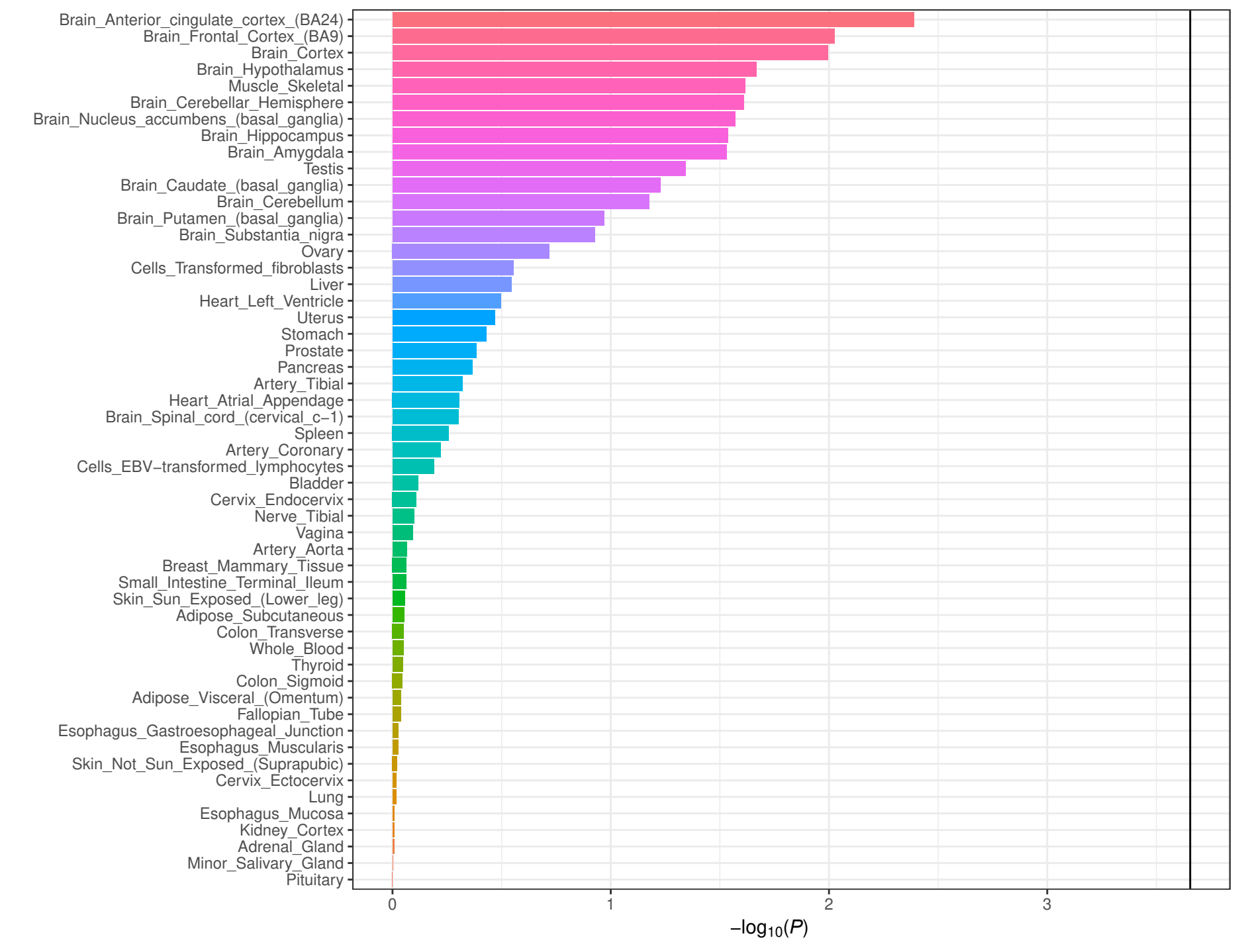
Supplementary Figure 10. *P* value of association between tissue specificity in 24 brain cell types (level 1) and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Medium Spiny Neuron
Pyramidal CA1
Pyramidal SS
Dopaminergic Neuroblast
Serotonergic Neuron
Striatal Interneuron
Vascular Leptomeningeal Cells
Neural Progenitors
Interneurons
Oligodendrocyte Precursor
Embryonic GABAergic Neuron
Embryonic Dopaminergic Neuron
Radial glia like cells
Microglia
Astrocytes ependymal
Oligodendrocytes
Embryonic midbrain nucleus neurons
Endothelial mural
Dopaminergic Adult
Hypothalamic Dopaminergic Neurons
Oxytocin Vasopressin Expressing Neurons
Neuroblasts
Hypothalamic GABAergic Neurons
Hypothalamic Glutamatergic Neurons
0
1
2
3
−log10(P)

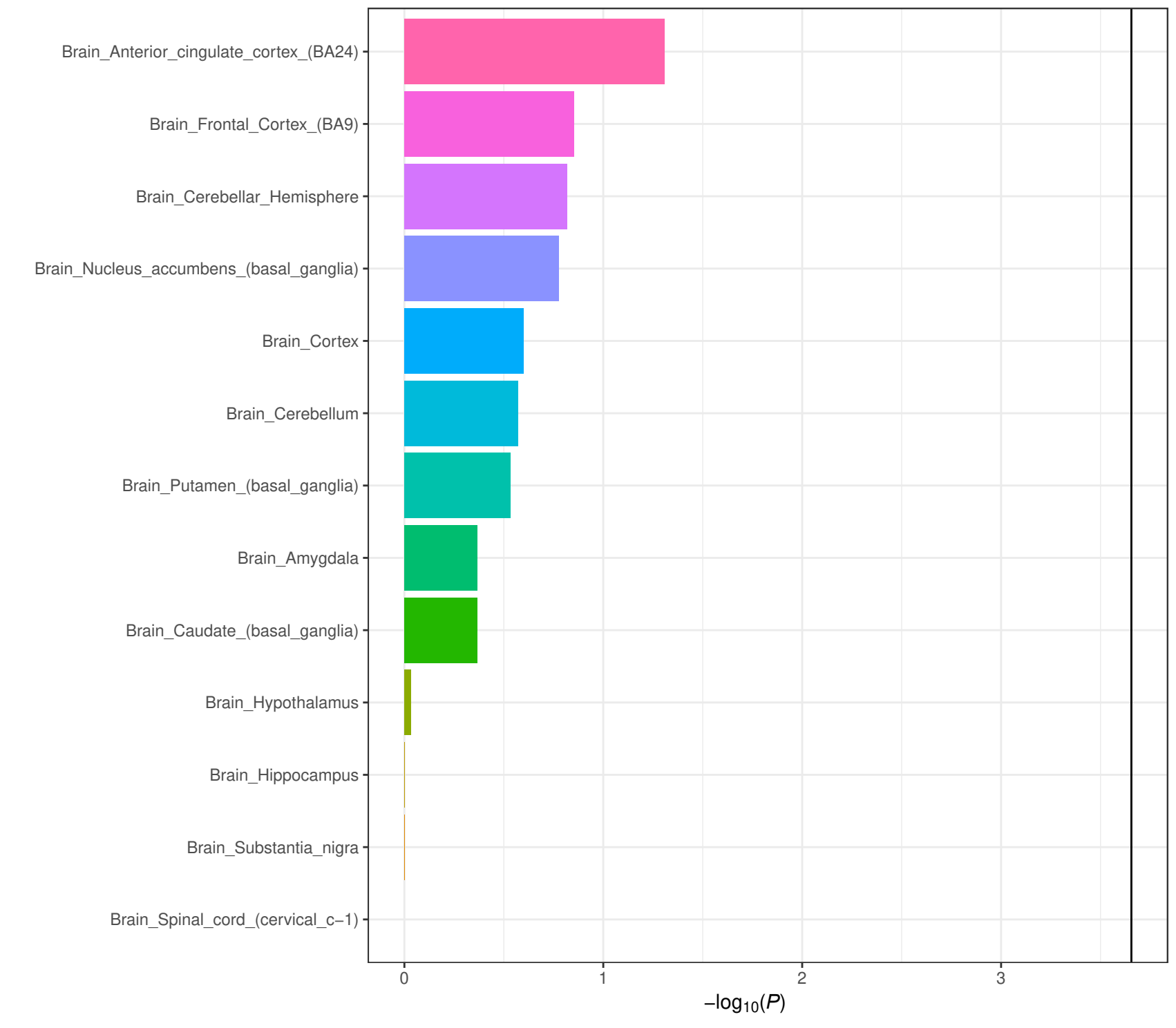
Supplementary Figure 11. *P* value of association between tissue specificity in 149 brain cell types (level 2) and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


CA1Pyr1
S1PyrL5
Medium Spiny Neuron D1R
S1PyrL6
Medium Spiny Neuron D2R
CA1PyrInt
S1PyrL4
Int11
Int12
S1PyrL23
Hypothalamic Nms VIP Avp lowcircadianSCHNeuron
CA1Pyr2
Hypothalamic Vglut2 Morn4 Prrc2a Neuron
Embryonic GABAergic Neuron 1a
Hypothalamic Gad low GnrhNeuron
S1PyrDL
Hypothalamic Vglut2 Gpr149PVH VMHNeuron
Int14
Hypothalamic Vglut2Col9a2PVHNeuron
Committed oligodendrocyte precursors
Mediolateral Neuroblasts 4
Int Pvalb
Striatal Interneuronsother
S1PyrL5a
Hypothalamic Vglut2 A930013F10Rik Pou2f2 Neuron
Newly formed oligodendrocytes 1
Hypothalamic Vglut2 A Neuron
CA2Pyr2
Serotonergic Neuron
Hypothalamic Pmch Neuron
SubPyr
Mediolateral Neuroblasts 5
Int5
Red nucleus embryonic neurons
Embryonic GABAergic Neuron 1b
Int6
ClauPyr
Hypothalamic Vglut2 Myt1 Lhx9 Neuron
Myelin forming oligodendrocytes 1
Newly formed oligodendrocytes 2
Astro2
Int16
Pvm1
Hypothalamic Vglut2 Prmt8 UgdhVMHNeuron
Hypothalamic Vglut2 Bdnf Gad1 Neuron
Striatal Pvalb Interneuron
Hypothalamic CrhGABA Ppr15IPVH PVH galoNeuron
Int13
Radial glia like cells 2
Dopaminergic Neuroblast
Radial glia like cells 1
S1PyrL6b
Astro1
Medial Neuroblasts
Embryonic Dopaminergic Neuron 1
Vascular Leptomeningeal Cells
Striatal CHAT Interneuron
Hypothalamic Otof Lhx1Neuron
Int9
Mature oligodendrocytes 3
Mediolateral Neuroblasts 1
Neural Progenitors
Embryonic Dopaminergic Neuron 2
Peric
Mediolateral Neuroblasts 3
Mature oligodendrocytes 4
Int8
Oligodendrocyte Precursor
Choroid
Int7
Mature oligodendrocytes 5
Int10
Mature oligodendrocytes 6
Mgl2
Mature oligodendrocytes 1
Epend
Vend1
Hypothalamic Vip GrpcircadianSCHNeuron
Hypothalamic Vglut2 Hcn1 6430411K18Rik Neuron
Embryonic Dopaminergic Neuron 0
Myelin forming oligodendrocytes 2
Hypothalamic Vglut2 Zfp458 Ppp1r12b Cacna1e highest Neuron
Hypothalamic Vglut2 Pgam Snx12 Neuron
Hypothalamic GABA Pnoc Tac2Neuron
Hypothalamic Qrfp Neuron
Hypothalamic Trh low Neuron
Mature oligodendrocytes 2
Hypothalamic Oxt Avp low Neuron
Hypothalamic Vglut2 Cck 2AG AEA Npr2 Npy1r Neuron
Hypothalamic Dopamine Tac1 Ghrh PnocDat GABA Neuron
Striatal Sst Interneuron
Hypothalamic Calcr high VMATLhx1SchNeuron
Hypothalamic Th Tac1 Ghrh Vmat2 low GABA Neuron
Hypothalamic Vglut2 Penk Oprk1Neuron
Hypothalamic Adcyap1 VMHNeuron
Hypothalamic Crh Lhx6 GABABSTMPONeuron
Mgl1
Vend2
Hypothalamic HmitNeuron
Embryonic GABAergic Neuron 2
Int15
Hypothalamic Nts Gal Pnoc Tac2GABA Neuron
Dopaminergic Adult Substantia nigra
Hypothalamic Nts Pnoc Tac2GABA Neuron
Hypothalamic Vglut2 Cnr1 Npr2 Cacna1h Neuron
Hypothalamic Galanin Neuron
Pvm2
Int4
Hypothalamic Avp high Oxt low Neuron
Hypothalamic Npr2 Gm5595 4930422G04Rik Tnr Neuron
Hypothalamic Gad1 Gad2 VGATPnoc Neuron
Hypothalamic DopamineDat Nmur2 GABA Neuron
Hypothalamic Oxt Avp medium ThPDYN Neuron
Radial glia like cells 3
Mediolateral Neuroblasts 2
Hypothalamic Oxt Avp medium Gad2 low Neuron
Dopaminergic Adult Ventral tegmental area4
Lateral Neuroblasts 1
Lateral Neuroblasts 2
Hypothalamic Oxt Avp low Th Cacna1H Neuron
Hypothalamic Vglut2 Gad1 low Crh lowVMHNeuron
Hypothalamic Dopamine TacGad1GABA Neuron
Hypothalamic Hcrt Neuron
Hypothalamic Npy AgrpARHNeuron
Hypothalamic Vglut2 Cnr1 Nrxn Rfx5 Zfp346 Neuron
Hypothalamic GABA 1 Neuron
Hypothalamic Npvf Neuron
Dopaminergic Adult Ventral tegmental area1
Dopaminergic Adult Ventral tegmental area3
Hypothalamic Sst medium Cartpt Neuron
Oculomotor and Trochlear nucleus embryonic neurons
Hypothalamic Trh medium Neuron
Int1
Int2
Hypothalamic GABA 2 Neuron
Hypothalamic Per2 circadianSCHNeuron
Hypothalamic Trh high Adcyap1 Cartpt Neuron
Hypothalamic Avp medium Neuron
Hypothalamic GABAGucy1a3 Neuron
Hypothalamic Npy medium Gad1 Gad2 Neuron
Hypothalamic Pomc ARHNeuron
Hypothalamic CrhGal lowPVHNeuron
Hypothalamic Sst low medium Neuron
Dopaminergic Adult Ventral tegmental area2
Vsmc
Hypothalamic Adcyap1Tac1VMHNeuron
Hypothalamic Ghrh high Th Vglut2 Neuron
Hypothalamic Avp high Gal Oxt low Neuron
Hypothalamic Sst high Cartpt Galr1 Neuron
0
1
2
3
4
$-\log_{10}(P)$

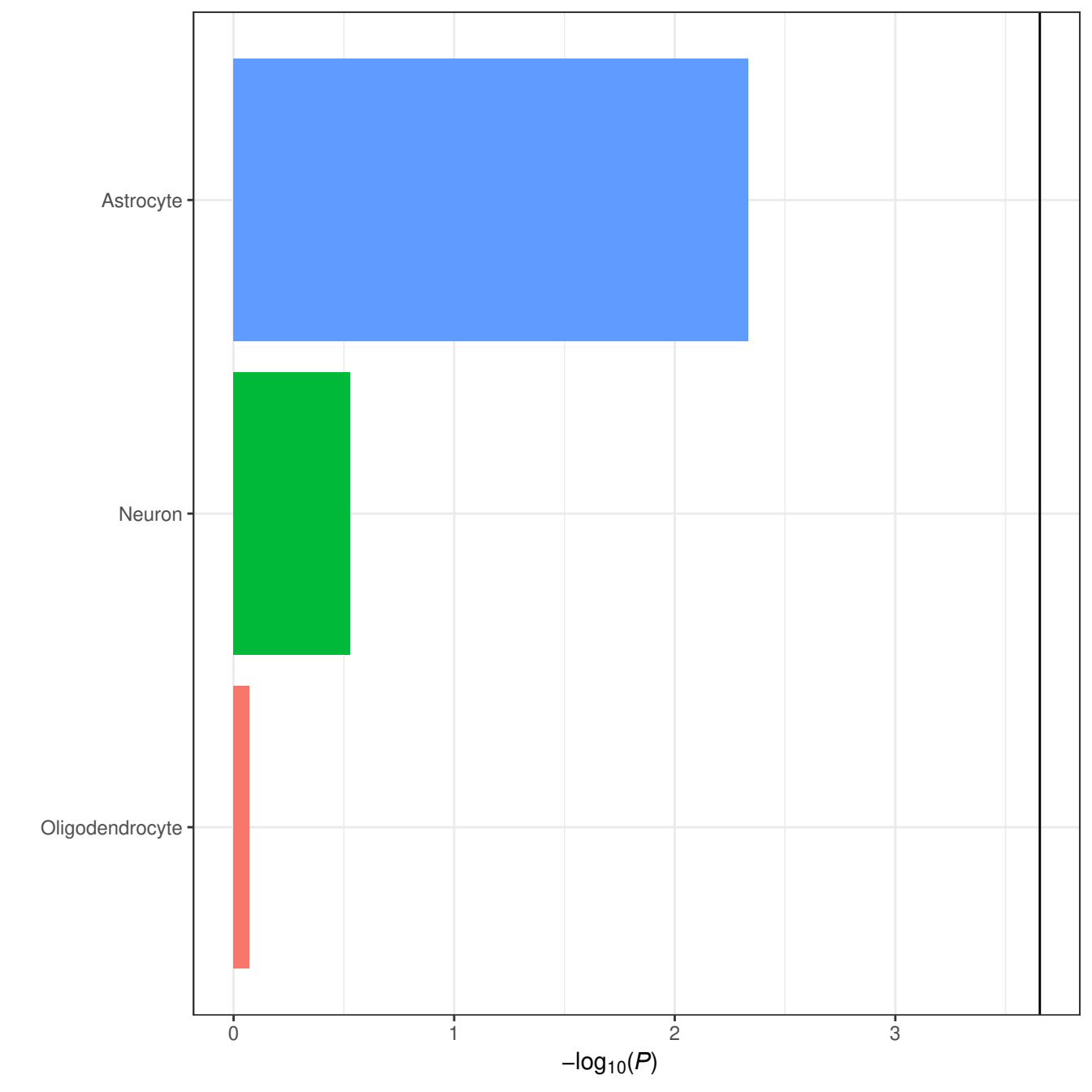
Supplementary Figure 12. *P* value of enrichment of heritability of anorexia nervosa in each tissue in GTEx using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Brain_Anterior_cingulate_cortex_(BA24)
Brain_Frontal_Cortex_(BA9)
Brain_Cortex
Brain_Hypothalamus
Muscle_Skeletal
Brain_Cerebellar_Hemisphere
Brain_Nucleus_accumbens_(basal_ganglia)
Brain_Hippocampus
Brain_Amygdala
Testis
Brain_Caudate_(basal_ganglia)
Brain_Cerebellum
Brain_Putamen_(basal_ganglia)
Brain_Substantia_nigra
Ovary
Cells_Transformed_fibroblasts
Liver
Heart_Left_Ventricle
Uterus
Stomach
Prostate
Pancreas
Artery_Tibial
Heart_Atrial_Appendage
Brain_Spinal_cord_(cervical_c−1)
Spleen
Artery_Coronary
Cells_EBV−transformed_lymphocytes
Bladder
Cervix_Endocervix
Nerve_Tibial
Vagina
Artery_Aorta
Breast_Mammary_Tissue
Small_Intestine_Terminal_Ileum
Skin_Sun_Exposed_(Lower_leg)
Adipose_Subcutaneous
Colon_Transverse
Whole_Blood
Thyroid
Colon_Sigmoid
Adipose_Visceral_(Omentum)
Fallopian_Tube
Esophagus_Gastroesophageal_Junction
Esophagus_Muscularis
Skin_Not_Sun_Exposed_(Suprapubic)
Cervix_Ectocervix
Lung
Esophagus_Mucosa
Kidney_Cortex
Adrenal_Gland
Minor_Salivary_Gland
Pituitary
0
1
2
3
−log10(P)

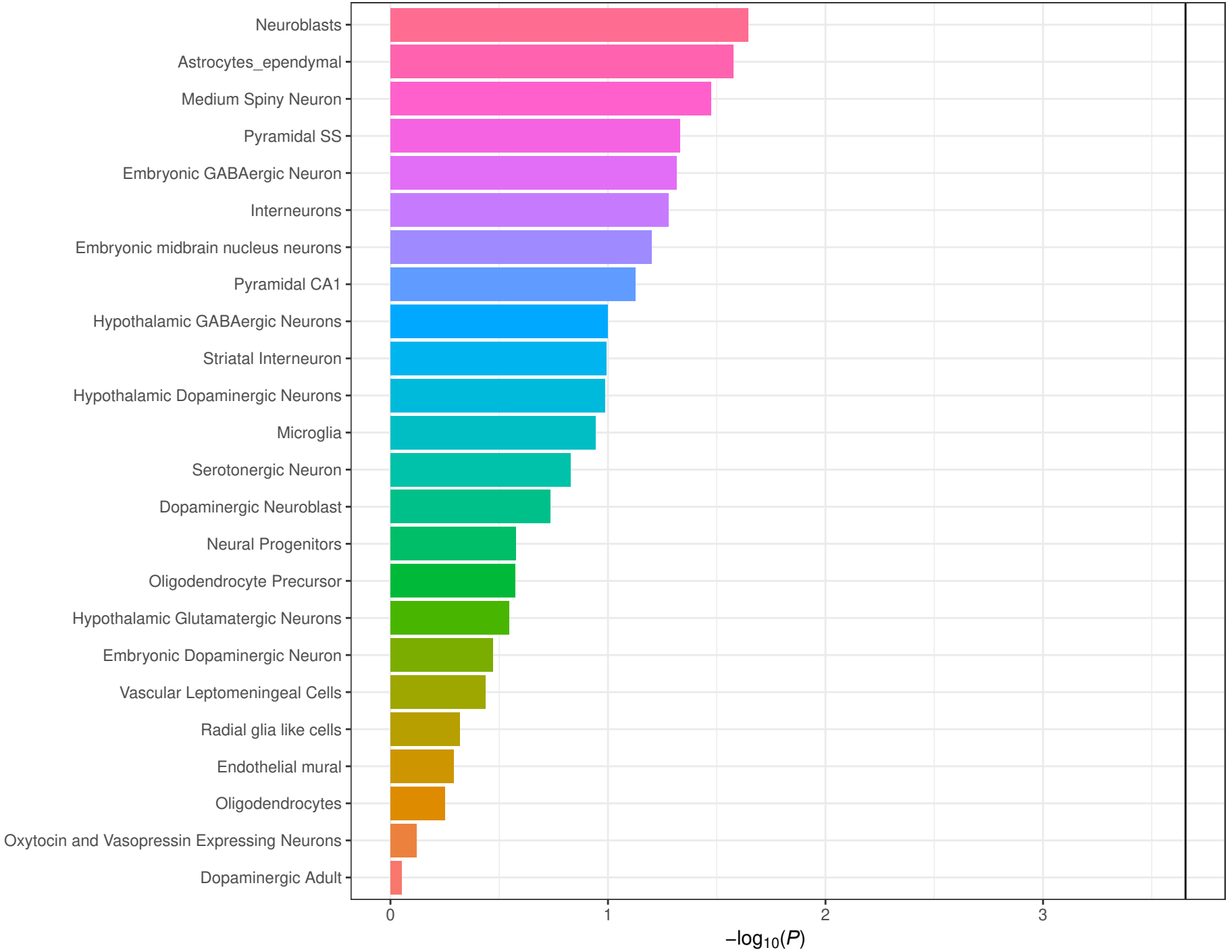
Supplementary Figure 13. *P* value of enrichment of heritability of anorexia nervosa in brain tissues in GTEx using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Brain_Anterior_cingulate_cortex_(BA24)
Brain_Frontal_Cortex_(BA9)
Brain_Cerebellar_Hemisphere
Brain_Nucleus_accumbens_(basal_ganglia)
Brain_Cortex
Brain_Cerebellum
Brain_Putamen_(basal_ganglia)
Brain_Amygdala
Brain_Caudate_(basal_ganglia)
Brain_Hypothalamus
Brain_Hippocampus
Brain_Substantia_nigra
Brain_Spinal_cord_(cervical_c−1)
0
1
2
3
−log10(P)

Supplementary Figure 14. *P* value of enrichment of heritability of anorexia nervosa in cell types in Cahoy database using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Astrocyte
Neuron
Oligodendrocyte
0
1
2
3
$-\log_{10}(P)$

Supplementary Figure 15. *P* value of enrichment of heritability of anorexia nervosa in 24 brain cell types from the single-cell RNA-sequencing database (broad categories) using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Neuroblasts
Astrocytes_ependymal
Medium Spiny Neuron
Pyramidal SS
Embryonic GABAergic Neuron
Interneurons
Embryonic midbrain nucleus neurons
Pyramidal CA1
Hypothalamic GABAergic Neurons
Striatal Interneuron
Hypothalamic Dopaminergic Neurons
Microglia
Serotonergic Neuron
Dopaminergic Neuroblast
Neural Progenitors
Oligodendrocyte Precursor
Hypothalamic Glutamatergic Neurons
Embryonic Dopaminergic Neuron
Vascular Leptomeningeal Cells
Radial glia like cells
Endothelial mural
Oligodendrocytes
Oxytocin and Vasopressin Expressing Neurons
Dopaminergic Adult
0
1
2
3
−log10(P)

Supplementary Figure 16. Polygenic risk score (PRS) leave-one-out analysis: results for each cohort. PRS was constructed with the leave-one-out method from a GWAS with all datasets excluding the target dataset. Then, PRS was used to predict change in residualized phenotype score for anorexia nervosa (AN) risk in the target dataset (shown as the center value and an error bar which represents the 95% confidence interval of this estimate). The decile with the lowest PRS (i.e., subjects whose AN PRS is in the bottom 10%) serves as the referent. A higher residualized phenotype score indicates a higher risk of AN.

-

Dataset no	PGC abbreviation	*Total N*
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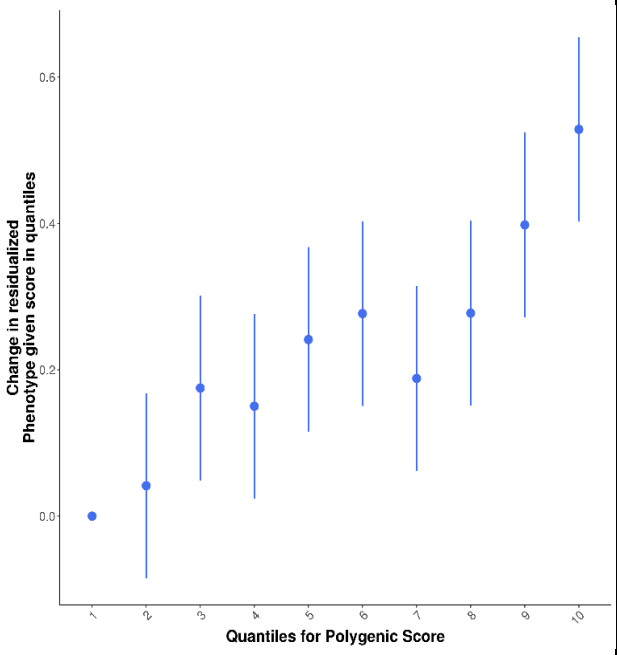

Dataset no	PGC abbreviation	*Total N*
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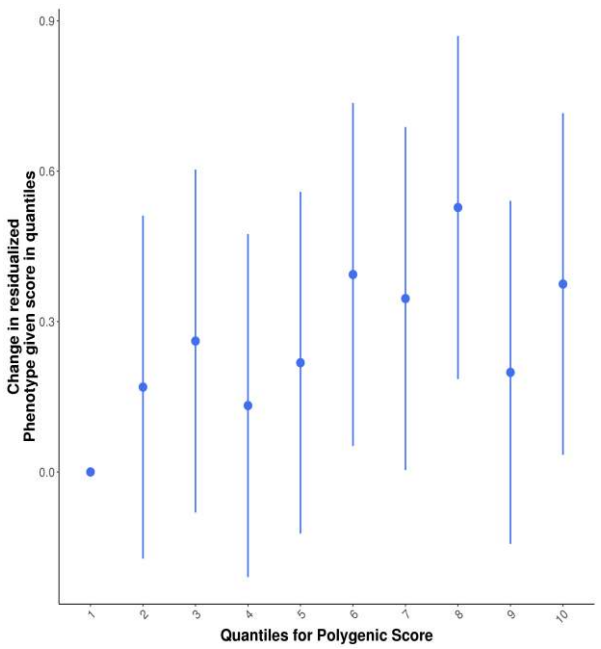

Dataset no	PGC abbreviation	*Total N*
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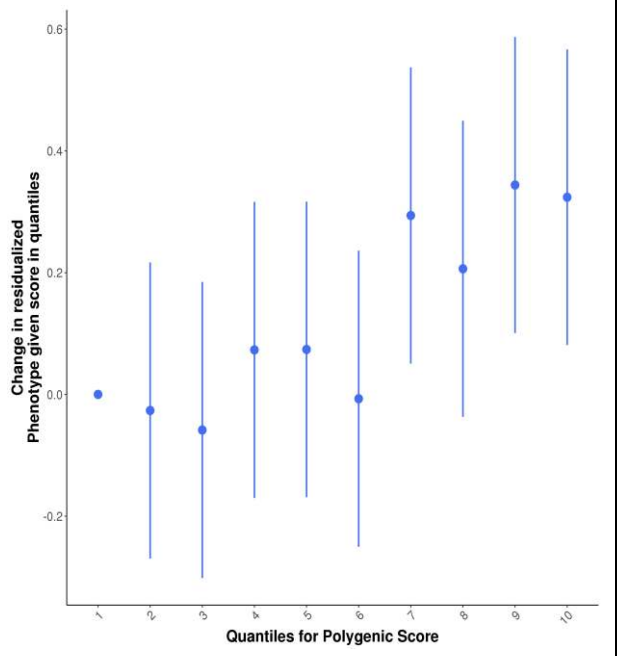

Dataset no	PGC abbreviation	*Total N*
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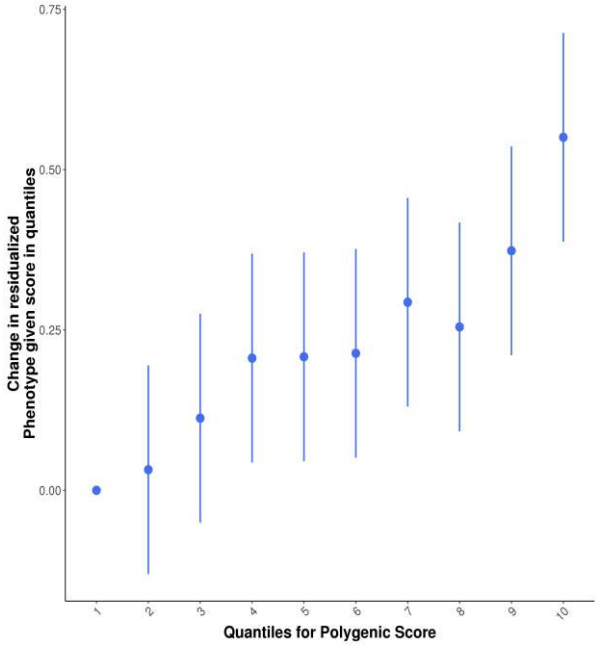

Dataset no	PGC abbreviation	*Total N*
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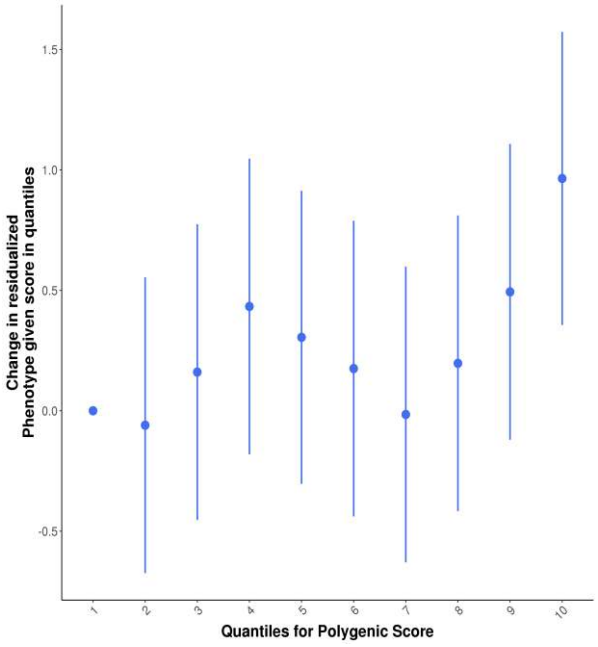

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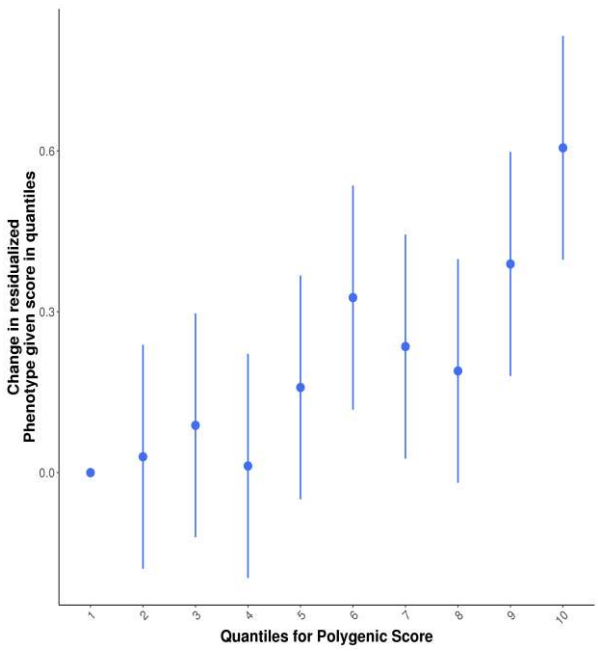
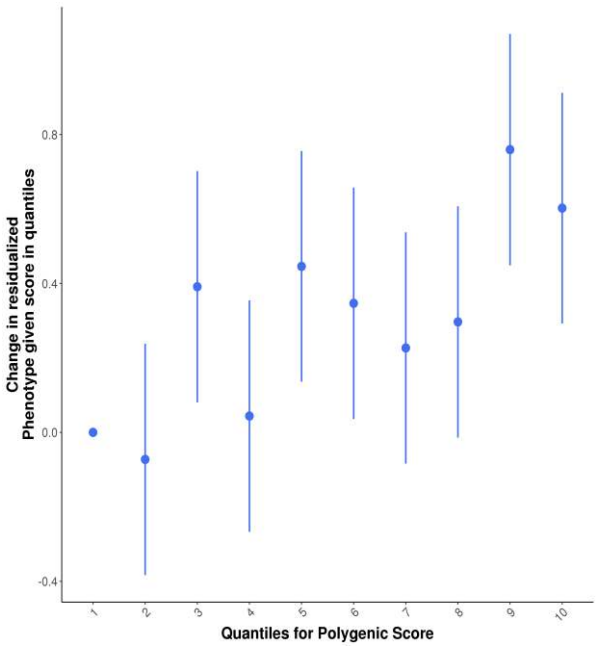


Dataset no	PGC abbreviation	*Total N*
7	poco	843



Dataset no	PGC abbreviation	*Total N*
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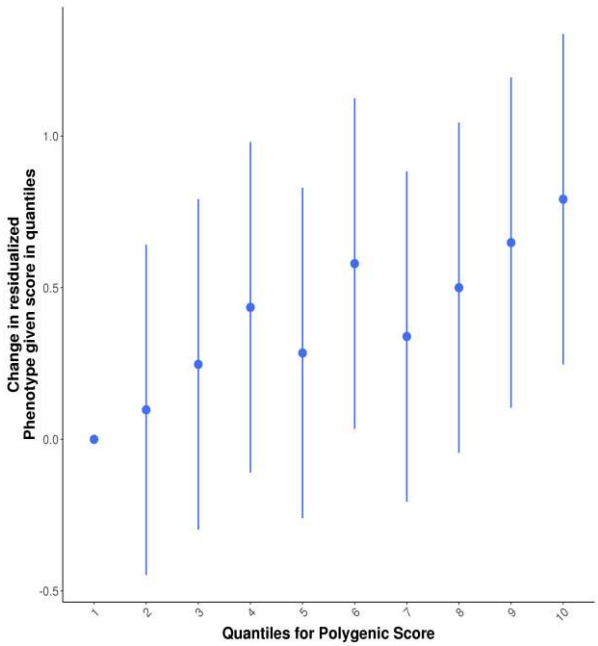

Dataset no	PGC abbreviation	*Total N*
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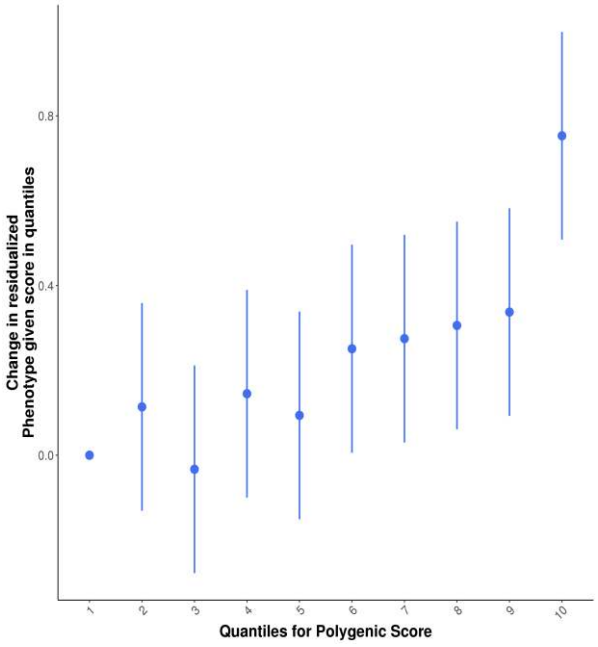

Dataset no	PGC abbreviation	*Total N*
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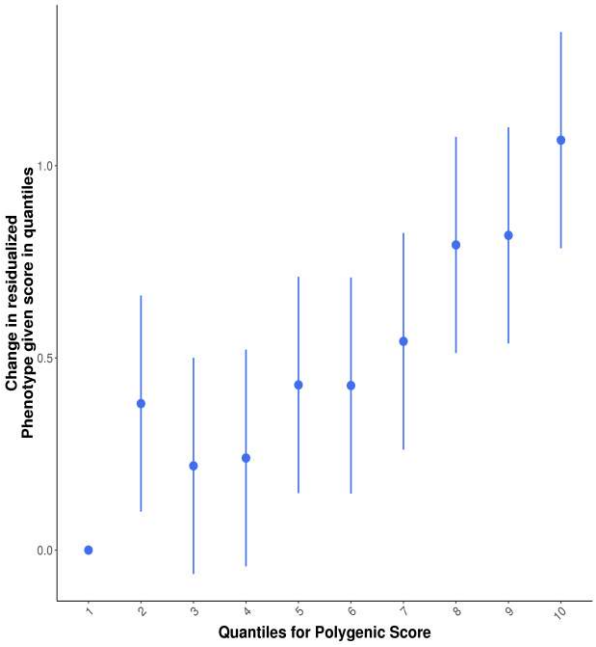

Dataset no	PGC abbreviation	*Total N*
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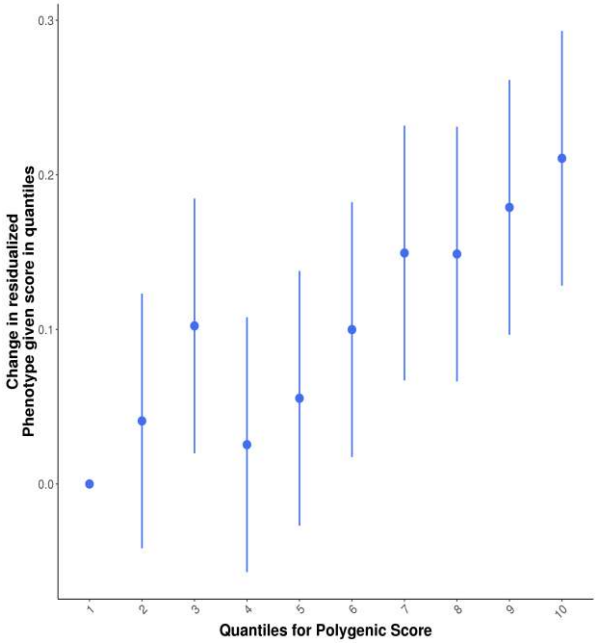

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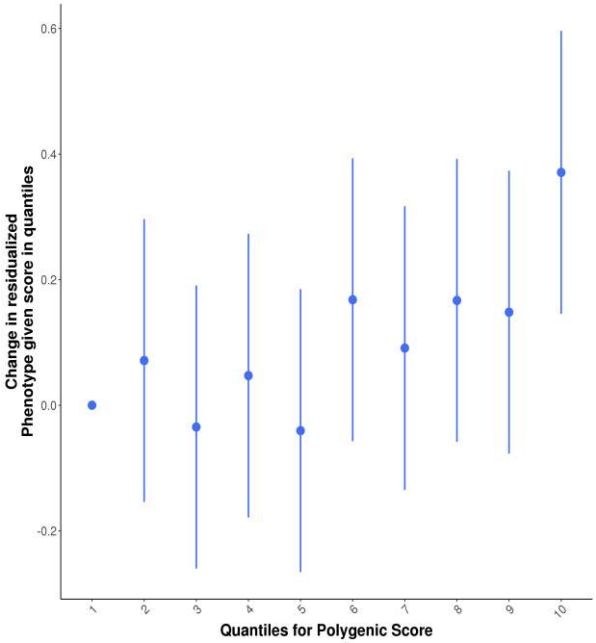

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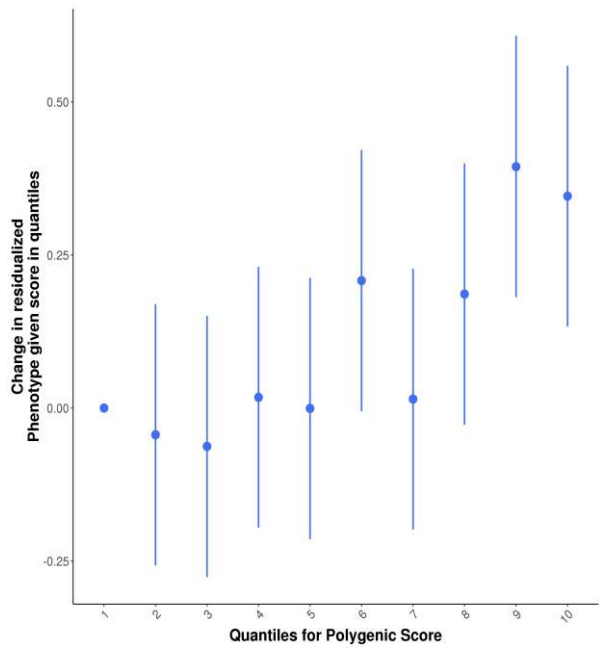

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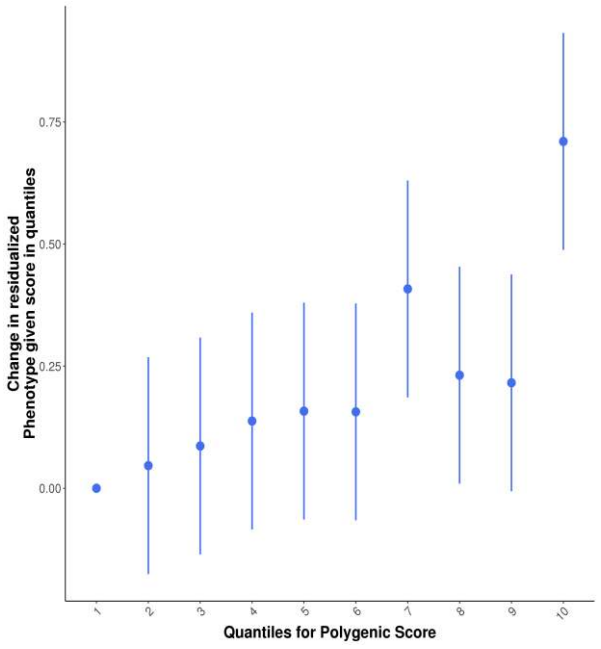

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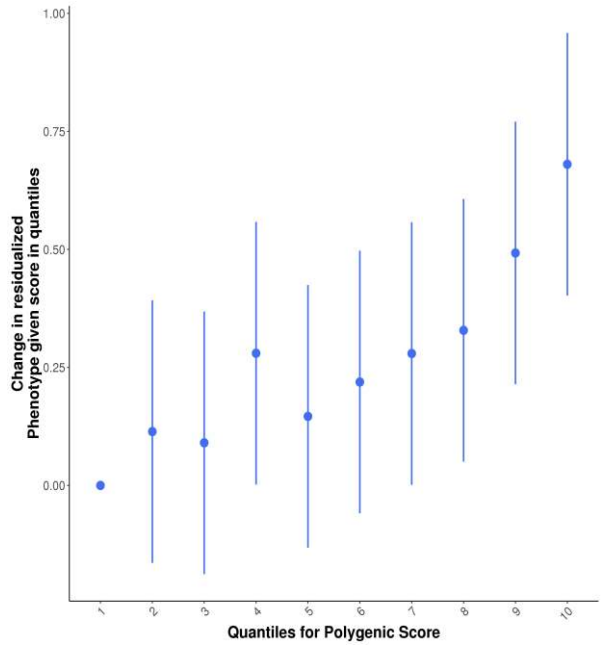

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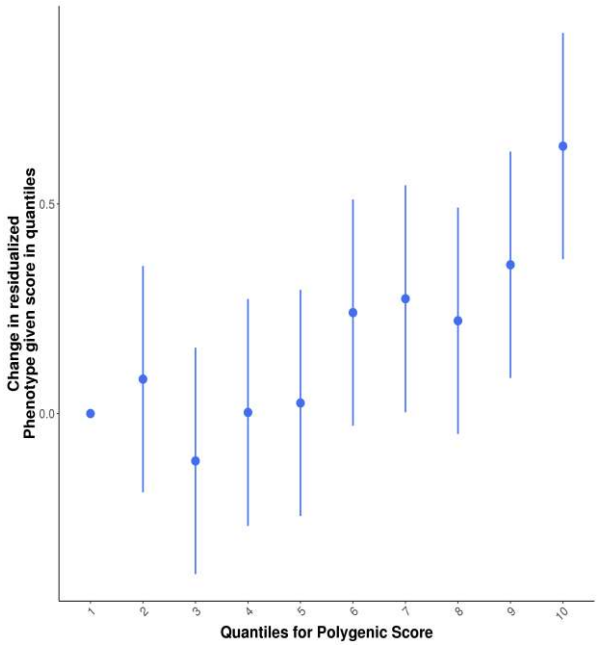

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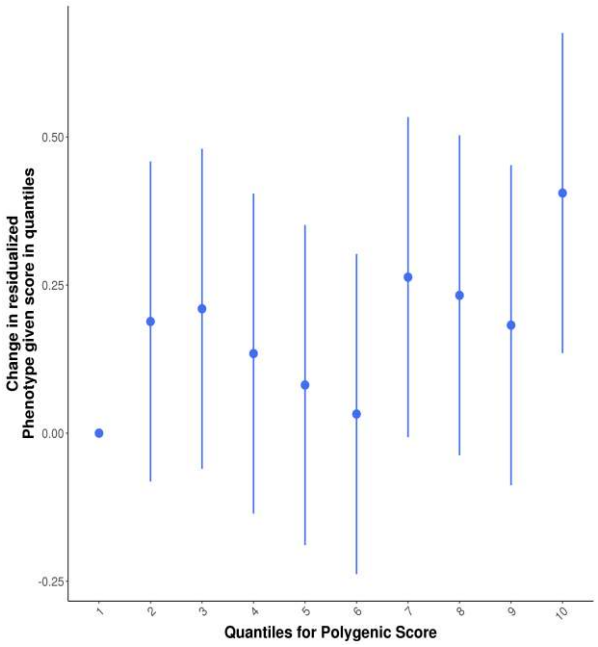

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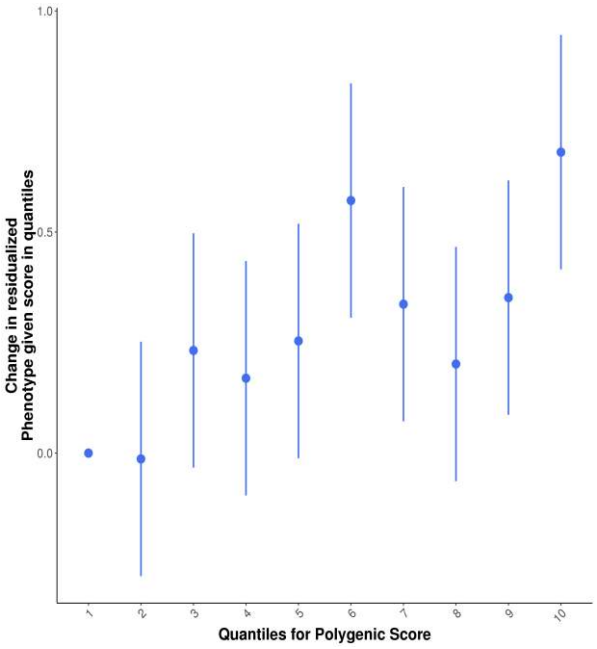

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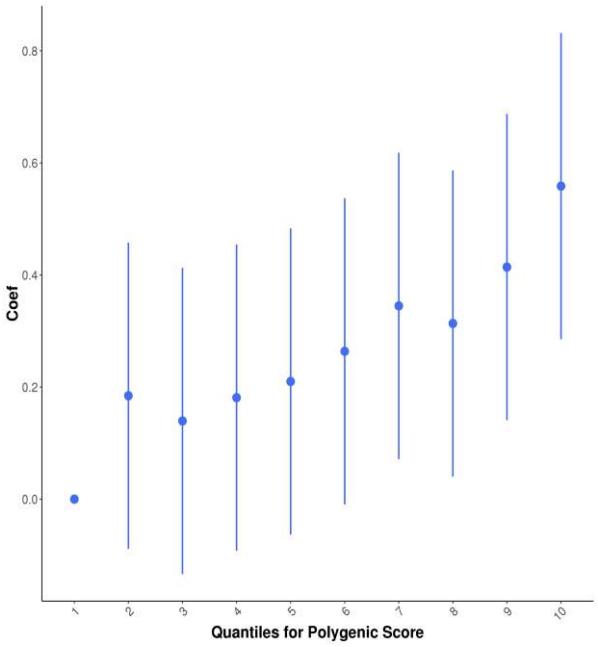

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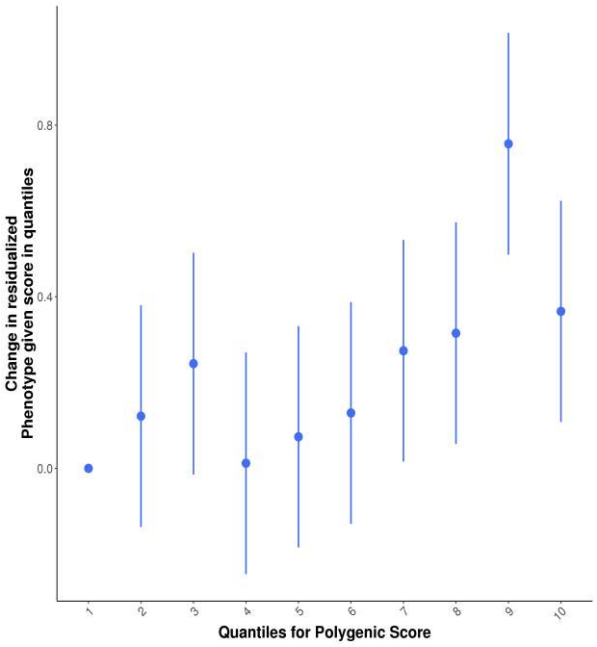

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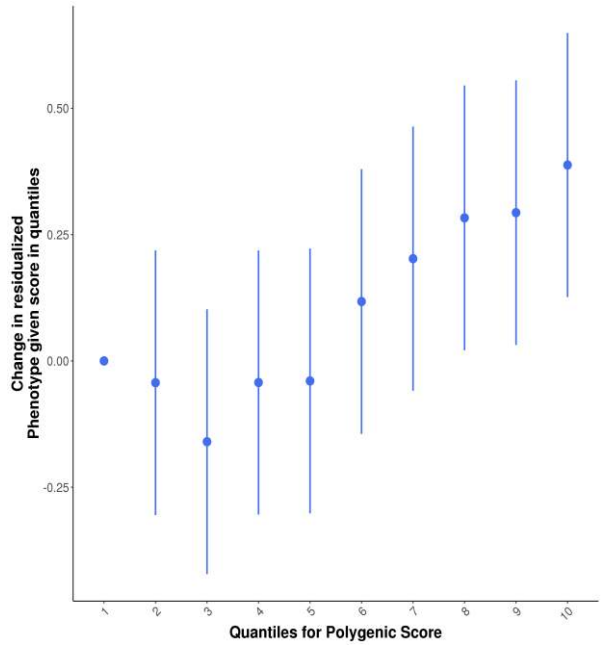

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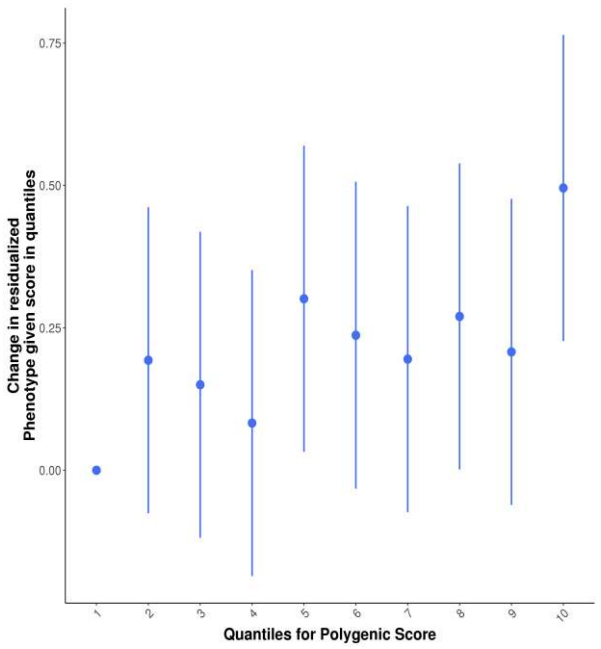

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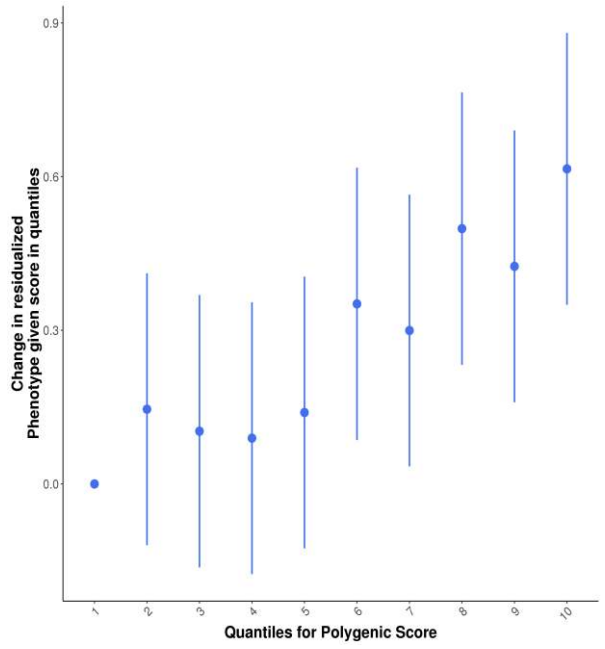

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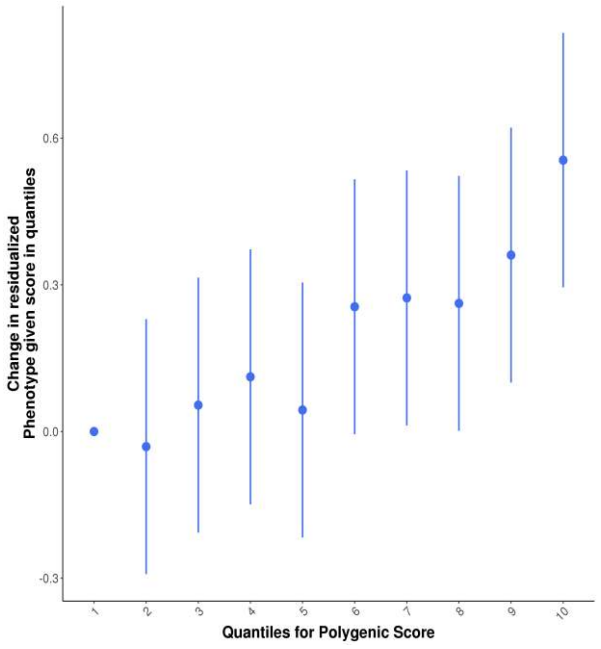

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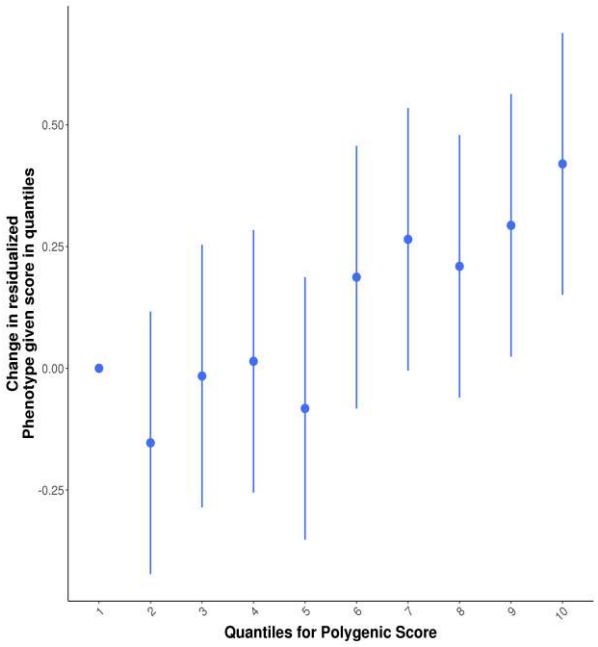

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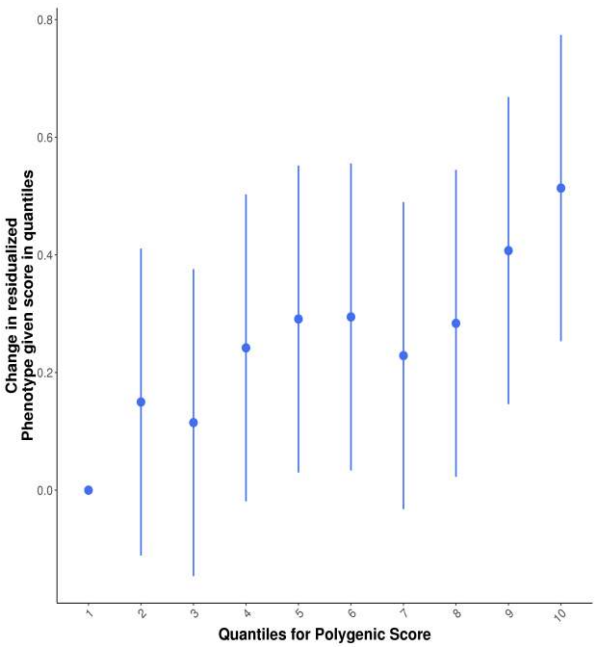

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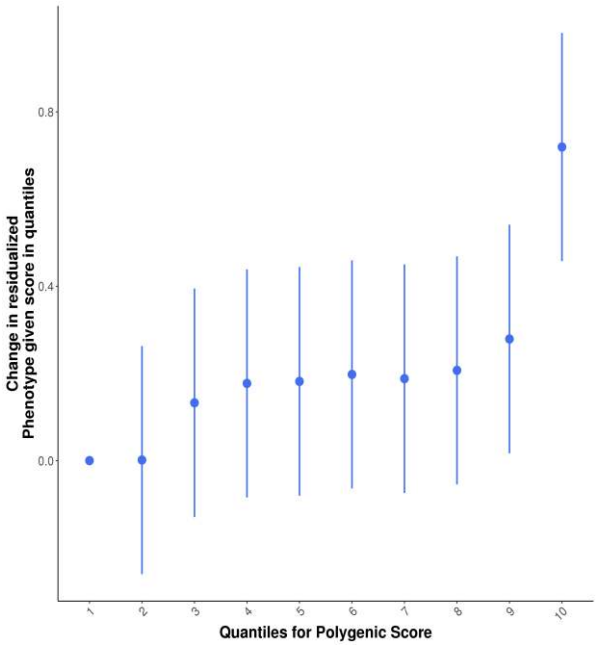

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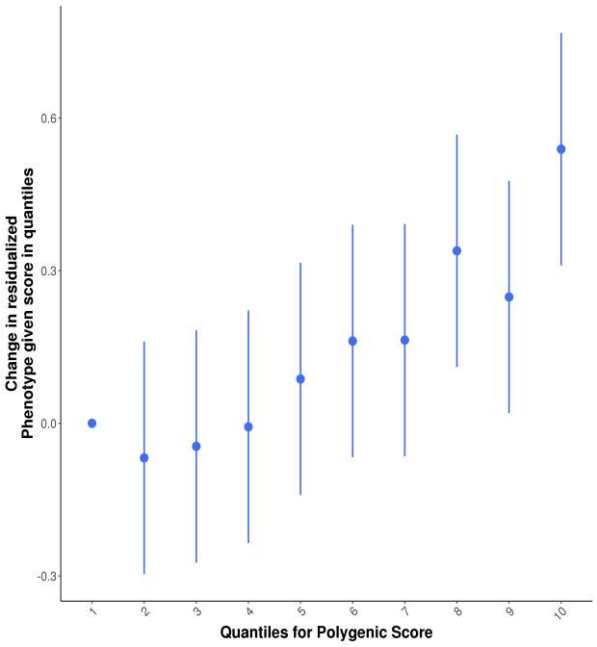

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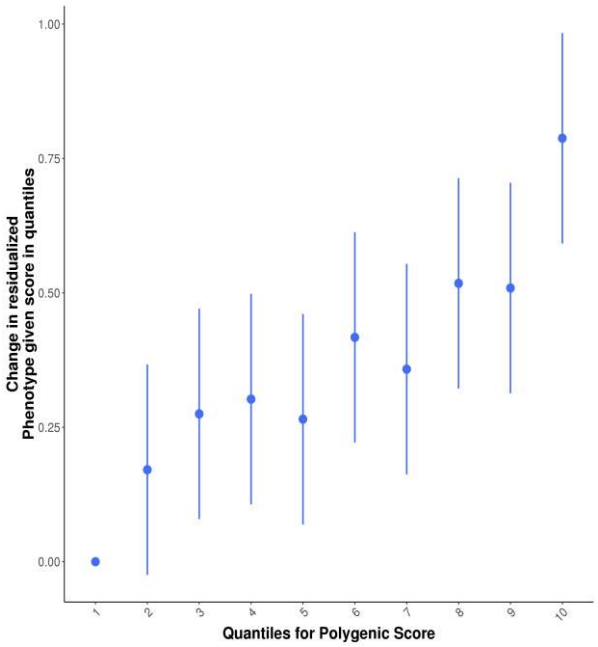

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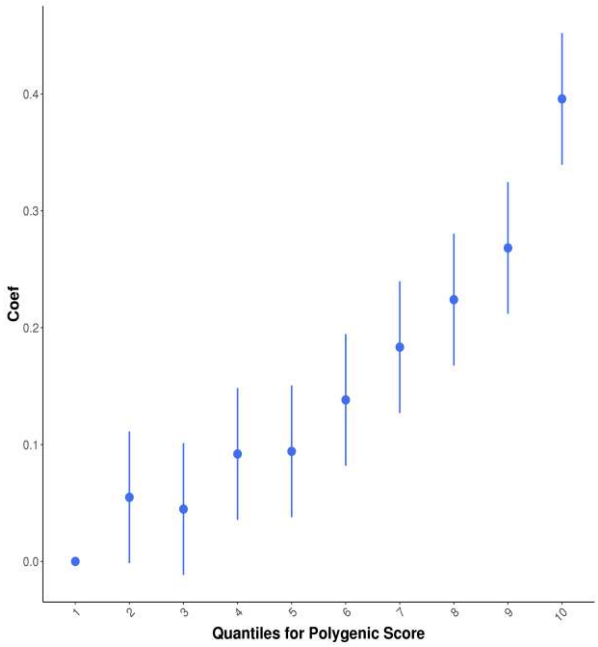

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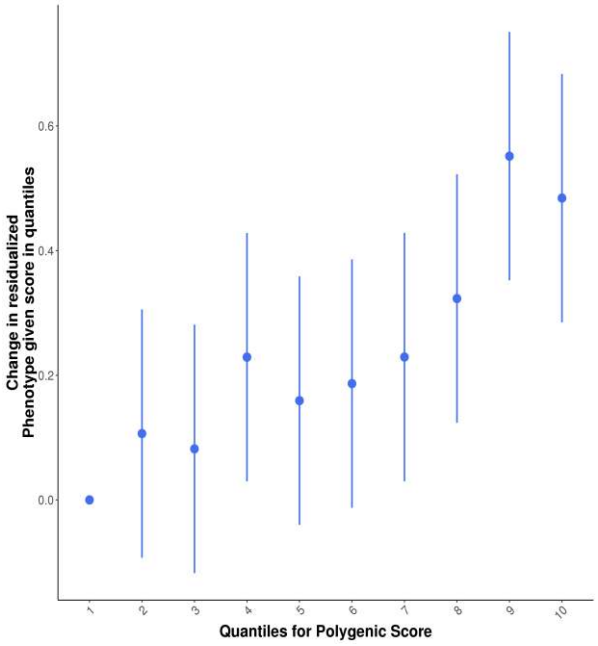

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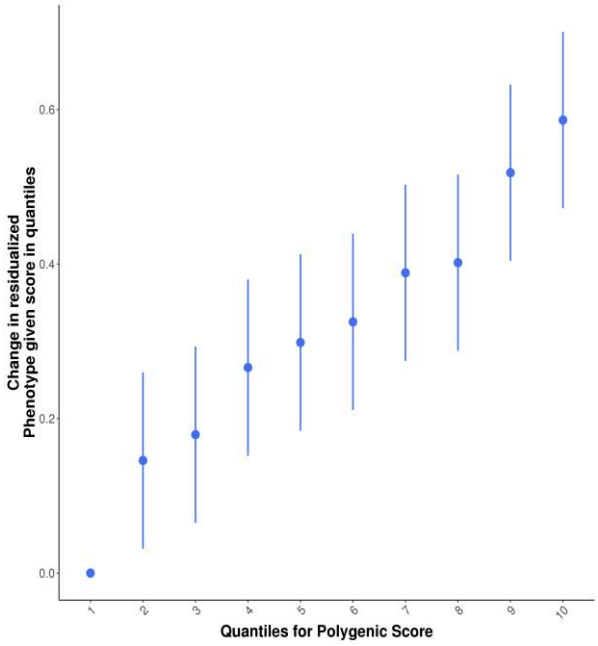

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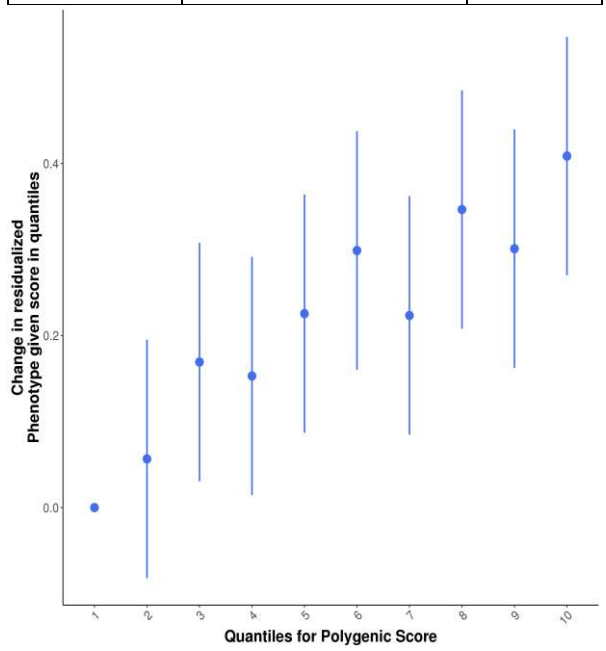

Watson, H. J., Yilmaz, Z., Thornton, L. M., Hübel, C., Coleman, J. R. I., Gaspar, H. A., . . . Bulik, C. M. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nature Genetics.

Supplementary Information

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Anorexia Nervosa Genetics Initiative

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Additional Methods

Samples and study design

Psychiatric Genomics Consortium (PGC) abbreviations for the 33 datasets meta-analyzed in this study are shown in **Supplementary Table 1**. **Supplementary Table 1** shows cohort case and control numbers, SNP numbers, and lambda at ascertainment [pre-quality control (QC)] and post-QC, **Supplementary Table 2** describes ascertainment including how cases were evaluated in the primary studies, and case and control sources and inclusion and exclusion criteria. **Supplementary Table 3** gives the genotyping platforms used. Details of the contributing studies and cohorts are provided below. The study is a secondary analysis of data collected from the studies described and did not involve direct recruitment and contact with participants or collection of identifiers linked to participants. The IRB of the University of North Carolina at Chapel Hill gave approval for this project (reference number 15-3307).

Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) Freeze 1

Full details of these data are given in the Freeze 1 paper of the PGC-ED (http://www.med.unc.edu/pgc) authored by Duncan et al.[1]

To summarize, Duncan et al. datasets included the Children's Hospital of Philadelphia/Price Foundation Collaborative Group (CHOP/PFCG) case-control data from the anorexia nervosa GWAS of Wang et al.[6], case-only data from the Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC-3; https://www.wtccc.org.uk) included in Boraska et al.[2], and since many of the controls used in Boraska et al. were not permitted to be re-used, control cohorts were sourced as described in Duncan et al.[1]. Control cohorts from a similar geographic location and genotyped on an Illumina platform were preferentially sought. Briefly, eethical approval for each site in GCAN/WTCCC3 was obtained from the local ethics committee. All participants provided written informed consent in accordance with the Declaration of Helsinki[1,2]. Ethical approval for each site in the PFCG was obtained separately from their own institution's human subjects committee. Informed consent was obtained from all study participants[3-5]. Controls for the PFCG cases were obtained from CHOP. The Research Ethics Board of CHOP approved the study, and written informed consent was obtained from all subjects or their parents[6]. All cases and controls in PGC-ED Freeze 1 were also included in the current analysis[1]. As per Freeze 1, the Italy-North cases from Boraska et al. were not included due to a lack of ancestrally-matched controls accessible for our study. Pre-QC datasets with < 100 cases were identified (Germany, Greece, Italy-South, Norway) and merged with other data to form larger datasets. The combinations were an excellent ancestral match according to principal components analysis (PCA). Italy-South and Greece were merged to form the cohort *itgr*. Czech and Poland data were merged and formed the cohort *poco*, and Norway, Germany, and Sweden data were merged and formed the cohort *gns2* (see the section below called "Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3" for information about Poland and Sweden data). These samples are included in *chop*, *fin1*, *fre1*, *itgr, gns2, net1, poco, spa1, ukd1, and usa1* (see the section below for other data in *poco* and *gns2*).

Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC-3)

Additional GCAN/WTCCC-3 cohorts that were not part of Duncan et al. due to a lack of controls (Poland) or small $N < 100$ of cases (Sweden) were included in our analysis as we were able to identify ancestrally matched cases and/or controls. We sourced Poland controls from the BoMa/MooDS-PGC study (Bonn/Mannheim Bipolar study; Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia study)[7,8]. These controls were also used in the PGC bipolar disorder GWAS[9]. These controls were produced by the International Agency for Research on Cancer (IARC; https://www.iarc.fr) and the Centre National de Génotypage (CNG; https://www.cng.fr) GWAS Initiative for a study of upper aerodigestive tract cancers[10] and genotyped on the Illumina HH317k. They were drawn from a hospital-based case-control sample recruited by the Nofer Institute of Occupational Medicine in Lodz and a population-based case-control sample recruited by the Cancer-Center and Institute of Oncology in Warsaw. Controls were not screened for neuropsychiatric phenotypes. These combinations above proved an excellent ancestral match according to PCA. These samples are included in *poco* and *gns2*.

Anorexia Nervosa Genetics Initiative (ANGI)

ANGI (https://www.med.unc.edu/psych/eatingdisorders/our-research/angi) is a multi-country effort to identify the genetic causes of anorexia nervosa and involves international research teams in the US, Sweden, Denmark, and Australia with assistance from New Zealand. Details on recruitment strategies, case definitions, and methods for ANGI have been reported previously and are outlined briefly below[11,12]. All ANGI controls were screened for eating disorder phenotypes and some for additional psychiatric phenotypes.

Australia and New Zealand (ANGI-ANZ).

Cases from ANGI-ANZ were recruited the following way. Individuals who resided in Australia (age ≥ 13 years) or New Zealand (age ≥ 14 years) self-identified or were referred to the study. Those interested in study participation completed the consent process and online diagnostic questionnaire (ED100K-V1). Cases met anorexia nervosa criteria based on DSM-IV-TR. Once the questionnaire was completed, the participant provided a blood sample. In New Zealand, witnessed informed consent was obtained prior to sample collection. Genotyping was conducted at the Broad Institute on the Illumina Global Screening Array. Controls were obtained from the QSkin Sun and Health Study (https://qskin.qimrberghofer.edu.au)[13]. Briefly, ~40,000 men and women aged 40-69 years were randomly sampled from Queensland, Australia. Those who indicated no eating disorders history from a checklist were included as controls. QSkin was established to study the etiology of cutaneous melanoma and other cancers of the skin; the cohort is followed up passively through linkage with health registers. QSkin participants provided Oragene saliva samples, and DNA was genotyped at Erasmus University Rotterdam in the Netherlands on the Illumina Global Screening Array. Ethical approval for the Australian component of the study was provided by the QIMR Berghofer Human Research Ethics Committee (QIMR-HREC approval P1339). Those interested in study participation completed the informed consent process via online submission prior to taking an online diagnostic questionnaire (ED100K-V1). Participants younger than 18 years then completed a paper questionnaire which required parent/guardian co-signature. Ethical approval for the New Zealand component was provided by the Health and Disability Ethics Committee of the New Zealand

Ministry of Health. In New Zealand, witnessed informed consent was obtained prior to sample collection. Participants under 18 years required parent/guardian co-signature. Ethical approval for the QSkin study was provided by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute (QIMR-HREC approval P1309). QSkin participants were given the option to provide written informed consent or to consent online in order to take part in the QSkin study. The samples described formed cohort *aunz*.

Denmark (ANGI-DK). National register and biobank. Cases and controls were identified primarily using the national register and biobank system. Genotypes came from Guthrie cards held by the Danish Neonatal Screening Biobank at Statens Serum Institute. Samples from this biobank are linked to the Danish register system via the unique Danish personal identification number. The individuals were born between 1981 and 2005 and had to be alive and a resident of Denmark on their first birthday and have a known mother. Cases had International Classification of Diseases (ICD-10) anorexia nervosa (F50.0)[14] diagnoses assigned by psychiatrists at inpatient and outpatient psychiatric services, and were identified using the Danish Psychiatric Central Research Register[15]. Controls were randomly selected from the same nationwide birth cohort. Cases and controls were specifically ascertained and genotyped as a part of ANGI, and additional control genotypes came from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; http://ipsych.au.dk)[16]. DNA from the dried blood spots was extracted, whole-genome amplified in triplicates, and genotyped in 23 batches based on birth year. The first wave (batch) contains the youngest participants (born in 2004) and wave 23 consists of the oldest participants (born in 1981). Wave 24, a supplementary batch, comprised all participants with an ICD-10 atypical anorexia nervosa lifetime diagnosis (F50.1, most commonly diagnosed when all anorexia nervosa criteria except amenorrhea were met) up to and including 2013 and F50.0 cases diagnosed during 2013. Comparisons showed that F50.0 and F50.1 samples matched on register information tested, i.e., age of diagnosis, frequency of lifetime psychiatric diagnoses and intellectual disability, urbanicity, and maternal and paternal age at childbirth. Genotyping was performed on the Illumina PsychChip array at the Broad Institute of Harvard and MIT. GenCall[17] and Birdseed[18] were used to call variants with MAF > 0.01. Call sets were merged after pre-QC on individual call sets. Data processing and GWAS analyses were performed on secure servers at the GenomeDK high-performance computing cluster (http://genome.au.dk).

DNA preparation, genotyping, genotype calling, QC methods, and imputation were performed on the broader iPSYCH cohort waves, which also included psychiatric cases with non-anorexia nervosa diagnoses (schizophrenia, depression, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder). The full iPSYCH cohort described contains ~86,000 individuals, including about 57,000 cases with at least one of the noted psychiatric disorders and around 30,000 controls. Each wave that was processed had ~3,500 participants.

Case-control data were filtered for the primary GWAS analysis such that cases required an anorexia nervosa or atypical anorexia nervosa lifetime diagnosis and controls required no lifetime anorexia nervosa or iPSYCH psychiatric diagnoses listed above. To address batch effects, a GWAS was conducted on waves separately, except waves 1 to 6 which were combined in a block due to smaller case sample sizes. Ancestry principal components (PCs) and PCs that

captured batch effects and other possible sources of variation were included as covariates (**Supplementary Table 18**). ANGI-DK samples formed cohorts *w1* to *w24*.

Individuals in ANGI-DK did not provide written informed consent. The register data collection is pseudo-anonymized (http://ipsych.au.dk/about-ipsych/data-processing-and-data-security-atipsych) and the re-identification key for linking the Danish civil registration number is stored separately from phenotype and genotype data. An exemption from consent is legally possible in Denmark if approved by The Danish Scientific Ethics Committee (Videnskabsetisk Komité). This exemption was given for all samples and was provided in 2012 to the iPSYCH study, with the most recent approval granted in 2018.

Denmark clinic samples**.** A Danish clinical cohort was obtained. Cases were defined as patients with at least one recorded hospital admission during which an ICD-10[14] diagnosis of F50.0 or F50.1 was given. Clinical cases consisted of women born 1947-1980 (age range: 35 to 68 years). Samples were genotyped at the Broad Institute on the Illumina Global Screening Array. Ethical approval with the protocol no. H-KF-01-024/01 was obtained from the competent Danish authority, De Videnskabsetiske Komiteer for Region Hovedstaden (The Capital Region of Denmark's Committees on Health Research Ethics). All participants provided written informed consent prior to being included into the study. The samples described are included in cohort *sedk*.

Sweden (ANGI-SE). The primary recruitment strategy involved Riksät-National Quality Register for Eating Disorders Treatment[19], which includes eating disorder-specific information from individuals seeking eating disorder treatment in Sweden since 1999. Potential cases identified through Riksät were sent a letter asking them to complete a follow-up questionnaire, which included the ED100K-V1 questionnaire. In the second recruitment strategy, study nurses at the Stockholm Centre for Eating Disorders (http://stockholmatstorningar.se) (SCÄ) recruited cases for ANGI. When patients with anorexia nervosa came into this center, a research nurse discussed the study with them and reviewed the consent. When participants consented, a blood sample was taken, and the participant was directed to complete the online diagnostic questionnaire. The third strategy was community outreach, specifically using traditional media (i.e., TV, radio, and newspapers) and social media including the Swedish ANGI website (http://www.angi.se), directly linking to the questionnaire. The final recruitment strategy for cases and controls involved LifeGene (https://www.lifegene.se)[20], an ongoing study initiated in 2010 to evaluate how genes, environment, and lifestyle affect health. Individuals enrolled in LifeGene completed an eating disorder assessment similar to the online diagnostic questionnaire and provided a blood sample. An anorexia nervosa algorithm for LifeGene was harmonized with the ED100K-V1 questionnaire for case and control identification. All cases met anorexia nervosa criteria based on DSM-IV-TR[21], and controls screened negative for a history of eating disorders. Genotyping was performed at the Broad Institute on the Illumina Global Screening Array. The Swedish component of ANGI (Riksät, SCÄ, and Community) was approved by the Regional Ethical Review Board in Stockholm (dnr: 2013/112-31/2). Individuals who wished to participate were mailed consent forms along with the vials for blood samples. Signed consent forms were returned with the samples. The Regional Ethical Review Board of Stockholm provided initial ethical approval of LifeGene. All participants provided consent online[20]. The Swedish component of ANGI obtained approval, as stated above, for use of LifeGene samples and data as

part of ANGI-SE. These samples described are included in cohort *sedk* (see the section above called "Denmark Clinic Samples" for other samples included in *sedk*.

United States (ANGI-US). Individuals who resided in the US (ages ≥ 12 years) self-identified or were referred to the study. Individuals completed a brief online screener to determine eligibility as a case or control for ANGI. Those deemed eligible completed the consent process and online diagnostic questionnaire (ED100K-V1). All cases met anorexia nervosa criteria based on DSM-IV-TR, and controls screened negative for a history of eating disorders. Once the questionnaire was completed, the participant provided a blood sample. Approximately 1,000 controls were recruited from the community. Additional control samples were obtained from The Price Foundation Anorexia Nervosa Trios Study[5,22]. These additional controls reported no history of eating disorders, had no first degree relative with an eating disorder, and screened negative for other Axis I psychopathology. Genotyping was performed at the Broad Institute on the Illumina Global Screening Array. Ethical approval for the US component of ANGI was granted by the University of North Carolina at Chapel Hill's Institutional Review Board (IRB# 13-0081). Individuals who were interested in study participation (and deemed eligible by the brief screen in the US) contacted the study team and completed the consent process. Although some provided written consent, most participants provided consent over the phone after a complete review of the consent forms. These samples formed cohort *usa2*.

UK Biobank

The UK Biobank (http://www.ukbiobank.ac.uk/) is a large prospective study of ~500,000 residents of the United Kingdom aged from 40 to 69 years old[23]. UK Biobank aims to provide insights into the causes, prevention, and treatment of various illnesses. Recruitment occurred between 2006-2010. The present study uses data from the July 2017 release including the second wave of genetic data. Cases were identified by primary and secondary ICD-10[14] diagnosis from linked health care records and self-report diagnosis of anorexia nervosa by a clinical professional in the UK Biobank mental health questionnaire. Controls were screened for any psychiatric disorder (Chapter V: Mental and behavioral disorders). UK Biobank participants provided electronic signed consent at their baseline assessment visit. UK Biobank was approved by the NHS Health Research Authority North West-Haydock Research Ethics Committee (reference 16/NW/0274). The current study was completed as part of approved UK Biobank application 27456. The samples described formed cohort *ukbb*.

Merging of case and control data

When sourcing control data, we prioritized controls that were ancestrally matched and genotyped on a similar platform to cases. There are two instances whereby cases were matched with controls from another country [i.e., *aunz* New Zealand cases (n = 430) were merged with Australian cases (n = 2,261) and controls (n = 17,158), and *sedk* Denmark cases (n = 129) were merged with Sweden cases (n = 4,118) and controls (n = 4,035)]. Country is unlikely to be confounded with case-control status in these cohorts. Ancestral matching was undertaken by visual inspection of a principal components analysis PC1 v PC2 plot for the merged data, and the matches were excellent with cases and controls randomly interspersed. Further, the first five ancestry PCs and any PCs that significantly differed ($P < 0.05$) between case and control cohort were included as covariates in GWAS to capture nuanced ancestry or batch effect differences.

Statistical power

Identified susceptibility variants in psychiatric genetics typically have an OR of ~1.1[24]. Our study was acceptably powered to detect susceptibility variants in this range (80% power to detect an OR of 1.09-1.19 with an additive model, 0.9% lifetime risk[25], $\alpha = 5 \times 10^{-8}$, MAF 0.05–0.5). Prior experience in other PGC disorders gives us reason to believe that when sample sizes reach an inflection point for power to detect multiple GWAS hits, the number of significant loci begins to increase linearly as samples were added after this inflection point. It is not surprising to see several borderline significant hits when first exceeding the inflection point, as has been observed in schizophrenia[26-28]. As more cases are added, it is probable that we will get more lead hits above this borderline range.

Quality control and covariates

For the GWAS analysis, the default QC parameters in Ricopili were used and are described as follows. Ricopili QC begins with a pre-filter SNP call rate of > 0.95, which is useful for cases and controls genotyped on different platforms. Next, QC involves sample filters, then SNP filters. Default sample filters are a call rate (cases/controls) ≥ 0.98, heterozygosity inbreeding coefficient ≤ 0.2 (cases/controls), and sex violations. Default SNP filters are a call rate ≥ 0.98, case-control missingness difference ≤ 0.02, no valid association *P* value (invariant), and violations of Hardy-Weinberg equilibrium (in controls $P > 10^{-6}$, in cases $P > 10^{-10}$). Some cohorts required the application of more stringent thresholds to reduce bias (**Supplementary Table 18**). Ancestry outliers were removed based on plotting the first two principal components (PCs) in a principal components analysis (PCA) containing each cohort and five reference cohorts (1000 Genomes Phase 3 EUR, AFR, EAS, SAS, AMR)[29] to retain European samples. Samples showing familial structure and/or cryptic relatedness, or duplicates were removed ($\hat{\pi} > 0.2$) during PCA. For the Danish waves, we conducted additional relatedness testing across all the waves combined, and then removed one individual from each related pair ($\hat{\pi} > 0.2$). PCs significantly associated with the phenotype were identified for inclusion as covariates. For the *aunz* cohort, QC and PCA was done externally. For QC, see **Supplementary Table 18**. PCA (20 principal components) were computed using smartpca (EigenSoft 6.0.1) on the cleaned data from all individuals used in the current paper in conjunction with the genotypes of ~50,000 additional individuals available at QIMR Berghofer, and the population reference data from the Genome-EUTWIN populations (https://ega-archive.org/datasets/EGAD00000000043) and HapMap Phase 3 populations[30]. Analyses were run using a filtered set of genotypes available across all genotyping projects (*N* SNPs ~40,000). Individuals beyond six standard deviations (*SD*s) of the European PC1 and PC2 centroid were excluded from analysis. The data were then put through Ricopili PCA module; the first five ancestry components and PCs significantly associated with the phenotype were always included as covariates (**Supplementary Table 18**). To the extent that national laws and regulations permitted, we examined sample overlap across cohorts by performing LD score bivariate regressions and estimating genetic covariance intercepts to assess sample overlap[31,32] (**Supplementary Table 19**).

Some of the cohorts required additional QC beyond the default process and parameters used in PGCs GWAS pipeline, Ricopili. **Supplementary Table 18** shows the additional QC steps applied, if any, and the PCs used as covariates, by cohort. The first five PCs were automatically

included to adjust for ancestry effects. Tests were done on post-QC data to investigate whether any of the PCs differ significantly between cases and controls, and if so, PCs nominally associated with the phenotype ($P < 0.05$) were also included in the GWAS as covariates.

Anorexia nervosa subtype phenotypes

We defined subtypes based on the presence or absence of binge eating. The rationale for this choice was that the current DSM-5[33] subtyping (i.e., restricting versus binge/purge) is a clinical, rather than a biological distinction. "Purging" behavior is a heterogeneous category and includes several behaviors either alone or in combination (e.g., self-induced vomiting, laxative abuse, diuretic abuse, other inappropriate compensatory behaviors), and our sample size is insufficiently powered—and phenotyping in several samples inadequately detailed—to identify individuals with various purging behavior constellations. In contrast, binge eating is more uniformly defined, represents a clear departure from restrictive eating behavior, and lies on the appetite continuum. Although the twin-based genetic correlation between binge eating and self-induced vomiting is high ($r_g = 0.74$)[34], less is known about other purging methods. Larger samples sizes will enable additional group distinctions and allow us to comment on the biological appropriateness of the current DSM-5 subtypes.

We defined anorexia nervosa with and without binge eating using available phenotypic data. We were able to use *chop*, *aunz*, and *usa2* datasets for this analysis. For *aunz* (ANGI-ANZ) and *usa2* (ANGI-US), anorexia nervosa with binge eating was defined as reporting ever 1) "having eating binges when you ate what most people would regard as an unusually large amount of food in a short period of time" and 2) "having a sense of loss of control during those eating binges". The absence of binge eating was determined by a "no" answer to either item. For *chop* (CHOP/PFCG), the presence of binge eating was defined as reporting a history of binge eating by structured or semi-structured interview. The no binge eating group had to report no lifetime history of bulimia nervosa and no history of binge eating. Purging was not used in these definitions and binge eating did not need to occur within episodes of anorexia nervosa. The percentage of available subtype data within these cohorts was 95% overall. Future analyses with larger samples sizes will increase confidence in results from this analysis.

GWAS of related traits in UK Biobank

Seven UK Biobank GWAS were performed to facilitate genetic correlation investigations. The phenotypes were BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), body fat percentage[35], fat mass (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), fat-free mass[35], physical activity[35], anxiety[36], and neuroticism[35].

Genotyping, imputation and QC

Briefly, blood samples were genotyped on two arrays, which share nearly all of their content: the UK BiLEVE array ($N = 49{,}949$) or the UK Biobank Axiom array ($N = 438{,}414$). Genotyping was conducted by Affymetrix across 33 different batches of approximately 4,700 samples each. UK Biobank provides extensive information on sample processing on its website (biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583). UK Biobank performed stringent QC on the genotyping data at the Wellcome Trust Centre for Human Genetics (WTCHG). For further

details, see: biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580. Prior to imputation, all variant sites with a call rate below 90% were filtered out. Imputation was carried out by UK Biobank using a merged UK10K-1000 Genomes Phase 3 reference panel and the Haplotype Reference Consortium (HRC) panel[37] (for further information, please see [38]). UK Biobank preferentially retained SNPs imputed to HRC for SNPs present in both imputation panels. Imputation was conducted using the IMPUTE4 program[38].

We excluded non-European participants identified by *k*-means clustering ($k = 4$) on the first two PCs derived from the genotype data, and related individuals (KING relatedness metric > 0.088, equivalent to an identical-by-descent coefficient of 0.25). SNPs were excluded if they had a MAF < 1%, if no call was made in > 2% of samples following imputation, if they were imputed with low confidence (INFO < 0.8), deviated substantially from Hardy-Weinberg equilibrium (HWE test, $P < 10^{-7}$), if they were not genotyped and were not part of the HRC panel. Additional QC and other information about these GWAS is given in **Supplementary Table 20**.

GWAS of BMI, body fat percentage, fat mass, and fat free mass

The GWASs on BMI, body fat percentage, fat mass, and fat free mass were a cross-sectional analysis of 155,961 healthy European participants from the UK Biobank. To identify genetic variation uniquely associated with body composition not confounded by illnesses and their downstream effects or metabolism-altering medication, we applied stringent exclusion criteria (e.g., psychiatric, gastrointestinal and endocrine illnesses, hormonal and antidiabetic medication). Body composition was assessed using Tanita BC-418 MA scale (Tanita Corporation, Arlington Height, IL). We included 7,794,483 genotyped and imputed SNPs and insertion-deletion variants with a MAF ≥ 1%. We covaried for assessment center, genotyping batch, smoking status, alcohol consumption, menopause, age, and socioeconomic status (measured by the Townsend Deprivation Index)[39]. We accounted for underlying population stratification by including the first six ancestry PCs, calculated on the European subsample GWAS cohorts. We used BGENIE v1.2 (https://jmarchini.org/bgenie) for sex-specific analyses and meta-analyzed these sex-specific GWAS using METAL[40] (http://csg.sph.umich.edu/abecasis/metal).

GWAS of physical activity

We calculated sex-specific GWAS of physical activity with imputed genotype data in 29,496 male and 36,758 female ($N = 66,254$) individuals in the UK Biobank, including age (at recruitment), genotyping array, and genetic PCs 1–20 as covariates. Physical activity in the UK Biobank was measured continuously over a period of seven days with a wrist-worn accelerometer. General physical activity quality control of raw data is described in detail elsewhere[41]. They used a wear-time adjusted 7-day average measure of activity, including only individuals meeting UK Biobank QC criterion: good wear-time, good calibration, calibration on own data, and no problem indicators. Analyses were performed on the intersection of this UK Biobank subset with those passing general genotyping QC: in European ancestry subset; used in the calculation of ancestry PCs; without excess relatives in the UK Biobank sample; no putative sex chromosome aneuploidy; and were not outliers for heterozygosity and genotype missingness. General genotyping considerations, raw data QC, and imputation procedure in the UK Biobank are described in detail elsewhere[38]. 20 PCs provided by the UK Biobank were used.

GWAS of anxiety

We conducted sex-specific GWAS of anxiety disorders with imputed genotype data on 25,443 cases and 58,113 controls[36]. Cases met criteria for probable lifetime anxiety disorder diagnosis if they either self-reported a professional diagnosis of any of the five core anxiety disorders (generalized anxiety disorder, panic disorder, specific phobia, agoraphobia, or social anxiety disorder) or met criteria for probable lifetime generalized anxiety disorder according to the Composite International Diagnostic Interview question set[42,43]. Cases did not report a diagnosis of schizophrenia, psychosis, attention-deficit/hyperactivity disorder (ADHD), autism, any eating disorder, or bipolar disorder. Controls were screened for any evidence of psychiatric or substance use disorders. Participants were limited to individuals of European ancestry, who were not excessively related, had no putative sex chromosome aneuploidy, and were not outliers for heterozygosity and genotype missingness. Stratified linear regressions were performed on ~7 million SNPs of high imputation quality (INFO > 0.9) with a minimum MAF ≥ 0.01 in BGENIE v1.2 controlling for six ancestry PCs calculated on the European subsample of UK Biobank, assessment center, genotyping batch, and age.

GWAS of neuroticism

We performed sex-specific GWAS on neuroticism using the genotype data supplied by UK Biobank in males (N = 142,875) and in females (N =144,660; total N = 287,535), following QC as described above and using PCs calculated on the European subsample of UK Biobank. The neuroticism phenotype was calculated as the sum score of neuroticism questions at the baseline assessment[44], corrected for age and sex-specific means and *SD*s from the UK population[45]. In a second analysis, individuals were excluded if they reported any psychiatric illness resulting in 83,413 males and 73,946 females (total N = 157,355). Sex-stratified linear regressions were performed in PLINK using eight ancestry PCs and genotyping batch (as a factor) as covariates and later meta-analyzed using METAL[40].

Gene expression

We first investigated whether anorexia nervosa heritability was enriched in tissue/cell type specifically expressed genes using publicly available gene expression data: GTEx[46] (RNA-seq of macroscopic samples from multiple human tissues) and Cahoy[47] (mouse neural cell-types transcriptome database). Stratified LDSC estimated common variant heritability enrichment in the top 10% of specifically expressed genes in each tissue or cell type, taking into account confounders such as gene size, LD, and functionally enriched genomic regions (e.g., conserved regions across mammals[48]. We followed a published method LDSC-SEG (LDSC applied to specifically expressed genes)[49]. From the datasets, the method has derived a genome annotation corresponding to each tissue or cell type of interest, which contains the top 10% specifically expressed genes of the tissue or cell type together with 100 Kb windows on each side of the transcribed region of each genes. We obtained the derived genome annotations from the LDSC-SEG GitHub repository (https://github.com/bulik/ldsc).

Second, we created a new annotation by performing differential expression analyses among 9,970 single cells, previously clustered into 24 different cell types[50], from five different mouse brain regions. Briefly, we used the scran R package[51] using the 50% of the genes with mean expression higher than the median to compute normalization factor for each single cell. The

normalization factors were computed after clustering cells using the scran package quickCluster function to account for cell type heterogeneity. We then performed 24 differential expression analysis using R package BPSC[52] testing each cell type against the 23 other cell types using the computed normalization factors as a covariate. We then selected the top 10% most upregulated genes for each cell type and used the coordinates of these genes extended by 100 Kb on each side as an extra annotation in LDSC.

We used the "munge_sumstats.py" script built in the LDSC software[31,32] to reformat the ANGI GWAS results. We then applied stratified LDSC regression to estimate heritability enrichment of the annotations[49] (tissue or cell type) conditional on 53 other annotations from the "baseline model" (e.g., conserved regions[48]). We used regression weights computed from phase 3 of the 1000 Genome Project[29] with HLA regions removed (https://data.broadinstitute.org/alkesgroup/LDSCORE/1000G_Phase3_weights_hm3_no_MHC.tgz).

We primarily report the regression coefficient of each annotation (corresponding to gene expression of each tissue or cell type) and an associated *P* value. A positive regression coefficient suggests that the annotation contributes to the heritability of anorexia nervosa while accounting for the contributions of other annotations[49,53]. The *P* value tests whether the regression coefficient was significantly positive (one-tailed), i.e., whether the contribution of the annotation is statistically significant. LDSC analyses are reported in **Supplementary Figs. 12-15**.

We also used MAGMA[54] (v1.06) (https://ctg.cncr.nl/software/magma), as done previously[50], to identify tissues/cell types underlying anorexia nervosa. GTEx data (V6p, median expression across individual per tissue) was downloaded from the GTEx website (https://gtexportal.org/home). Genes not expressed in any tissues (median = 0 for all tissues) were excluded. Gene expression from the different brain cell types was obtained as previously described. Briefly, we performed single cell RNA-seq from 9,970 single cells from five brain regions (neocortex, hippocampus, hypothalamus, striatum, midbrain, plus samples enriched for oligodendrocytes, dopaminergic neurons, and cortical parvalbuminergic interneurons), which allowed us to identify 24 cell types at level 1 (broad clustering) (pyramidal neurons, oligodendrocytes, etc…) and 149 cell types at level 2 (fine grained clustering) (pyramidal neurons from layer 6, layer 4, etc…).

For each gene expression dataset, we computed an index of specificity for each gene in each tissue/cell type by dividing the expression of a gene in a given tissue/cell type by the total expression of the gene in all tissues/cell types (range of specificity: 0-1). For each tissue/cell type, we then binned the specificity measure into 41 bins (0 representing a gene not expressed in the tissue/cell type, 1 gene in the bottom 2.5% quantile of specificity, …, 40 genes that are in the 97.5% to 100% most specific genes in the tissue/cell type). We then used MAGMA to test for a positive correlation between binned tissue specificity and gene-level genetic association with anorexia nervosa for each tissue/cell type. The gene-level genetic association was computed with MAGMA (v1.06) using a window surrounding the gene by 35 kb upstream to 10 kb downstream of the gene. The gene-level association is computed by summing the association *P* value of SNPs located in the gene windows taking into account the LD structure of the region. MAGMA takes

into account confounders such as gene length, LD, and gene-gene correlation. MAGMA analyses are reported in **Supplementary Figs 9-11.**

Predicted tissue-specific gene expression

We predicted differential gene expression using S-PrediXcan v1.0[55] and genomic and transcriptomic reference data from the brain regions assayed in the GTEx project v7[46] and Depression Genes and Networks (DGN) whole-blood cohort[56]. A total 258,158 gene-tissue pairs were tested (**Supplementary Table 13**). Significant genes were compared to genes in the gene-wise analysis performed with MAGMA.

A general note on multiple testing correction

Carrying out multiple testing runs the risk of inflating Type I error and increases the probability of false positive results. To manage this risk, we took the general approach of setting a conservative *a priori P* Bonferroni correction threshold. We did this generally on a within-analysis basis, since different analyses tested different underlying hypotheses, rather than paper-wide. Readers can identify the Bonferroni threshold used for a given analysis in Table and Figure notes.

Additional Results

Primary GWAS meta-analysis

Pre- and post-QC lambda, number of single-nucleotide polymorphisms (SNPs), and *N*s in each of the final 33 datasets analyzed within the primary GWAS can be found in **Supplementary Table 1**. The meta-analysis LD intercept was 1.02 (s.e. = 0.01). The meta-analysis quantile-quantile (Q-Q) plot is shown in **Supplementary Fig. 1**. The LD score regression intercepts for each cohort after QC ranged from 0.98 (s.e. = 0.01) to 1.03 (s.e. = 0.01) (**Supplementary Table 1**). The genetic covariance intercepts in LD score bivariate regression analyses were close to 0 and indicated no evidence of sample overlap among the cohorts (**Supplementary Table 19**). Eight genome-wide significant loci were identified. Follow-up analyses included using genome-wide complex trait analysis (GCTA-COJO)[57] to conduct stepwise regression on markers with *P* values < 10^{-8}. GCTA-COJO identified eight independent signals taking into account the LD correlations between SNPs and running a conditional and joint analysis[58]. All eight identified markers were equivalent to the SNPs resulting from distance- and LD-based clumping shown in **Table 1** (for conditional analyses please see **Supplementary Table 5**).

Genomic inflation and residual confounding

Here we provide detailed information to illustrate that confounding due to population stratification or other reasons was minimal in our primary GWAS. Two relevant parameters were estimated using linkage-disequilibrium (LD) score regression[29]. Firstly, we estimated an LD intercept of 1.02 (s.e. = 0.01) for the meta-analysis and between 0.98-1.03 for individual datasets (**Supplementary Table 1**). The LD score intercept is significantly greater than one, but is in line with the expected small levels of inflation caused by sample size and heritability described in Loh et al.[59]. A second measure, the attenuation ratio [(LDSC intercept – 1) / (mean χ^2 – 1)] for the meta-analysis was 0.07 (s.e. = 0.04) (**Supplementary Fig. 1**), also suggesting a lack of confounding. Together these suggest that deviation from the null was due to polygenic signal and not population structure or bias.

The overall inflation of summary statistics genomewide or λ_{GC} for individual datasets post-QC ranged between 1.00-1.06 (**Supplementary Table 1**) and for the meta-analysis was 1.22 **(Supplementary Fig. 1**). Inflation of tests statistics is known to be due to a combination of polygenicity, uncorrected population stratification, and confounding. The larger λ_{GC} value observed for our GWAS meta-analysis is indeed expected at this sample size, trait polygenicity, and heritability[59]. The LD score regression method for GWAS of highly polygenic phenotypes such as anorexia nervosa and large sample sizes separates the polygenetic component (the slope) from population stratification and other systematic biases (estimated by the intercept and attenuation ratio) [29].

Correcting for λ_{GC} in large GWAS samples of polygenic phenotypes can cause loss of signal and power, as evidenced by the LD intercept of the GWAS summary statistics from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium 2015 body mass index (BMI) paper (0.65)[60,61]. Correction for λ_{GC} at the individual study level has also been shown to bias heritability estimates downward[29].

Previous hit

The chr12 locus identified in Duncan et al.[1] did not reach genome-wide significance. The OR for the index variant at this locus (rs4622308) was in the same direction in the present meta-analysis compared with Duncan et al. (present: A1 = C, A2 = T, OR = 1.06, s.e. = 0.01, $P = 7.02 \times 10^{-5}$; Duncan et al.: A1 = C, A2 = T, OR = 1.20, s.e. = 0.03, $P = 4.25 \times 10^{-9}$) and in 22 of the 33 cohorts ($z = 2.00$, $P = 0.05$, 2-tailed). To further assess this locus, a random-effects meta-analysis was conducted. Similar to the fixed-effect meta-analysis, the random-effects meta-analysis indicated that the effect of this locus was not genome-wide significant (OR = 1.06, s.e. = 0.05, $P = 0.02$) and showed evidence of heterogeneity, $I^2 = 53.7$ (**Supplementary Fig. 4**). There are many possible reasons why the result was not replicated, including winner's curse[62], moderator variables given the heterogeneity observed (such as environmental risks), between-study heterogeneity in ascertainment, and differences in LD structure across cohorts in addition to true non-replication.

Chromosome X

The separate analysis of chrX included $n = 14{,}915$ cases and $n = 27{,}854$ controls. There were no genome-wide ($P < 5 \times 10^{-8}$) or suggestive ($P < 1 \times 10^{-5}$) significant loci.

Female-only secondary GWAS

A supplementary analysis conducted on female cases and controls only—to determine the similarity of results to the main GWAS analysis which included females and males—had 14,896 cases and 27,865 controls. The female-only GWAS revealed one genome-wide significant locus ($P < 5 \times 10^{-8}$) on chr3 (rs9812977; 48.2-49 Mb; $P = 1.31 \times 10^{-9}$; OR = 1.08; 95% CI: 1.03-1.14), which was the top locus in the main GWAS analysis.

eQTL and Hi-C interactions

For locus 1 (multigenic, chr3:47.5-51.3 Mb, **Supplementary Fig. 5a**), our data implicate 100 brain-expressed genes. Locus 1 is gene-dense with a large number of brain eQTLs and regulatory chromatin interactions. Notably, 16 genes with regulatory chromatin interactions mapping to the locus lie outside the LD-defined locus. Locus 3 (multigenic, chr2:53.8-54.3 Mb, **Supplementary Fig. 5c**) is less complex that locus 1. Nonetheless, we implicate 12 genes, six within and 6 outside the LD-defined locus.

For all four single-gene loci, eQTL and/or chromatin interaction connections implicated the gene intersecting the locus. For locus 2 (chr11:114.9-115.4 Mb, **Supplementary Fig. 5b**), both eQTL and regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *CADM1*. Genetic variants near to *CADM1* (cell adhesion molecule 1) have been implicated by GWAS for body mass and age at menarche. CADM1 protein levels appear to be elevated in the hypothalamus of BMI risk variant carriers. Obese mice have been reported to show elevated *CADM1* expression and *CADM1* knockout mice show reduced body weight[63]. For locus 4 (chr10:131.2-131.4 Mb, **Supplementary Fig. 5d**), eQTL data connected to the locus-intersecting gene *MGMT*. *MGMT* (O-6-methylguanine-DNA methyltransferase) encodes an epigenetic regulator important in multiple cancers, including glioblastoma. For locus 5 (chr3:70.6-71.0 Mb, **Supplementary Fig. 5e**), regulatory chromatin interaction data confirmed the connection to the

locus-intersecting gene *FOXP1* (forkhead box P1), which encodes a transcription factor in the forkhead box family. Brain-specific deletion of *FOXP1* results in defects in striatal development and changes in the hippocampus[64]. Interestingly, *FOXP1* knockout mice exhibit a significant reduction in body weight as compared to littermate controls. For locus 5, eQTL data also suggested a functional connection to the more distal *GPR27*, which encodes an orphan G-protein coupled receptor, and is highly expressed in the brain[65]. It has recently been associated with insulin secretion[66]. Finally, for locus 6 (chr1:96.6-97.2 Mb, **Supplementary Fig. 5f**), both eQTL and regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *PTBP2*. The protein encoded by this gene binds to intronic polypyrimidine clusters in pre-mRNA molecules and is implicated in controlling the assembly of other splicing-regulatory proteins.

One intergenic locus (locus 8, chr5:93.9-95.0 Mb, **Supplementary Fig. 5h**) had eQTL connections to *PROS1* and *ARL13B*. *PROS1* encodes an anticoagulation factor that plays a role in blood-brain-barrier integrity[67]. *ARL13B* encodes a member of the ADP-ribosylation factor-like (ARL) small Ras GTPase family. ARL13B protein is expressed in the cilia of all organs; mutations are associated with Joubert syndrome 8, which like other ciliopathies has been associated with obesity[68,69]. Mutations are also associated with intellectual disability (University of Chicago's Intellectual Disability Exome Panel). Thomas et al.[69] found *ARL13B* expression throughout the developing human brain. Additionally, they identified *ARL13B* expression in primary cilia of hypothalamic neurons of newborn mice. Furthermore, Higginbotham et al.[70] found that mutant ARL13B disrupts the development and migration of interneurons.

For locus 7 (intergenic, chr5:24.9-25.3 Mb, **Supplementary Fig. 5g**), there were no supporting eQTL or regulatory chromatin interactions.

Multi-trait conditional and joint analysis (mt-COJO)

Seven of the eight genome-wide significant loci showed only slight changes in their effect sizes (i.e., betas) after conditioning on education years[71], type 2 diabetes[72], high-density lipoprotein (HDL) cholesterol[73], BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report; see **Additional Methods**), schizophrenia[28], or neuroticism[35]. The results suggest that the loci are independent of the traits on which they were conditioned and that the traits may not share genetic association at these loci. The association of locus 2 on chr11 tagged by rs6589488 with anorexia nervosa may not be independent of genetic associations with type 2 diabetes as the beta was diminished after conditioning. This suggests, at locus 2, that the association with anorexia nervosa may not be independent of genetic underpinnings of glycemic alterations seen in type 2 diabetes.

Clinical investigations

Anorexia nervosa subtype

One potential source of genetic heterogeneity lies in differing clinical presentations of anorexia nervosa (i.e., with or without the presence of binge eating). This was not supported in preliminary analyses. The SNP-based genetic correlation (SNP-r_g) between the anorexia nervosa subtypes was 0.74 (s.e. = 0.16; $P = 1.74 \times 10^{-6}$). To test for heterogeneity in the genetic variation

associated with these two subtypes, we tested whether their SNP-r_g was significantly different from unity. We used a block jackknife approach using the LD score regression software (LDSC) v1.0[29]. The genetic correlation between anorexia nervosa with and without binge eating was not significantly different from 1 ($P = 0.08$). There were no significant differences in the mean polygenic risk score (PRS) between subtypes in the three cohorts for which anorexia nervosa subtype data were available (**Supplementary Fig. 6**). We also calculated SNP-r_g by anorexia nervosa subtype (**Supplementary Table 9)** and found no significant differences in SNP-r_g with external traits, although small sample sizes limit interpretation. In summary, our preliminary subtype analyses do not indicate significant differences in the genetic architectures of anorexia nervosa with and without binge eating; however, larger sample sizes are necessary for confirmation.

Males with anorexia nervosa

The number of males identified on the basis of genotype sex in the meta-analysis was 447 cases and 20,347 controls. Anorexia nervosa PRS scores derived using the female-only GWAS were associated with a higher risk of anorexia nervosa in males. Those at the highest decile had 4.13 (95% CI: 2.58, 6.62) times the odds of lifetime anorexia nervosa compared with those at the lowest decile. Anorexia nervosa PRS accounted for ~1.8% of the total variance in anorexia nervosa in males for the discovery cohort *P* threshold (pT) = 0.5, comparable to ~1.7% at *P* threshold (pT) = 0.5 in the cohort as whole. Taken together, these preliminary results do not provide evidence for a major sex-specific difference in the common genetic architecture of anorexia nervosa, although our conclusions are limited due to the small sample size.

Within-trait prediction: polygenic risk scoring

We observed that across cohorts, anorexia nervosa cases were more likely to be in the PRS higher deciles than controls based on their anorexia nervosa genetic load **(Supplementary Fig. 16)**. Visual inspection of the decile plots showed that the score distributions across deciles were relatively uniform across target datasets; thus, there was no indication of any extreme outlying datasets. PRS applied to the largest target dataset, *sedk*, showed that those at the highest decile had 2.59 times higher odds (95% CI: 2.12-3.18) of lifetime anorexia nervosa compared with those at the lowest decile. The results also provide evidence of the replicability of the main GWAS results (**Supplementary Fig. 16**).

Gene-wise analysis

Results of MAGMA gene-wise associations are reported in **Supplementary Table 11**. Seventy-nine genes were Bonferroni-significant (threshold = 2.62×10^{-6}), and 506 had a Benjamini and Hochberg[74] FDR *q* value < 0.05. None of the 79 Bonferroni-significant genes are part of the MHC, but 57 genes are located in a gene-rich locus on chr3. The top genes on chr3 were *NCKIPSD*, *CELSR3,* and *IP6K2*. Through the MAGMA analysis we identified 16 additional genes which were not annotated via clumping. These 16 genes are located in loci on chr 1, 2, 3, 7, 10, 11, 12, 17, and 22. Some of these Bonferroni-significant genes have been indicated to be involved in glycemic and metabolic disease phenotypes (*CTNNB1*[75]; *EXOC4*[76]; *FAM19A2*[77]; *VAMP2*[78]).

Pathway analysis

The Bonferroni-significant pathway (**Supplementary Table 12**) GO:positive_regulation_of_embryonic_development (Gene Ontology, 32 genes, 6.31×10^{-6}) has two Bonferroni-significant genes: *DAG1* and *CTNNB1*. *CTNNB1* encodes beta-catenin, an essential component of the canonical Wnt signaling pathway. Beta-catenin can regulate neuronal progenitor proliferation and affect cortical size[79]. *CTNNB1* expression has been associated with adipogenesis, glucose metabolism, and obesity[75]. Metabolic diseases including obesity and type 2 diabetes are influenced by genetic and functional variations in the Wnt signalling pathway[75]. *DAG1* encodes dystroglycan, an essential member of the dystrophin-glycoprotein complex that has been mainly studied in the context of muscular dystrophies. Dystroglycan and other members of the dystrophin-glycoprotein complex are also found in neurons and glia and their disruption has been linked to intellectual disability and altered brain development[80]. Specific ablation of dystroglycan in neurons or glia results in distinct phenotypes[81]. Dystroglycan is expressed in pyramidal cells of the cortex and hippocampus, where it appears to be essential for the establishment and maintenance of CCK-positive basket cell terminals[82].

Tissue and cell type analyses

We first used partitioned heritability analyses in LDSC using annotation of elements in the genome with specific functions. Considering general annotations, enrichment in conserved regions was the main finding (enrichment (s.e.) = 24.97 (3.29), $P = 3.32 \times 10^{-11}$, **Supplementary Fig. 7**). Partitioned heritability analysis was then used to test for cell type-specific enrichment in the GWAS of anorexia nervosa among 10 cell type groups: adrenal and pancreas; cardiovascular; CNS; connective and bone; gastrointestinal; immune and hematopoietic; kidney; liver; skeletal muscle; and other tissue (which includes adipose tissue). The CNS cell type group showed a 2.8-fold significant enrichment (**Supplementary Fig. 8**).

We next investigated whether there were tissue or cell type associations with anorexia nervosa using gene expression data to annotate gene sets characteristic of specific cells or tissues (for details see[50]). Gene expression datasets used were: GTEx (RNA-seq of samples from multiple human tissues); gene expression from neurons; astrocytes and oligodendrocytes from developing and mature mouse forebrain[47]; and gene expression from 149 mouse brain cell types (KI level 1: 24 broad categories, KI level 2: 149 cell types underlying the 24 broad categories)[50].

Using MAGMA[54], the majority of brain tissues in GTEx were significantly associated with anorexia nervosa (**Supplementary Fig. 9**), the strongest hits being brain cerebellum and brain cerebellar hemispheres. Enrichment in muscle-skeletal tissues also appeared likely (**Supplementary Fig. 9**). Medium spiny neurons and pyramidal neurons from the CA1 region of the hippocampus were significantly associated with anorexia nervosa at a Bonferroni threshold in the 24 level 1 cell types (**Supplementary Fig. 10**). Among the 149 level 2 cell types, pyramidal neurons from the CA1 region of the hippocampus and pyramidal neurons from the somatosensory cortex layer 5 were Bonferroni-significant (**Supplementary Fig. 11**).

Medium spiny neurons (MSNs) are dopaminergic and inhibitory. They are the primary cell type of the striatum. The dorsal striatum has been linked to feeding behaviors including food

motivation and reward[83]. D1R-medium-spiny-neurons (medium spiny neurons that express the D1-type dopamine receptor) afferents have been reported to be the primary source of nucleus accumbent inhibition to the lateral hypothalamus[84]. Furthermore, in that study, inhibition of D1R-MSNs increased feeding, while activation decreased feeding[84]. Pyramidal neurons are excitatory and are the primary excitatory cell type found in cortical structures[85]. Kim et al.[86] recently found that *PPP1R1B*-expressing pyramidal neurons from the basolateral amygdala project to DR1-expressing central amygdala neurons, which are known to modulate appetitive behaviors.

Using the LDSC partitioned heritability approach[53], no significant signal was found in the GTEx database for tissues (**Supplementary Figs. 12-13**), in the Cahoy database for cells (**Supplementary Fig. 14**), or in the single-cell RNA-sequencing database (**Supplementary Fig. 15**). Nevertheless, in GTEx, the enrichment of heritability was more common in cell types in the brain, although enrichment in muscle-skeletal tissues was also evident, though no cell type reached significance (**Supplementary Fig. 13**). In the Cahoy database, the enrichment appeared more common in astrocytes compared with neurons and oligodendrocytes, although none of these reached statistical significance after Bonferroni correction (**Supplementary Fig. 14**). In the single-cell RNA-sequencing database, signal was strongest in neuroblasts (**Supplementary Fig. 15**).

Predicted tissue-specific gene expression

The PrediXcan analysis suggested significant effects on the expression of 36 genes across 44 GTEx tissues ($P \leq 1.94 \times 10^{-7}$; **Supplementary Table 13**). *MGMT* is located on chr10 (131.2-131.4 Mb). The majority of others are located within the multi-genic region on chr3. Downregulation and upregulation are presented in **Supplementary Table 13**.

Cross-trait analysis

Genetic correlations

Full results are shown in **Supplementary Table 10** and Bonferroni-significant results are shown graphically in **Fig. 2**. In instances where the same phenotype appears in multiple study sources, the main manuscript and **Fig. 2** report the result from the study source with the largest sample and/or of European ancestry.

Generalized summary data-based Mendelian randomization (GSMR)

BMI. We used GSMR[87] to investigate causal associations between BMI and anorexia nervosa using an extension of GCTA[57] (**Supplementary Table 16**). A one standard deviation (*SD*) decrease in genetically-estimated BMI increased the risk for anorexia nervosa by 4% (OR = 1.04; s.e. = 0.01; $P_{GSMR} = 0.008$) while an increase in genetically-estimated anorexia nervosa had a BMI-lowering effect ($b_{xy} = -0.28$, s.e. = 0.07, $P_{GSMR} = 5.15 \times 10^{-5}$). We only used eight SNPs to build the multiple SNP instrument for anorexia nervosa as an exposure and, hence, these results should be interpreted with caution.

To further separate effects of BMI from the anorexia nervosa phenotype, we used GCTA-mtCOJO[57,87] (multi-trait-based conditional & joint analysis using GWAS summary data) to adjust the anorexia nervosa GWAS summary statistics for BMI, using BMI summary statistics

from our UK Biobank analysis, which excluded individuals with a mental health diagnosis or taking a psychiatric or weight changing medication (see **Additional Methods**) and re-ran the GSMR analysis. The anorexia nervosa and BMI GWAS were performed on independent samples. As expected, after conditioning on BMI, the bidirectional pattern was no longer observable with $OR_{BMI \rightarrow AnorexiaNervosaAdjBMI} = 1.00$ (s.e. = 0.01; $P_{GSMR} = 0.78$). However, the putative causal association from AnorexiaNervosaAdjBMI to BMI was still statistically significant ($b_{xy} = -0.22$, s.e. = 0.08, $P_{GSMR} = 0.004$). The results are consistent with a causal relationship not due to pleiotropy (in the case of the anorexia nervosa→BMI effect) between these two traits.

Type 2 diabetes. We also investigated the causal relationship between Type 2 diabetes and anorexia nervosa using GSMR. The association with Type 2 diabetes as an exposure and anorexia nervosa as an outcome was not statistically significant (bxy = -0.02, s.e. = 0.03, $P_{GSMR} = 0.035$), nor was the association with anorexia nervosa as an exposure and Type 2 diabetes as an outcome (bxy = -0.09, s.e. = 0.09, $P_{GSMR} = 0.30$). These results do not support either phenotype as having a putative causal effect on the other. The analysis with anorexia nervosa as an exposure had only 7 instrumental variables rather than the recommended minimum of 10, therefore results are to be interpreted cautiously and may change once the anorexia nervosa GWAS sample size increases.

References

1. Duncan, L. *et al.* Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. *Am. J. Psychiatry* **174**, 850-858 (2017).
2. Boraska, V. *et al.* A genome-wide association study of anorexia nervosa. *Mol. Psychiatry* **19**, 1085-1094 (2014).
3. Kaye, W.H. *et al.* A search for susceptibility loci for anorexia nervosa: methods and sample description. *Biol. Psychiatry* **47**, 794-803 (2000).
4. Kaye, W.H. *et al.* Genetic analysis of bulimia nervosa: methods and sample description. *Int. J. Eat. Disord.* **35**, 556-570 (2004).
5. Reba, L. *et al.* Relationships between features associated with vomiting in purging-type eating disorders. *Int. J. Eat. Disord.* **38**, 287-294 (2005).
6. Wang, K. *et al.* A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. *Mol. Psychiatry* **16**, 949-959 (2011).
7. Hou, L. *et al.* Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Hum. Mol. Genet.* **25**, 3383-3394 (2016).
8. Mühleisen, T.W. *et al.* Genome-wide association study reveals two new risk loci for bipolar disorder. *Nat. Commun.* **5**, 3339 (2014).
9. Stahl, E. *et al.* Genomewide association study identifies 30 loci associated with bipolar disorder. *bioRxiv*, 173062.1 (2018).
10. McKay, J.D. *et al.* A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. *PLoS Genet.* **7**, e1001333 (2011).
11. Kirk, K.M. *et al.* The Anorexia Nervosa Genetics Initiative: study description and sample characteristics of the Australian and New Zealand arm. *Aust. N. Z. J. Psychiatry* **51**, 583-594 (2017).
12. Thornton, L.M. *et al.* The Anorexia Nervosa Genetics Initiative (ANGI): overview and methods. *Contemp. Clin. Trials* **74**, 61-69 (2018).
13. Olsen, C.M. *et al.* Cohort profile: the QSkin Sun and Health Study. *Int. J. Epidemiol.* **41**, 929-929i (2012).
14. World Health Organization. *ICD-10: international statistical classification of diseases and related health problems: 10th revision*, (World Health Organization, Geneva, 1992).
15. Mors, O., Perto, G.P. & Mortensen, P.B. The Danish Psychiatric Central Research Register. *Scand. J. Public Health* **39**, 54-57 (2011).
16. Pedersen, C.B. *et al.* The iPSYCH2012 case-cohort sample: new directions for unravelling genetic and environmental architectures of severe mental disorders. *Mol. Psychiatry* **23**, 6-14 (2018).
17. Illumina. *Illumina GenCall Data Analysis Software*, Number of (2005) Available at: https://support.illumina.com/content/dam/illumina-marketing/documents/products/technotes/technote_gencall_data_analysis_software.pdf (Accessed: March 18, 2019).
18. Wysoker, J.N. *et al.* Integrated genotype calling and association analysis of SNPs, common copy number polymorphisms and rare CNVs. *Nat. Genet.* **40**, 1253-1260 (2008).

19. Swedish Association of Local Authorities and Regions. *National healthcare quality registries in Sweden*, Number of (Edita, Stockholm, 2007) Available at: https://webbutik.skl.se/bilder/artiklar/pdf/7164-096-7.pdf (Accessed: March 18, 2019).
20. Almqvist, C. *et al.* LifeGene—a large prospective population-based study of global relevance. *Eur. J. Epidemiol.* **26**, 67-77 (2011).
21. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, text revision*, (American Psychiatric Association, Washington, DC, 2000).
22. Jonassaint, C.R. *et al.* Absence of association between specific common variants of the obesity-related FTO gene and psychological and behavioral eating disorder phenotypes. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **156B**, 454-461 (2011).
23. Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).
24. Smoller, J.W. *et al.* Psychiatric genetics and the structure of psychopathology. *Mol. Psychiatry* **24**, 409-420 (2019).
25. Hudson, J.I., Hiripi, E., Pope, H.G. & Kessler, R.C. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol. Psychiatry* **61**, 348-358 (2007).
26. Ripke, S. *et al.* Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* **45**, 1150-1159 (2013).
27. Ripke, S. *et al.* Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* **43**, 969-976 (2011).
28. Schizophrenia Working Group of the Psychiatric Genomics Consortium *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421-427 (2014).
29. 1000 Genomes Project Consortium *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56-65 (2012).
30. International HapMap 3 Consortium. Integrating common and rare genetic variation in diverse human populations. *Nature* **467**, 52-58 (2010).
31. Bulik-Sullivan, B.K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291-295 (2015).
32. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236-1241 (2015).
33. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5®)*, (American Psychiatric Association, Washington, DC, 2013).
34. Sullivan, P.F., Bulik, C.M. & Kendler, K.S. Genetic epidemiology of binging and vomiting. *Br. J. Psychiatry* **173**, 75-79 (1998).
35. Hübel, C. *et al.* Genomics of body fat percentage may contribute to sex bias in anorexia nervosa. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **in press**.
36. Purves, K.L. *et al.* The common genetic architecture of anxiety disorders. *bioRxiv*, 203844 (2017).
37. McCarthy, S. *et al.* A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279 (2016).
38. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203-209 (2018).
39. Townsend, P. Deprivation. *J. Soc. Policy* **16**, 125-146 (1987).
40. Willer, C.J., Li, Y. & Abecasis, G.R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190-2191 (2010).

41. Doherty, A. *et al.* Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank study. *PLoS One* **12**, e0169649 (2017).
42. Kessler, R.C., Andrews, G., Mroczek, D., Ustun, B. & Wittchen, H.-U. The World Health Organization composite international diagnostic interview short-form (CIDI-SF). *Int. J. Methods Psychiatr. Res.* **7**, 171-185 (1998).
43. Davis, K.A. *et al.* Mental health in UK Biobank: development, implementation and results from an online questionnaire completed by 157 366 participants. *BJPsych Open* **4**, 83-90 (2018).
44. Smith, D.J. *et al.* Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PloS One* **8**, e75362 (2013).
45. Eysenck, S.B., Eysenck, H.J. & Barrett, P. A revised version of the psychoticism scale. *Pers. Individ. Dif.* **6**, 21-29 (1985).
46. GTEx Consortium. Genetic effects on gene expression across human tissues. *Nature* **550**, 204-213 (2017).
47. Cahoy, J.D. *et al.* A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. *J. Neurosci.* **28**, 264-278 (2008).
48. Lindblad-Toh, K. *et al.* A high-resolution map of human evolutionary constraint using 29 mammals. *Nature* **478**, 476-482 (2011).
49. Finucane, H. *et al.* Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621-629 (2018).
50. Skene, N.G. *et al.* Genetic identification of brain cell types underlying schizophrenia. *Nat. Genet.* **50**, 825-833 (2018).
51. Lun, A.T.L., McCarthy, D.J. & Marioni, J.C. A step-by-step workflow for low-level analysis of single-cell RNA-seq data with Bioconductor. *F1000Res.* **5**(2016).
52. Vu, T.N. *et al.* Beta-poisson model for single-cell RNA-seq data analyses. *Bioinformatics* **32**, 2128-2135 (2016).
53. Finucane, H.K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228-1235 (2015).
54. de Leeuw, C.A., Mooij, J.M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
55. Barbeira, A.N. *et al.* Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat. Commun.* **9**, 1825 (2018).
56. Battle, A. *et al.* Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals. *Genome Res.* **24**, 14-24 (2014).
57. Yang, J., Lee, S.H., Goddard, M.E. & Visscher, P.M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76-82 (2011).
58. Yang, J. *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369-75, S1-3 (2012).
59. Loh, P.-R. *et al.* Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nat. Genet.* **47**, 284-290 (2015).
60. Locke, A.E. *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197 (2015).

61. Yang, J. *et al.* Genomic inflation factors under polygenic inheritance. *Eur. J. Hum. Genet.* **19**, 807-812 (2011).
62. Ioannidis, J.P., Ntzani, E.E., Trikalinos, T.A. & Contopoulos-Ioannidis, D.G. Replication validity of genetic association studies. *Nat. Genet.* **29**, 306-309 (2001).
63. Rathjen, T. *et al.* Regulation of body weight and energy homeostasis by neuronal cell adhesion molecule 1. *Nat. Neurosci.* **20**, 1096-1103 (2017).
64. Bacon, C. *et al.* Brain-specific Foxp1 deletion impairs neuronal development and causes autistic-like behaviour. *Mol. Psychiatry* **20**, 632-639 (2015).
65. Matsumoto, M. *et al.* An evolutionarily conserved G-protein coupled receptor family, SREB, expressed in the central nervous system. *Biochem. Biophys. Res. Commun.* **272**, 576-582 (2000).
66. Ku, G.M., Pappalardo, Z., Luo, C.C., German, M.S. & McManus, M.T. An siRNA screen in pancreatic beta cells reveals a role for Gpr27 in insulin production. *PLoS Genet.* **8**, e1002449 (2012).
67. Zhu, D. *et al.* Protein S controls hypoxic/ischemic blood-brain barrier disruption through the TAM receptor Tyro3 and sphingosine 1-phosphate receptor. *Blood* **115**, 4963-4972 (2010).
68. Cantagrel, V. *et al.* Mutations in the cilia gene ARL13B lead to the classical form of Joubert syndrome. *Am. J. Hum. Genet.* **83**, 170-179 (2008).
69. Thomas, S. *et al.* Identification of a novel ARL13B variant in a Joubert syndrome-affected patient with retinal impairment and obesity. *Eur. J. Hum. Genet.* **23**, 621-627 (2015).
70. Higginbotham, H. *et al.* Arl13b in primary cilia regulates the migration and placement of interneurons in the developing cerebral cortex. *Dev. Cell* **23**, 925-938 (2012).
71. Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539-542 (2016).
72. Morris, A.P. *et al.* Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* **44**, 981-990 (2012).
73. Teslovich, T.M. *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707-713 (2010).
74. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Series B Stat. Methodol.* **57**, 289-300 (1995).
75. Morikawa, T. *et al.* Prospective analysis of body mass index, physical activity, and colorectal cancer risk associated with beta-catenin (CTNNB1) status. *Cancer Res.* **73**, 1600-1610 (2013).
76. Laramie, J.M. *et al.* Polymorphisms near EXOC4 and LRGUK on chromosome 7q32 are associated with type 2 Diabetes and fasting glucose; the NHLBI Family Heart Study. *BMC Med. Genet.* **9**, 46 (2008).
77. Walford, G.A. *et al.* Genome-wide association study of the modified Stumvoll Insulin Sensitivity Index identifies BCL2 and FAM19A2 as novel insulin sensitivity loci. *Diabetes* **65**, 3200-3211 (2016).
78. Dhar, M.S., Yuan, J.S., Elliott, S.B. & Sommardahl, C. A type IV P-type ATPase affects insulin-mediated glucose uptake in adipose tissue and skeletal muscle in mice. *J. Nutr. Biochem.* **17**, 811-820 (2006).

79. Chenn, A. & Walsh, C.A. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* **297**, 365-369 (2002).
80. Waite, A., Brown, S.C. & Blake, D.J. The dystrophin–glycoprotein complex in brain development and disease. *Trends Neurosci.* **35**, 487-496 (2012).
81. Satz, J.S. *et al.* Distinct functions of glial and neuronal dystroglycan in the developing and adult mouse brain. *J. Neurosci.* **30**, 14560-14572 (2010).
82. Früh, S. *et al.* Neuronal dystroglycan is necessary for formation and maintenance of functional CCK-positive basket cell terminals on pyramidal cells. *J. Neurosci.* **36**, 10296-10313 (2016).
83. Berridge, K.C., Ho, C.Y., Richard, J.M. & DiFeliceantonio, A.G. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. *Brain Res.* **1350**, 43-64 (2010).
84. O'Connor, E.C. *et al.* Accumbal D1R neurons projecting to lateral hypothalamus authorize feeding. *Neuron* **88**, 553-564 (2015).
85. Spruston, N. Pyramidal neurons: dendritic structure and synaptic integration. *Nat. Rev. Neurosci.* **9**, 206-221 (2008).
86. Kim, J., Zhang, X., Muralidhar, S., LeBlanc, S.A. & Tonegawa, S. Basolateral to central amygdala neural circuits for appetitive behaviors. *Neuron* **93**, 1464-1479.e5 (2017).
87. Zhu, Z. *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun.* **9**, 224 (2018).