

Identifying tissues implicated in Anorexia Nervosa using Transcriptomic Imputation

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39 PhD 102,103, Claes Norring, PhD 104, Ioanna Ntalla, PhD 32, Julie O'Toole, MD 105, Jacques
40 Pantel, PhD 106, Hana Papezova, MD, PhD 75, Richard Parker, 92, Raquel Rabionet, PhD 107,
41 Anu Raevuori, MD, PhD 81, Andrzej Rajewski, MD, PhD 36, Nicolas Ramoz, PhD 108, N.William
42 Rayner, PhD 48,109,110, Ted Reichborn-Kjennerud, MD 111, Valdo Ricca, MD 101, Stephan
43 Ripke, MD, PhD 112, Franziska Ritschel, MSc 113, Marion Roberts, PhD 23,182, Alessandro
44 Rotondo, MD 114, Filip Rybakowski, MD, PhD 115, Paolo Santonastaso, MD 21, André Scherag,
45 PhD 116, Ulrike Schmidt, MD, PhD 23, Nicholas Schork, PhD 117, Alexandra Schosser, PhD 68,
46 Jochen Seitz, MD 63, Lenka Slachtova, PhD 75, P. Eline Slagboom, PhD 95, Margarita Slof-Op 't
47 Landt, PhD 118, Agnieszka Slopian, MD 119, Tosha Smith, PhD 65, Sandro Sorbi, MD 101, 120,
48 Eric Strengman, BS 121, Michael Strober, PhD 122, Patrick Sullivan, MD, FRANZCP 28,29, Jin
49 Szatkiewicz, PhD 65, Neonila Szeszenia-Dabrowska, MD, PhD 123, Ioanna Tachmazidou, PhD 48,
50 Elena Tenconi, MD 21, Laura Thornton, PhD 65, Alfonso Tortorella, MD 90,124, Federica Tozzi,
51 MD 125, Janet Treasure, PhD, FRCP, FRCPsych 23, Artemis Tsitsika, MD, PhD 126, Konstantinos
52 Tziouvas, MD, MSc 127, Annemarie van Elburg, MD, PhD 128,129, Eric van Furth, PhD 130,
53 Tracey Wade, PhD 131, Gudrun Wagner, Dr, MSc, DPO 68, Esther Walton, Dr. rer. nat., PhD
54 132,133, Hunna Watson, PhD 134,135,136, D.Blake Woodside, MD 137, Shuyang Yao, MSc, BSc
55 138, Zeynep Yilmaz, PhD 65, Eleftheria Zeggini, PhD 48, Stephanie Zerwas, PhD 65, Stephan
56 Zipfel, MD 139, Alfredsson Lars, PhD 22, Andreassen Ole, MD, PhD 140,141, Harald Aschauer,
57 MD 142, Jeffrey Barrett, PhD 143, Vladimir Bencko, MD, PhD 144, Laura Carlberg, MD 68, Sven
58 Cichon, PhD 145, Sarah Cohen-Woods, PhD 146, Christian Dina, PhD 147, Bo Ding, PhD 148,
59 Thomas Espeseth, PhD 140,141, James Floyd, PhD 149, Steven Gallinger, MD 76, Giovanni

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61 153, Antonio Julià, PhD 154, Lars Klareskog, MD 22, Stephanie Le Hellard, PhD 155, Marion
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64 MD, PhD 160,161,162,163,164, Dalila Pinto, PhD 165,166, Samuli Ripatti, PhD 81, Dan Rujescu,
65 MD 151,167, Stephen Scherer, PhD, FRSC 168, Laura Scott, PhD 169, Robert Sladek, MD
66 170,171, Nicole Soranzo, PhD 172,173,174, Lorraine Southam, BSc 48,110, Vidar Steen, MD,
67 PhD 155, Wichmann H-Erich, PhD 175, Elisabeth Widen, MD, PhD 176, Bernie Devlin, PhD 177,
68 Solveig K. Sieberts, PhD 178, Nancy Cox, PhD 179, Hae Kyung Im, PhD 180,179, Gerome Breen,
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Abstract

Anorexia nervosa (AN) is a complex and serious eating disorder, occurring in ~1% of individuals. Despite having the highest mortality rate of any psychiatric disorder, little is known about the aetiology of AN, and few effective treatments exist.

Global efforts to collect large sample sizes of individuals with AN have been highly successful, and a recent study consequently identified the first genome-wide significant locus involved in AN. This result, coupled with other recent studies and epidemiological evidence, suggest that previous characterizations of AN as a purely psychiatric disorder are over-simplified. Rather, both neurological and metabolic pathways may also be involved.

In order to elucidate more of the system-specific aetiology of AN, we applied transcriptomic imputation methods to 3,495 cases and 10,982 controls, collected by the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED). Transcriptomic Imputation (TI) methods approaches use machine-learning methods to impute tissue-specific gene expression from large genotype data using curated eQTL reference panels. These offer an exciting opportunity to compare gene associations across neurological and metabolic tissues. Here, we applied CommonMind Consortium (CMC) and GTEx-derived gene expression prediction models for 13 brain tissues and 12 tissues with potential metabolic involvement (adipose, adrenal gland, 2 colon, 3 esophagus, liver, pancreas, small intestine, spleen, stomach).

We identified 35 significant gene-tissue associations within the large chromosome 12 region described in the recent PGC-ED GWAS. We applied forward stepwise conditional analyses and FINEMAP to associations within this locus to identify putatively causal signals. We identified four independently associated genes; *RPS26*, *C12orf49*, *SUOX*, and *RDH16*. We also identified two further genome-wide significant gene-tissue associations, both in brain tissues; *REEP5*, in the dorso-lateral pre-frontal cortex (DLPFC; $p=8.52 \times 10^{-07}$), and *CUL3*, in the caudate basal ganglia ($p=1.8 \times 10^{-06}$). These genes are significantly enriched for associations with anthropometric phenotypes in the UK BioBank, as well as multiple psychiatric, addiction, and

306 appetite/satiety pathways. Our results support a model of AN risk influenced by both metabolic
307 and psychiatric factors.

Introduction

Anorexia nervosa (AN) is a serious neuropsychiatric disorder presenting with low body weight, a fear of weight gain or behaviours that interfere with weight gain, and a lack of recognition of the seriousness of the illness. AN has the highest mortality rate of any psychiatric disorder¹, and ranks among the leading cause of disability in young women worldwide. Despite this, little is known about the biological mechanisms underlying AN development, and few effective therapies and medications are available.

Findings from genetic and epidemiological research have encouraged broadening our conceptualization of the aetiology of AN beyond purely psychiatric causes to incorporate metabolic and other somatic factors in risk models. Recently, genome-wide association studies have revealed the first significantly associated genomic locus for anorexia nervosa², as well as a number of promising sub-threshold associations³⁻⁵, and intriguing pathway associations. Results have implicated genes with both psychiatric and metabolic relevance, while polygenic risk score analyses and LD-Score approaches have revealed significant genetic overlap with psychiatric, metabolic and autoimmune diseases, as well as anthropometric traits.

The research findings underscore clinical observations as individuals with AN have an uncanny ability to reach and maintain extraordinarily low body mass indices (BMI) and after successful renourishment, their bodies often quickly revert to what may be an abnormally low set point². Other observations include that individuals with AN tend to find eating aversive, and feelings of fullness unpleasant; dieting, restricting, and binge-purge behaviours tend to alleviate uncomfortable or painful associations with fullness in these individuals and reduce anxiety⁶. Although aversion to fullness and low appetite could be driven by dysfunction of neurobiological satiety pathways or altered levels of orexigenic hormones⁷, it is also possible that specific metabolic or gastric dysfunction enables and perpetuates dieting behaviours.

Transcriptomic Imputation (TI) provides an opportunity to test the involvement of metabolic, endocrine, adipose, and gastrointestinal (GI) tissues, as well as brain tissues, in the

development of AN. These approaches leverage well curated eQTL panels to create predictors of genetically regulated gene expression (GREX)⁸⁻¹⁰. These predictors may be applied to large groups of genotyped individuals, to identify case-control associations with predicted differential gene expression. This approach circumvents many of the complications inherent in traditional transcriptomic analysis; for example, the need to collect large number of inaccessible tissues, which is particularly complicated in studies of early-onset psychiatric disorders¹¹. Further, the prediction of genetically-regulated gene expression means that there is no ambiguity in direction of effect; unlike in RNA-seq studies, where changes in gene expression may result from medication, diet, exercise, or environmental exposures, genetically regulated gene expression necessarily precedes disease onset⁸.

An intriguing aspect of transcriptomic imputation is the opportunity to calculate predicted gene expression in a tissue-specific manner, and to use this to further inform our understanding of disease aetiology. In this study, we used gene expression predictor models for 13 brain regions (derived from CMC^{12,13} and GTEX^{8,14} data), as well as fifteen gastrointestinal, endocrine, and adipose tissues, and compared patterns of gene expression changes between cases and controls. We identified 37 significant gene-tissue associations, constituting eleven independent signals. These genes together explained 2.38% of the phenotypic variance in our study, including substantial proportions of variance explained by genes in brain tissues (51.5%), gastrointestinal tissues (16.01%), endocrine (18.6%), and adipose tissues (13.9%), supporting our theory of both psychiatric and metabolic contributions to AN risk. We identify genes with intriguing patterns of association with anthropometric traits; for example, seven of our gene-tissue associations are also significantly associated with BMI, weight, and waist circumference in the UK BioBank.

Methods

Samples

Genotype data were obtained from the PGC-ED collection. These data included 3,495 cases and 10,982 ancestry-matched controls². Detailed diagnostic criteria used are described in the PGC-ED GWAS of these data². Briefly, cases include individuals with lifetime diagnoses of either AN (including both binge-purge and restrictive subtypes) or “eating disorder not otherwise specified (EDNOS)”, AN subtype. A small number of individuals with bulimia nervosa diagnoses were also included if they also had histories of AN. Amenorrhoea was not required for diagnosis, as it does not increase diagnostic specificity^{15–17}. Exclusion criteria included schizophrenia, intellectual disability, and medical and neurological conditions which may cause weight loss.

Transcriptomic Imputation

We imputed genetically regulated gene expression (GREX) using the CommonMind Consortium derived Dorso-lateral pre-frontal cortex (CMC DLPFC) predictor database¹², as well as GTEx-derived predictor databases including 12 brain regions, four endocrine tissue, eight gastrointestinal/digestive tissues, and subcutaneous adipose tissue^{8,14} (Table 1). We imputed GREX in all cohorts for which we had access to raw data using PrediXcan⁸.

We tested for association between GREX and case-control status in each cohort separately, using a standard linear regression test in R. We included ten principal components as covariates to correct for population stratification. Principal components were calculated from genotype data. Raw genotype-based and summary-statistics based cohorts were meta-analysed using an odds-ratio based approach in METAL¹⁸.

Establishing a threshold for genome-wide significance

We applied two significance thresholds to our data. First, we applied a threshold for each tissue, correcting for the number of genes tested within that tissue (Table 1). Second, we applied a stricter, overall threshold, correcting for all genes tested across all tissues simultaneously (234,896 tests in total, $p=2.31 \times 10^{-7}$).

GREX is highly correlated across tissues^{14,19}, and consequently the tests across different tissues are not independent. A Bonferroni correction may therefore be overly conservative, and underestimate the true degree of association in this study.

Identifying independent associations

We identified a number of genomic regions with multiple associations, as well as genes with significant associations across multiple tissues. In particular, we identified a very large number of gene-tissue associations (35 significant gene-tissue associations), in the same chromosome 12 locus identified in a recent GWAS by the PGC-ED group²⁰.

We applied two methods to identified independent signals in these complex genomic regions. First, in regions with a small number of associated gene-tissue pairs (<5), we used “CoCo”, an extension to GCTA-CoJo²¹. Briefly, CoCo applies the same stepwise forward conditional analysis as in GCTA-CoJo, but allows specification of a custom linkage disequilibrium (LD) or correlation matrix instead of obtaining LD from a reference panel. Here, we calculated a GREX correlation matrix used this as the correlation matrix input to CoCo.

We used FINEMAP²², a shotgun stochastic search algorithm which identifies and ranks plausible causal configurations for a region, to disentangle the complex gene-tissue association patterns on chromosome 12. As for CoCo, we substituted a GREX correlation matrix in place of the standard LD-matrix input file. We constructed a 95% credible set from probable configurations specified by FINEMAP in order to identify significant gene-tissue associations within the region.

Additionally, we visually inspected patterns of correlation among the 35 gene-tissue associations in the chr12 locus using the ‘heatmap.2’ function in the ‘gplots’ R package²³, and identified distinct clusters of GREX within this heatmap using a dendrogram cut at height 4.

Proportion of variance explained by tissue

We calculated the proportion of phenotypic variance in our study jointly explained by all genes reaching $p < 1 \times 10^{-04}$ in our analysis. We corrected for ten principal components and study variables using a nested model.

We divided gene-tissue associations into four categories; brain, endocrine, gastrointestinal/digestive, and subcutaneous adipose tissue. We used a series of nested models to calculate the variance explained by gene-tissue associations for each category. For example, the amount of variance explained by adipose-gene associations was calculated as the difference between the variance explained by all genes, and the variance explained by all genes except those associated in adipose tissue (eqn 1).

Equation 1: Nested model to calculate proportion of variance explained by adipose tissue

$$\text{Var}_{\text{Adipose}} = \text{Var}_{\text{All genes}} - \text{Var}_{\text{All genes except adipose}}.$$

UK BioBank analysis

We obtained publicly available GWAS summary statistics for the UK BioBank sample^{24,25}. We analyzed summary statistics relating to three anthropometric traits; BMI (336,107 individuals), weight (in kg; 336,227 individuals), and waist circumference (in cm; 336,639 individuals). We obtained distributions of each trait from the UK BioBank search portal²⁶ (Suppl. Table 1).

Descriptions of phenotype curation, quality control, and association models used for the UK BioBank sample are available elsewhere²⁵. Briefly, quantitative traits within the sample were normalized using a rank-based inverse normal transform (INRT) prior to analysis, and analysis was carried out using a linear regression. Beta values from these associations correspond not to the 'unit' of the original trait (e.g., cm or kg), but to the 'unit' of the INRT, i.e., the standard deviation of the original trait distribution. We confirmed this by simulating distributions matching the UK Biobank traits in R, and performing an INRT on each trait.

We used MetaXcan²⁷, a summary statistic based software analogous to PrediXcan, to compute gene-tissue associations for genes with $p < 1 \times 10^{-04}$ in our prediXcan PGC-ED analysis. In order to compare association statistics between our PGC-ED and UK BioBank studies, we normalized betas to account for the variance of a gene's GREX within each study.

Pathway Analysis

Pathway analysis was carried out using an adaptation to MAGMA²⁸. We manually assigned prediXcan genic p-values to genes in order to carry out only the gene-set enrichment analysis in MAGMA. We used Bonferroni-corrected prediXcan p-values as input for our MAGMA analyses, in three stages; first, a Bonferroni-correction for the overall best p-value for each gene across tissues; second, for the best p-value across brain regions; third, for the best p-value across non-brain tissues.

We carried out two sets of pathway analysis. First, we tested a subset of pathways for which we had prior hypotheses of involvement with psychiatric disorders^{29,30}, as well as genesets related to orexigenic hormones, hunger, and satiety. Second, we carried out an agnostic pathway enrichment test including ~8,500 pathways obtained from publicly available databases, including KEGG^{31,32}, GO³³, REACTOME³⁴, PANTHER^{35,36}, BIOCARTA³⁷, and MGI³⁸. We included only gene sets with at least 10 genes. Gene set enrichment results from the “competitive” MAGMA analysis were used, and an FDR-correction applied within each stratum of our analysis.

Results

Association Tests

We calculated predicted gene expression for thirteen brain regions, four endocrine tissues, eight gastrointestinal and digestive tissue, and subcutaneous adipose tissue (derived from CMC and GTEx data^{8,14,19,39}) in 3,495 cases and 10,982 controls from the PGC-ED consortium, and tested for association between predicted gene expression (GREX) and case-control status.

We identified 37 significant gene-tissue associations, and a further 22 sub-threshold associations ($p < 1 \times 10^{-04}$; Suppl. Table 2). The majority of the significant associations (35/37) correspond to the only known genome-wide significant locus for AN²⁰. We used FINEMAP²² to identify independent signals within this region. We identified 12 likely gene-tissue associations within this region, including four unique genes; *SUOX*, *RPS26*, *RDH16*, and *C12orf49* (Suppl. Table 3). Visual inspection (Suppl. Figure 1) and hierarchical clustering (Suppl. Figure 2) of GREX correlation patterns within this region indicate three distinct groups of associated genes, and follow our FINEMAP results closely.

We identified two additional genome-wide significant gene-tissue associations (Table 2). First, a region on chromosome two with three gene-tissue associations; increased expression of *CUL3* in the caudate basal ganglia ($p = 1.86 \times 10^{-06}$), and increased expression of *WDFY1* and *FAM124B*, in adipose tissue ($p = 6.11 \times 10^{-05}$, 6.73×10^{-05} , respectively). We applied a stepwise forward conditional analysis in CoCo (following GCTA-COJO), using GREX correlations for all three genes (Suppl. Table 4). Neither adipose tissue association remained significant after conditioning on *CUL3*-Caudate ($p = 0.042$, 0.25 , respectively). Second, we identified decreased expression of *REEP5* in the DLPFC ($p = 8.34 \times 10^{-07}$), and in the adrenal gland ($p = 6.68 \times 10^{-05}$); conditioning *REEP5*-adrenal on *REEP5*-DLPFC completely ameliorates the signal ($p = 0.085$).

Additionally, we identified 22 sub-threshold associations ($p < 1 \times 10^{-04}$), including 17 independent associations after stepwise conditional analysis (Table 2). In particular, we identified two genes on chromosome 10 with decreased expression in the small intestine and colon (*MGMT*-small

intestine, *MGMT*-pituitary, and *FOXI2*-colon), and two genes with increased brain expression on chromosome 17 (Supplementary table 2; *YWHAE*-hypothalamus, *NTN1*-nucleus accumbens).

Comparing Tissue types

Jointly, the genetically regulated gene expression (GREX) of our 28 gene-tissue associations ($p < 1 \times 10^{-04}$) explain 2.38% of the phenotypic variance in our study. The majority of this variance (51.5%) was explained by brain-gene associations, followed by endocrine (18.6%), gastrointestinal/digestive (16.01%), and adipose tissues (13.9%).

Associations with anthropometry

We used publicly available GWAS summary statistics from the UK BioBank to test whether our AN associated genes were associated with anthropometric phenotypes such as BMI, weight, and waist circumference. We used a summary-statistics based approach analogous to predixcan⁴⁰ ("MetaXcan") to identify gene-tissue associations across all three traits, for all genes reaching $p < 1 \times 10^{-04}$ in our analysis.

Three genes within our chromosome twelve locus were significantly associated with at least one anthropometric phenotype in the UK BioBank sample (Table 3). The direction of effect was epidemiologically consistent with our predixcan analysis across all genes. For example, increased expression of *SUOX* in the colon, esophagus and spleen results in increased BMI (~ 0.04 BMI units/unit of gene expression; $p < 1.28 \times 10^{-07}$), increased weight (~ 0.135 kg/unit of gene expression; $p < 5.8 \times 10^{-08}$) in the UK BioBank, and decreased risk of AN in PGC-ED ($OR = 0.98$ /unit of gene expression; $p < 5 \times 10^{-07}$) (Figure 2A). Similarly, increased expression of *RPS26* and *RDH16* across multiple tissues is associated with increased AN risk, decreased BMI, decreased waist circumference, and decreased weight (Figure 2B).

Increased expression of *REEP5* is associated with increased weight ($p < 2 \times 10^{-08}$) and decreased AN risk. Three sub-threshold AN genes (*BARX1*, *MGMT*, *TRIM38*) are also associated with BMI ($p < 2 \times 10^{-13}$), weight ($p < 2 \times 10^{-07}$), and waist circumference ($p = 1.35 \times 10^{-08}$), again with highly

significant concordance of direction of effect between studies. Three sub-threshold associated genes, *BARX1*, *MGMT*, *TRIM38*, also follow this pattern of association.

This degree of shared signal and concordance of direction of effect is highly unlikely to occur by chance (binomial test $p=2.39 \times 10^{-270}$). Interestingly, of the seven genes within our study that are associated with BMI, weight, and waist circumference within the UK BioBank, six are associated with AN in gastrointestinal tissues. The only brain-tissue based associated gene, *REEP5*, is an olfactory gene with a potential role in taste and appetite. Although it is difficult to draw firm conclusions given the small set of genes tested and the limited sample size of our study, these results suggest that gene expression changes in metabolic tissues are more likely to have general relevance for anthropometry and weight maintenance.

Pathway analysis

We performed pathway analyses on our AN prediXcan results across (1) all tissues, (2), brain tissues, and (3) all non-brain tissues. For each set of results, we tested 174 gene sets with prior hypotheses for involvement in psychiatric disorders, and ~8,500 pathways obtained from publicly available databases.

Using the best p-value across all tissues, we identified 17 significantly enriched pathways (fdr-corrected $p\text{-value} < 0.05$; Table 4). These include multiple calcium-gated voltage channel pathways ($p < 0.002$), axon guidance ($p = 1.07 \times 10^{-04}$), Wnt signalling (9.93×10^{-04}), the post-synaptic density (0.003), targets of the FMRP protein⁴¹⁻⁴⁵ ($p = 0.003$), as well as gene sets corresponding to neurological disease such as Alzheimer's, Huntington's, and Prion Disease ($p < 0.007$). We also noted enrichment of a pathway related to circadian entrainment ($p = 0.0013$).

Interestingly, genes involved in synthesis secretion and deacylation of ghrelin were significantly enriched within our results ($p = 0.0011$). Examining individual genes within this pathway indicates that no single gene is driving the association; rather, the pathway includes multiple

sub-threshold associations across *KLF4*, *BCHE*, *IGF1*, *SPCS2*, *ACHE*, *PCKS1*, and *SPSC3*. Taken together, these associations indicate lower baseline ghrelin expression in individuals with AN than in controls. For example, AN cases have lower GREX of *KLF4*, *SPCS2* and *SPCS3*, all of which stimulate ghrelin secretion⁴⁶. AN cases also have increased expression of *ACHE*, *IGF1*, *PCKS1*, and *BCHE*, which inhibit ghrelin expression⁴⁷⁻⁴⁹. We also noted that GREX of ghrelin (GHRL) was lower in AN cases than controls across 11/12 tissues tested.

Using exclusively brain-gene association statistics as an input to our MAGMA analysis resulted in 51 significantly enriched pathways. 35/51 pathways were from the hypothesis-driven test; these included circadian entrainment ($p=2.6 \times 10^{-04}$), addictive behaviors (nicotine, alcohol, cocaine, and morphine dependence, $p<0.0045$), calcium-gated voltage channels, and a large number of pathways related to processes in the post-synaptic density (Table 4), in line with pathway results from other psychiatric disorders^{10,30,50,51}. A further 25 significantly enriched pathways were identified in the agnostic analysis, including further evidence of circadian entrainment ($p=1.39 \times 10^{-06}$), long-term potentiation ($p=4.44 \times 10^{-06}$), as well as multiple pathways implicating ear and neuronal system development in mice ($p<1.2 \times 10^{-04}$). We noted enrichment in cyclic-AMP metabolism pathways ($p<9.3 \times 10^{-05}$). This pathway includes dopamine receptor gene *DRD1* ($p=8.85 \times 10^{-05}$), and *DRD5* ($p=3.5 \times 10^{-04}$), two receptors which are part of the dopaminergic pathways affected by ghrelin in the VTA and nucleus accumbens^{52,53}, as well as *GCG* (Glucagon; $p=1.3 \times 10^{-03}$), and *APOE* ($p=1.0 \times 10^{-03}$) which is associated with risk for Alzheimer's disease. CREB phosphorylation through activation of CaMKII pathway was enriched in our results ($p=5.25 \times 10^{-05}$). This pathway includes *AKAP9* ($p=2.1 \times 10^{-04}$), which regulates levels of cAMP activity in the brain, and co-localizes with NMDA receptor NR1 which in certain brain regions is involved in appetite and weight regulation⁵⁴⁻⁵⁶, as well as *GRIN2B* ($p=5.1 \times 10^{-04}$), which is associated with neurite outgrowth and risky decision making^{57,58}.

Excluding brain-gene associations statistics from our pathway analysis results in only one subthreshold association ($p=3.2 \times 10^{-04}$; *fdr*-corrected *p*-value 0.06) in our hypothesis-driven pathway analysis, concerning circadian rhythms (albeit through a different pathway than

identified in the brain-only analysis). Our agnostic pathway analysis identified only one significant association, with hyaluronic acid binding ($p=2.32 \times 10^{-08}$).

Discussion

AN is a complex and serious neuropsychiatric disorder, with one of the highest mortality rates of any psychiatric disorder. As our research into the aetiology of AN develops and grows, we identify increasing levels of complexity and heterogeneity; for example, recent GWAS studies, LD Score analysis, and epidemiological evidence indicates both psychiatric and metabolic risk factors for the disorder.

Here, we used gene expression prediction models for brain, gastrointestinal/digestive, endocrine, and adipose tissues to predict genetically regulated gene expression (GREX) in 3,495 individuals with anorexia nervosa (AN) and 10,982 controls. We identified 12 independent gene-tissue associations reaching tissue-specific significance, the majority of which lie in the same chromosome 12 locus identified in a recent AN GWAS²⁰. In line with our hypothesis of both psychiatric and metabolic risk having a role in AN, we identified genes with differential expression in endocrine and gastrointestinal/digestive tissues, as well as in brain.

We calculated the phenotypic variance explained by the genetically regulated expression of these 28 genes, and used a nested model to partition the variance according to tissue type. Jointly, these explain 2.38% of the phenotypic variance in our study. The majority of this variance (51.5%) was explained by brain-gene associations, followed by endocrine (18.6%), gastrointestinal/digestive (16.01%), and adipose tissues (13.9%). The proportion of variance explained by brain- and endocrine-gene associations is in line with the proportion of tests carried out in each tissue (46.3% and 16.8%, respectively). Gastrointestinal/digestive genes explain significantly less variance than we would expect given the large proportion of test performed (16.01% vs. 32.3%, binomial test, $p=3.6 \times 10^{-04}$), while adipose tissue-genes explain significantly more variance than we would expect (13.9% vs. 4.6%, $p=2 \times 10^{-04}$). This enrichment of signal within adipose tissue is of particular interest given the demonstrated overlap between adiposity and disordered eating patterns⁵⁹, AN risk factors^{60–62}, and clinical outcomes^{63,64}, as well as our findings relating AN risk genes to anthropometric traits in the UK Biobank.

However, these calculations are based on the assumption that all gene-tests are independent; in fact, we note high correlation of GREX between tissues, including a large number of co-linear genes and tissues. The number of independent tests carried out is therefore likely to be substantially lower than the number of tests used in our estimate, perhaps explaining why gastrointestinal/digestive genes explain less variance than we would expect.

Among our gene-tissue associations are a number of genes which may be of particular interest. For example, decreased expression of *REEP5* in the DLPFC is associated with increased risk of AN. *REEP5* is a receptor accessory protein which promotes expression of olfactory receptors⁶⁵. *Reep5*, together with *RTP1* and *RTP2*, is required for cell surface expression of odorants, and is primarily expressed in olfactory neurons. The DLPFC has a high localized concentration of olfactory neurons, and DLPFC volume is decreased in anosmic individuals⁶⁶. Olfaction is of particular interest in eating disorders given its role in taste and desire for food, as well as in a number of neurological disorders such as Alzheimer's and Parkinson's^{67,68}. Individuals with AN have high rates of reported hyposmia and anosmia^{67,69-72}, and perform poorly in odor discrimination tests, compared to healthy controls. Importantly, odor discrimination ability and hyposmic status correlates more strongly with BMI than with any specific disordered eating behavior, even among individuals with AN⁷³. Previous studies have also demonstrated differential expression of olfactory genes following eight restoration in individuals with Anorexia Nervosa⁷⁴. In line with this, we identified a direct correlation between *REEP5* expression and body weight in the UK BioBank; each additional unit of gene expression corresponds to ~140 g additional body weight, and an AN OR of 0.85. Taken together these results suggest that *REEP5* may have a general role in body size and BMI through altered olfactory cues, and may be of interest to researchers studying appetite and satiety, as well as obesity, normal variation in BMI, and AN. *REEP5* has also been implicated in major depressive disorder and antidepressant response in previous studies⁷⁵.

We identified four significantly associated genes within our complex chromosome 12 locus. Three of these genes (*SUOX*, *RPS26*, *RDH16*) are significantly associated with AN across a range of gastrointestinal tissues (Figure 1), and have highly correlated expression across almost all

non-brain tissues tested. All three of these genes are significantly correlated with anthropometric traits in the UK BioBank analysis (Figure 2), and all have consistent directions of effects with our AN prediXcan analysis: that is, the change in expression which increases body size also decreases AN risk.

Little is known about the function of *C12orf49*, the fourth gene in this locus, although SNPs within the gene have also previously been associated with BMI, waist circumference, and waist-hip ratio⁷⁶. Taken together, this evidence implies that the locus on chromosome 12 is likely to be generally associated with BMI and body size, rather than any specific eating disordered behaviours. The fine-mapping and characterization of this locus supports our hypothesis of a role for metabolic dysregulation in AN.

Increased expression of *CUL3* (Cullin 3) in the caudate basal ganglia was associated with increased risk of AN in our study (OR=1.07). Dysregulation of *CUL3* is associated with pseudohypoaldosteronism⁷⁷, a disorder characterized by sodium imbalance in the body and often presenting with low body weight. Mutations in *CUL3* are associated with schizophrenia⁷⁸, autism⁷⁹ and non-response to anti-depressants⁸⁰. Variants lying near to *CUL3* were identified in the first GWAS of AN, although these did not reach genome-wide significance⁸¹.

Among our subthreshold gene-tissue associations, we identified a number of genes previously associated with psychiatric^{13,78} and neurological disorders (for example, *FURIN*^{13,78,82}, *ADAMTS9*⁸³⁻⁸⁶, *MGMT*^{86,87}, *SMDT1*⁷⁸, *TMEM108*⁸⁸), as well as with abnormal behavioural responses in knock-out mice models^{38,89-91} (*ADAMTS9*, *CITED4*, *FOXI2*, *FURIN*, *SMDT1*, *TMEM108*). We also noted a number of genes with prior associations with anthropometric traits, both in humans (*ADAMTS9*^{92,92-96}, *MGMT*^{94,97,98}) and in mice^{38,89-91} (*CITED4*, *FOXI2*, *FURIN*, *RDH16*, *SMDT1*, *TMEM108*), as well as genes associated with gastric and esophageal complaints (*BARX1*⁹⁹) in humans, and abnormal defecation patterns in mice^{38,89-91,100} (*RDH16*, *CITED4*), and with disorders and traits known to be comorbid with AN (*TMEM108*¹⁰¹⁻¹⁰⁴).

Our pathway analysis identified a large number of significantly enriched pathways. In particular, multiple pathways indicate a role for the post-synaptic density (including PSD95, targets of the FMRP protein, glutamate receptor genes, among others), which has previously been implicated in other psychiatric disorders. Four pathways are associated with addiction and addictive behaviours, including nicotine addiction, alcoholism, cocaine addiction, and amphetamine addiction. Illicit drug use is significant enriched among individuals with eating disorders, in particular AN¹⁰⁵, although this is, to our knowledge, the first study identifying shared genetic risk factors.

Circadian entrainment and clock genes are highly enriched among our data. Longstanding hypotheses implicated disrupted circadian rhythms in a range of mood disorders, particularly depression and bipolar disorder^{106–108}. Further, behavioural patterns in individuals with AN (for example excessive exercise^{109–111} and lack of sleep) have long provided epidemiological evidence for circadian rhythm disruption in AN. Circadian rhythms may also have a role is regulating appetite and satiety pathways^{7,112,113}.

Our analysis also implicates pathways concerning taste and olfactory transduction, as well as ghrelin secretion. Ghrelin is an orexigenic hormone with a documented role in appetite and satiety^{114–118} as well as in gut motility^{117–119}. Our results suggest that individuals with AN may have decreased circulating ghrelin levels due to increased genetically regulated expression of ghrelin inhibitors, and decreased GREX of Ghrelin stimulators. Ghrelin enhances appetite and increases food intake in humans; lowered baseline circulating ghrelin levels may begin to explain decreased hunger and desire for food in individuals with AN. Previous studies have documented dysregulation of ghrelin, leptin and glucagon in individuals with AN¹²⁰. However, these studies are by definition performed after long periods of starvation or food restriction, meaning that causation is difficult to disentangle from consequences of eating disordered behaviours; it is likely that the increased ghrelin levels seen in these studies is a consequence of long-term fasting, rather than causative. In this study, we assess only genetically regulated gene expression (GREX), meaning that any associations identified are not affected by diet or

environment. Instead, these results may indicate an altered “baseline” level of circulating ghrelin in individuals with AN.

There are a number of limitations that should be taken into account. First, the sample size of our study is small, especially compared to GWAS sample sizes in other psychiatric disorders^{121,122}. It is likely that increasing sample size substantially will yield many new insights into the aetiology of anorexia nervosa, and that current sub-threshold associations may lose significance as sample size increases. Similarly, transcriptomic imputation approaches rely on large, well-curated reference panels in order to build GREX predictor models; here, we have used reference panels constructed from GTEx^{8,14} and CommonMind Consortium data^{10,13}, including the largest collections of publicly available post-mortem brain tissues. We have shown previously that there is a significant correlation between the sample sizes used to construct these predictors and the number of genes included in each predictor database, and that a number of these databases are therefore likely underpowered¹⁰.

Our analysis highlights the need for greater investigation into the complex aetiology of anorexia nervosa. Transcriptomic Imputation allows us to identify significant gene-tissue associations with anorexia nervosa, and indicates an excess of signal in adipose tissue. It is clear from these results that both psychiatric and metabolic risk factors play a role in AN risk; these factors should be carefully considered in the design of future studies, as well as in how AN is perceived and considered by clinicians treating individuals with AN.

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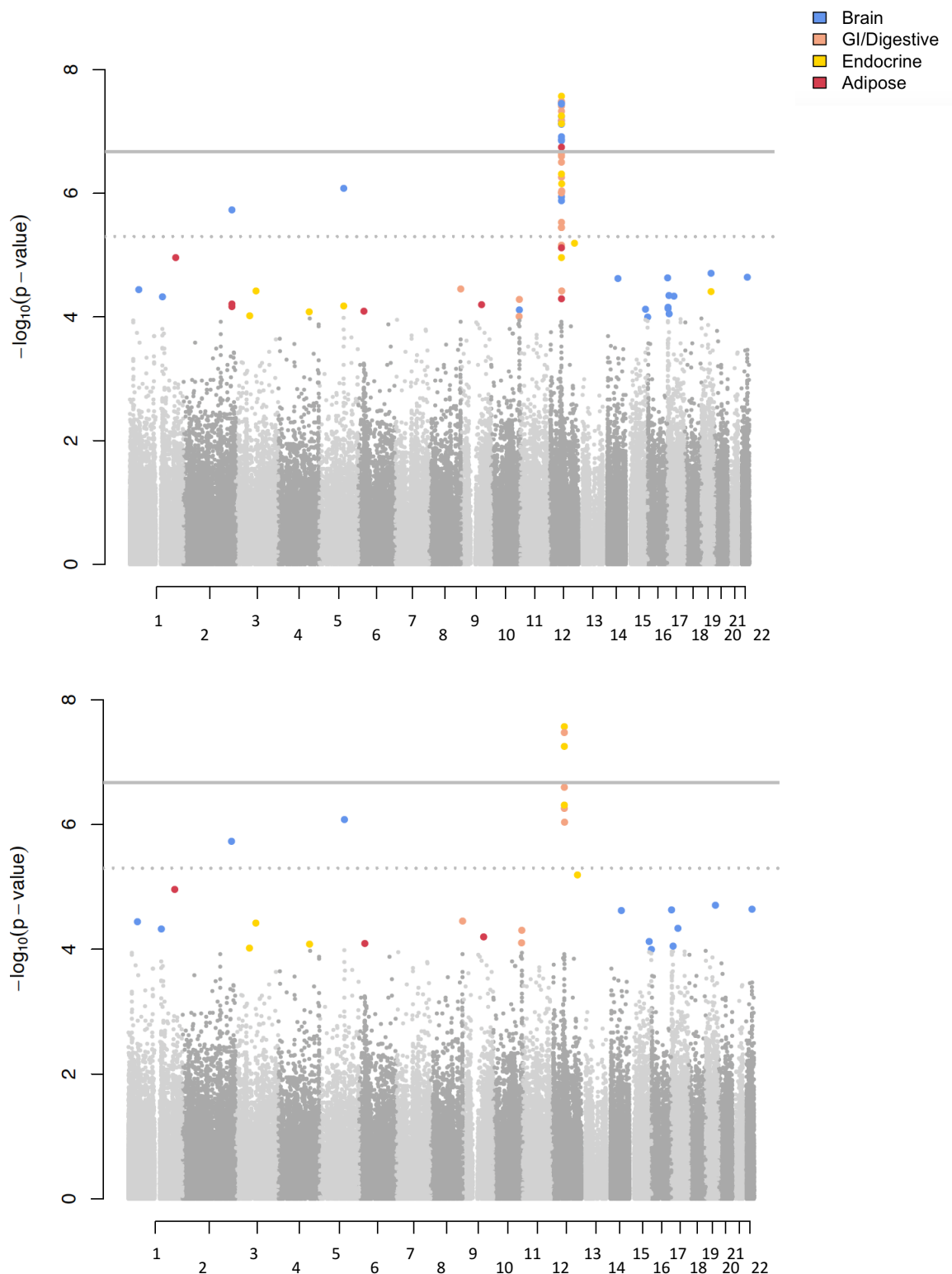
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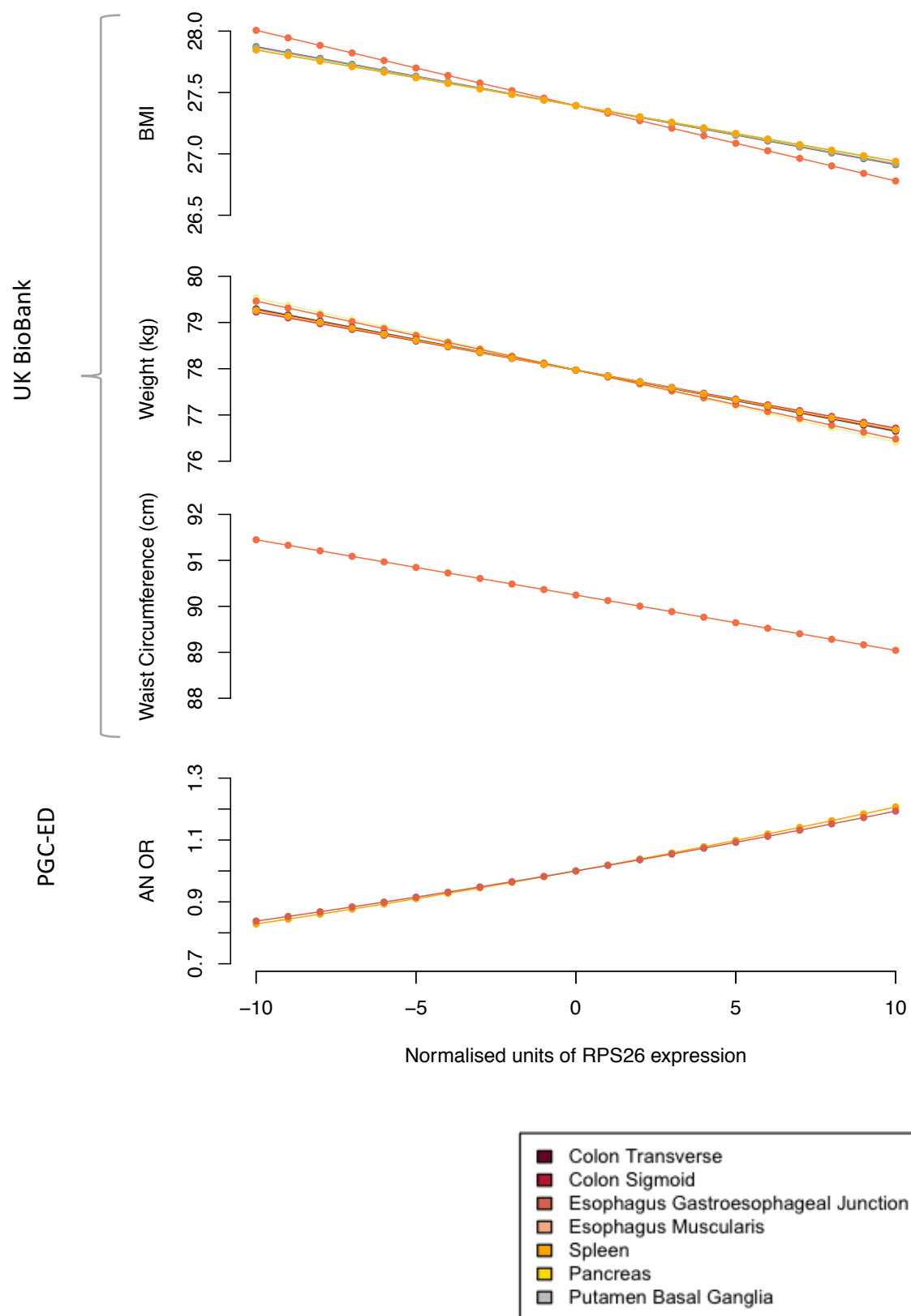


Figure 2A: Genetically regulated expression of *RPS26* is significantly associated with BMI, weight and waist circumference in the UK BioBank, and with AN in PGC-ED

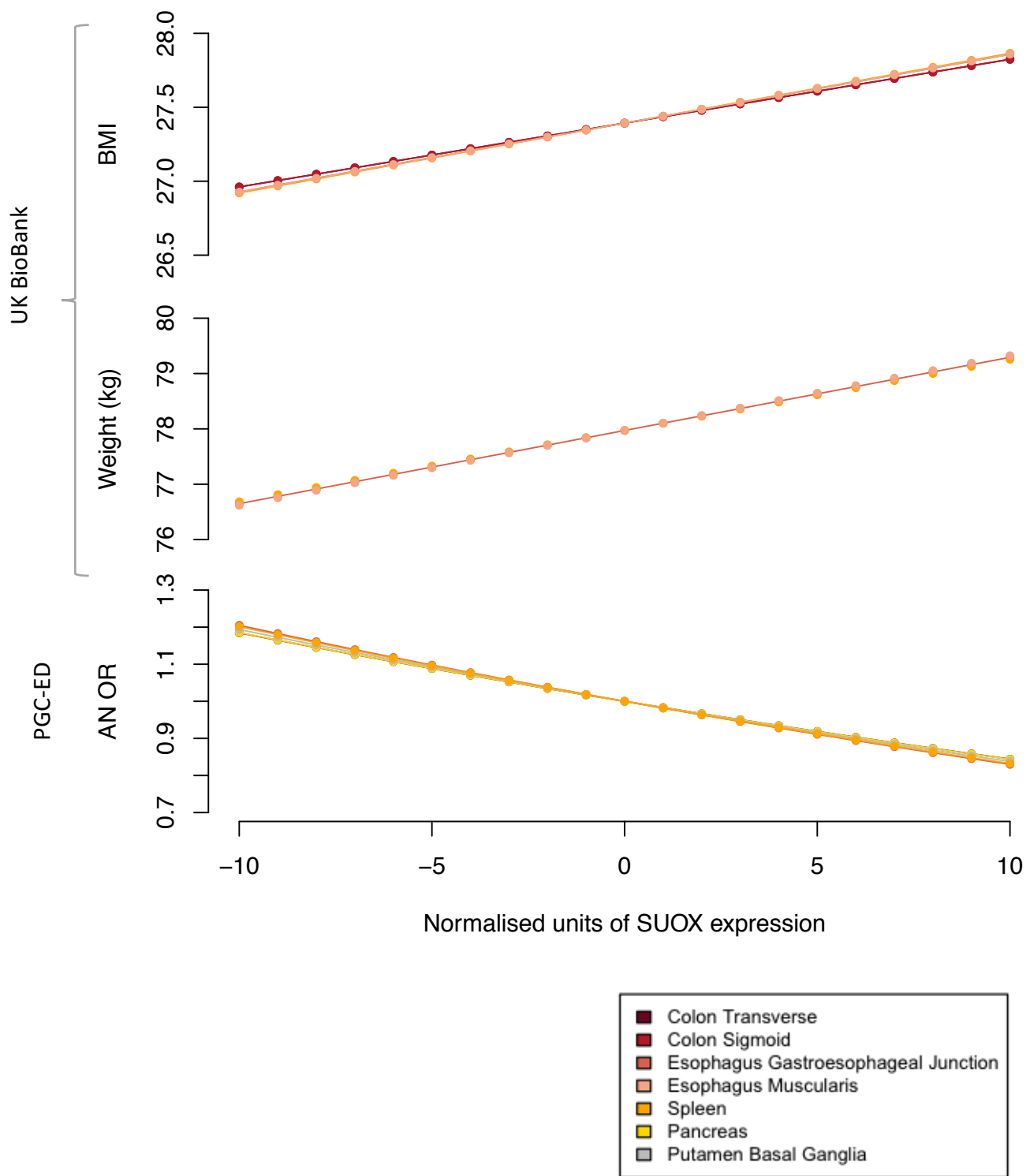


Figure 2B: Genetically regulated expression of *SUOX* is significantly associated with BMI and weight in the UK BioBank, and with AN in PGC-ED

Tissue	Source	Ngenes	P-val threshold
Adipose Subcutaneous	GTEX	10861	4.60E-06
Adrenal Gland	GTEX	9222	5.42E-06
Anterior Cingulate Cortex BA24	GTEX	8717	5.74E-06
Caudate Basal Ganglia	GTEX	9113	5.49E-06
Cerebellar Hemisphere	GTEX	9441	5.30E-06
Cerebellum	GTEX	9983	5.01E-06
Colon Sigmoid	GTEX	9323	5.36E-06
Colon Transverse	GTEX	9464	5.28E-06
Cortex	GTEX	9132	5.48E-06
DLPFC	CMC	9571	5.22E-06
Esophagus Gastroesophageal Junction	GTEX	9306	5.37E-06
Esophagus Mucosa	GTEX	10700	4.67E-06
Esophagus Muscularis	GTEX	10336	4.84E-06
Frontal Cortex BA9	GTEX	9009	5.55E-06
Hippocampus	GTEX	8510	5.88E-06
Hypothalamus	GTEX	8555	5.84E-06
Liver	GTEX	8528	5.86E-06
Nucleus Accumbens Basal Ganglia	GTEX	8887	5.63E-06
Pancreas	GTEX	9732	5.14E-06
Pituitary	GTEX	9138	5.47E-06
Putamen Basal Ganglia	GTEX	8728	5.73E-06
Small Intestine Terminal Ileum	GTEX	8838	5.66E-06
Spleen	GTEX	9324	5.36E-06
Stomach	GTEX	9352	5.35E-06
Thyroid	GTEX	11126	4.49E-06
		234896	2.13E-07

gene	gene name	tissue	beta	se	p	dirs
ENSG0000001	CITED4	Putamen Bas	0.021	0.0051	3.63E-05	+++++-----+
ENSG0000001	LYSMD1	Cerebellar Hc	-0.068	0.0166	4.78E-05	+++-----
ENSG0000001	VASH2	Adipose Sub	-0.152	0.0345	1.10E-05	-----+--+
ENSG0000000	CUL3	Caudate Bas	0.072	0.0151	1.86E-06	+-----+
ENSG0000001	ADAMTS9	Adrenal Glan	0.078	0.02	9.56E-05	+++-----+
ENSG0000001	ARL13B	Pancreas	0.382	0.0929	3.84E-05	+++-----+
ENSG0000001	INPP4B	Pancreas	-0.160	0.0407	8.30E-05	-----+--+
ENSG0000001	REEP5	DLPFC	-0.160	0.0325	8.34E-07	-----++-
ENSG0000001	TRIM38	Adipose Sub	0.091	0.0231	8.05E-05	+++++-----+
ENSG0000001	FBXL6	Liver	-0.133	0.0323	3.58E-05	-----+--+
ENSG0000001	BARX1	Adipose Subc	0.085	0.0211	6.38E-05	+++++-----+
ENSG0000001	FOXI2	Colon Transv	-0.650	0.1667	9.73E-05	-----+--
ENSG0000001	MGMT	Small Intestir	-0.031	0.0076	5.22E-05	-----+---
ENSG0000001	RPS26	Spleen	0.120	0.0215	2.70E-08	+++++-----+
ENSG0000001	SUOX	Esophagus G	-0.059	0.0107	3.41E-08	-----+---
ENSG0000001	SUOX	Spleen	-0.053	0.0098	5.61E-08	-----+---
ENSG0000001	SUOX	Putamen Bas	-0.077	0.0147	1.42E-07	-----+---
ENSG0000001	RPS26	Esophagus G	0.141	0.0274	2.54E-07	+++++-----+
ENSG0000001	SUOX	Pancreas	-0.035	0.007	4.95E-07	-----+---
ENSG0000001	SUOX	Colon Transv	-0.059	0.0117	5.47E-07	-----+---
ENSG0000001	RDH16	Small Intestir	0.098	0.0199	9.09E-07	+++-----+
ENSG0000001	C12orf49	Thyroid	0.352	0.0779	6.49E-06	-----+---
ENSG0000001	FURIN	Putamen Bas	0.114	0.0287	7.64E-05	+++-----+
ENSG0000000	CTNS	Hippocampu	0.028	0.0071	6.90E-05	+++-----+
ENSG0000000	NTN1	Nucleus Accu	0.395	0.1008	8.88E-05	+++-----+
ENSG0000001	TMEM108	Cortex	0.602	0.1475	4.47E-05	+++-----+
ENSG0000001	YWHAE	Hypothalamu	0.050	0.0119	2.37E-05	+++++-----+
ENSG0000000	ZNF207	Anterior Cing	-0.026	0.0063	4.55E-05	-----+---
ENSG0000002	ZNF225	Spleen	0.104	0.0252	3.92E-05	+++++-----+
ENSG0000001	ZNF235	Frontal Corte	0.433	0.1014	1.96E-05	+++-----+
ENSG0000001	SMDT1	Cerebellar Hc	0.018	0.0043	2.29E-05	+++-----+

chr	pos1	pos2
1	41326729	41328018
1	151132224	151138424
1	213123862	213165379
2	225334867	225450110
3	64501333	64673676
3	93698983	93774512
4	142944313	143768585
5	112212084	112258236
6	25963030	25987384
8	145579091	145583036
9	96713905	96717654
10	129535499	129539450
10	131265448	131566271
12	56435637	56438116
12	56390964	56400425
12	56390964	56400425
12	56390964	56400425
12	56435637	56438116
12	56390964	56400425
12	56390964	56400425
12	57345219	57353158
12	117153593	117175875
15	91411822	91426688
17	3539762	3564836
17	8924859	9147317
17	8076555	8079717
17	1247566	1303672
17	30677136	30708905
19	44616334	44637027
19	44732882	44809199
22	42475695	42480288

Weight	ENSG0000001 RDH16
Weight	ENSG0000001 REEP5
Weight	ENSG0000001 REEP5
Weight	ENSG0000001 REEP5
Weight	ENSG0000001 REEP5
Weight	ENSG0000001 REEP5
Weight	ENSG0000001 RPS26
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Weight	ENSG0000001 SUOX
Weight	ENSG0000001 SUOX
Weight	ENSG0000001 SUOX
Weight	ENSG0000001 TRIM38
Weight	ENSG0000001 TRIM38

Tissue	Z	Beta	P
Colon-Transverse	-7.7773617	-0.0738614	7.41E-15
Artery-Coronary	-7.375406	-0.0468271	1.64E-13
SmallIntestine-TerminalIleum	-6.4889742	-0.0593701	8.64E-11
Heart-AtrialAppendage	-7.5878365	-0.0824355	3.25E-14
Breast-MammaryTissue	-6.3491046	-0.0346515	2.17E-10
Skin-SunExposed-Lowerleg	-6.2404842	-0.0575258	4.36E-10
Cells-EBV-transformedlymphocytes	-6.0618266	-0.0634271	1.35E-09
Adipose-Subcutaneous	-5.9677586	-0.0508896	2.41E-09
DLPFC	-5.8095616	-0.0229857	6.26E-09
Liver	-5.6989127	-0.0674398	1.21E-08
Lung	-5.626001	-0.0401266	1.84E-08
Spleen	-5.58502	-0.058693	2.34E-08
Skin-NotSunExposed-Suprapubic	5.85012331	0.02616247	4.91E-09
Spleen	5.84007447	0.02813843	5.22E-09
Esophagus-Muscularis	5.74811528	0.03123837	9.02E-09
Esophagus-GastroesophagealJunction	5.74185611	0.03005111	9.36E-09
Cells-EBV-transformedlymphocytes	5.43805266	0.0320962	5.39E-08
Skin-SunExposed-Lowerleg	5.31919323	0.02376405	1.04E-07
Colon-Sigmoid	5.3137019	0.04097991	1.07E-07
Ovary	5.29633119	0.0319386	1.18E-07
Colon-Transverse	5.28102353	0.03099286	1.28E-07
Thyroid	5.2735135	0.02241977	1.34E-07
Pancreas	5.21840847	0.03451622	1.80E-07
Colon-Transverse	-5.6792371	-0.0484106	1.35E-08
Artery-Coronary	-5.2353944	-0.0297862	1.65E-07
Heart-AtrialAppendage	-5.9156355	-0.0575675	3.31E-09
Stomach	6.03116147	0.01516222	1.63E-09
Adipose-Subcutaneous	5.8432158	0.01219944	5.12E-09
Heart-LeftVentricle	5.75450038	0.01803554	8.69E-09
Liver	5.618464	0.02565575	1.93E-08
Thyroid	5.5459707	0.01493591	2.92E-08
Esophagus-Mucosa	5.48046854	0.0136585	4.24E-08
Testis	5.41629516	0.01918677	6.08E-08
Colon-Transverse	5.40371016	0.01607542	6.53E-08
Esophagus-Muscularis	5.31591259	0.01452058	1.06E-07
Brain-Nucleusaccumbens-basalganglia	5.31093287	0.02756249	1.09E-07
WholeBlood	5.28285769	0.01756255	1.27E-07
Nerve-Tibial	5.27563136	0.01348915	1.32E-07
Brain-Anteriorcingulatecortex-BA24	5.26659324	0.0193856	1.39E-07
Skin-SunExposed-Lowerleg	5.24941963	0.01402023	1.53E-07
AdrenalGland	5.20926148	0.01385548	1.90E-07

SmallIntestine-TerminalIleum	-5.8900719	-0.0474498	3.86E-09
Artery-Tibial	6.11566191	0.03833574	9.62E-10
WholeBlood	5.73480599	0.08610324	9.76E-09
Skin-NotSunExposed-Suprapubic	5.63609068	0.03540437	1.74E-08
Esophagus-Mucosa	5.63078519	0.04224336	1.79E-08
Testis	5.52861547	0.0502847	3.23E-08
Breast-MammaryTissue	-6.530904	-0.0315872	6.54E-11
Skin-SunExposed-Lowerleg	-6.2850329	-0.0513608	3.28E-10
Heart-AtrialAppendage	-6.2593475	-0.0602814	3.87E-10
DLPFC	-5.5731241	-0.019474	2.50E-08
Liver	-5.4913367	-0.0573873	3.99E-08
Spleen	-5.4182093	-0.0502923	6.02E-08
Cells-EBV-transformedlymphocytes	-5.4039068	-0.0498926	6.52E-08
Adipose-Subcutaneous	-5.2552273	-0.0399848	1.48E-07
Brain-Anteriorcingulatecortex-BA24	6.41507712	0.04309815	1.41E-10
Skin-NotSunExposed-Suprapubic	6.03928432	0.02410321	1.55E-09
Cells-EBV-transformedlymphocytes	5.9137031	0.03136303	3.35E-09
Heart-LeftVentricle	5.80708153	0.04596199	6.36E-09
Esophagus-Muscularis	5.68045296	0.02726121	1.34E-08
Esophagus-GastroesophagealJunction	5.55841118	0.02569696	2.72E-08
Spleen	5.42427892	0.02307607	5.82E-08
Thyroid	7.79117755	0.02939098	6.64E-15
Pancreas	7.34532675	0.0430497	2.05E-13

SET	NGENES	COMP P	FDR	
ANABOLIC STEROIDS		34	0.0011139	0.08075775
PROGESTOGENS		44	0.00089785	0.08075775
Polycystic ovary syndrome		14	2.84E-05	0.0040274
Schizophrenia, schizoaffective disorder or bipolar disorder		33	0.00027732	0.01968972
LDL cholesterol		116	0.00052673	0.02493189
Hemoglobin		35	0.0013392	0.03803328
Sex hormone-binding globulin levels		26	0.0012608	0.03803328
Fasting glucose-related traits		31	0.0052364	0.05724238
Fibrinogen		35	0.0050973	0.05724238
Hematocrit		35	0.0030755	0.05724238
Hematology traits		33	0.0052405	0.05724238
Mean corpuscular volume		56	0.0036234	0.05724238
Non-albumin protein levels		12	0.0044993	0.05724238
Protein C levels		13	0.004335	0.05724238
Schizophrenia or bipolar disorder		26	0.0044133	0.05724238
Iron status biomarkers		24	0.0057116	0.05793194
Cardiovascular disease risk factors		35	0.0074585	0.07060713
Mean corpuscular hemoglobin		59	0.010082	0.08947775
Cav2::modulators & sma...		20	6.75E-05	0.01012985
Axon guidance		119	0.00010663	0.01012985
MID		10409	0.00020205	0.0127965
HIGH		2715	0.00056599	0.0253175
Wnt signaling pathway		134	0.00099255	0.0253175
Prion diseases		33	0.0010036	0.0253175
Cav2::ion channels tra...		43	0.0010086	0.0253175
	701224	16	0.001066	0.0253175
Circadian entrainment		94	0.0012742	0.02689978
Cav2::ion channels tra...		36	0.0020532	0.0390108
Huntington's disease		163	0.0027021	0.04620483
ARC+NMDAR+PSD95+mGluR5		122	0.0029182	0.04620483
FMRP-targets		735	0.0032083	0.04689054
MAPK signaling pathway		239	0.004037	0.05478786
Gap junction		86	0.0062529	0.07862759
Nucleus		127	0.0068123	0.07862759
Alzheimer's disease		148	0.0070351	0.07862759

ANALYSIS

Brain RegionDrug targets

Brain RegionDrug targets

Brain RegionGWAS gene sets

Brain RegionGWAS gene sets

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Brain RegionGWAS gene sets

Brain RegionGWAS gene sets

Brain RegionGWAS gene sets

Brain RegionGWAS gene sets

Brain RegionHypothesis Driven

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GENE SET	NGENES
ANTIEPILEPTICS	221
OTHER DERMATOLOGICAL PREPARATIONS	204
Mean corpuscular volume	56
Polycystic ovary syndrome	14
Sex hormone-binding globulin levels	26
Mean corpuscular hemoglobin	59
Lipid metabolism phenotypes	35
Dehydroepiandrosterone sulphate levels	29
LDL cholesterol	116
Calcium levels	17
Hematology traits	33
Circadian entrainment	94
Cav2::modulators & sma...	20
HIGH	2714
Long-term potentiation	62
Gap junction	86
Nicotine addiction	35
FMRP-targets	735
Alcoholism	151
Retrograde endocannabi...	94
Pre post synaptic genes	429
Glutamatergic synapse	108
Neuroactive ligand-rec...	286
Ionotropic Glutamate R...	14
GABAergic synapse	80
Cocaine addiction	46
Porphyrin and chloroph...	36
Amphetamine addiction	64
Synaptic vesicle	309
Taste transduction	48
All Ion Channels	220
Glutamate Receptor Genes	21
ARC	24
Cav2::ion channels tra...	43
Pre-synapse	387
Neurotransmitter recep...	69
Cav2::ion channels tra...	36
CLOCK-CONTROLLED WEAK	399
Nucleus	127

GABA Receptor Genes	17
ASD	65
Amyotrophic lateral sc...	49
Olfactory transduction	292
Cholinergic synapse	109
Morphine addiction	85
MAPK signaling pathway	238
 KEGG CIRCADIAN ENTRAINMENT	 94
positive regulation of cAMP metabolic process	59
KEGG LONG-TERM POTENTIATION	66
positive regulation of cAMP biosynthetic process	58
positive regulation of cyclic nucleotide metabolic process	69
interstitial matrix	15
positive regulation of cyclic nucleotide biosynthetic process	65
positive regulation of nucleotide biosynthetic process	67
positive regulation of nucleotide metabolic process	72
positive regulation of purine nucleotide biosynthetic process	67
positive regulation of purine nucleotide metabolic process	71
protein palmitoylation	13
ear development	184
inner ear morphogenesis	91
ear morphogenesis	112
retinoid X receptor binding	13
CREB phosphorylation through the activation of CaMKII	14
Neuronal System	269
abnormal brain white matter morphology	118
KEGG VASCULAR SMOOTH MUSCLE CONTRACTION	116
KEGG GAP JUNCTION	86
regulation of cAMP metabolic process	96
inner ear development	157
Unblocking of NMDA receptor glutamate binding and activation	15
Muscarinic acetylcholine receptor 2 and 4 signaling pathway	51
regulation of cAMP biosynthetic process	88
KEGG PANCREATIC SECRETION	90
Ras activation upon Ca ²⁺ influx through NMDA receptor	16
morphogenesis of embryonic epithelium	127
abnormal embryonic tissue morphology	638
Metabotropic glutamate receptor group I pathway	22
5HT ₁ type receptor mediated signaling pathway	39
abnormal optic nerve morphology	63
regulation of oxidoreductase activity	61

CREB phosphorylation through the activation of Ras	24
thin cerebellar molecular layer	16
KEGG NICOTINE ADDICTION	35
increased circulating aspartate transaminase level	33
KEGG NEUROACTIVE LIGAND-RECEPTOR INTERACTION	246
magnesium ion transmembrane transporter activity	11
magnesium ion transport	13
abnormal cranial nerve morphology	142
Metabotropic glutamate receptor group III pathway	59
abnormal chemoreceptor morphology	19
Activation of NMDA receptor upon glutamate binding and postsynaptic events	33
GPCR downstream signaling	648
Pausing and recovery of Tat-mediated HIV elongation	26
Tat-mediated HIV elongation arrest and recovery	26
KEGG GLUTAMATERGIC SYNAPSE	110
Post NMDA receptor activation events	30

SELF P	COMP P	FDR
	1	0.00054783 0.03971768
	1	0.00038437 0.03971768
0.75095	0.00011617	0.00818999
1.83E-05	9.77E-05	0.00818999
0.022136	0.00047961	0.02254167
0.92453	0.00090675	0.03196294
0.99103	0.0018655	0.0526071
0.98229	0.0034203	0.06889461
1	0.0030833	0.06889461
0.99597	0.0048546	0.08556233
0.31855	0.0056112	0.0879088
0.99713	1.39E-06	0.00026328
5.07E-05	1.46E-05	0.00137913
1	4.67E-05	0.00242511
0.99998	5.13E-05	0.00242511
0.99999	8.62E-05	0.00325662
0.99996	0.00034877	0.01098626
1	0.00058824	0.01588248
1	0.00071347	0.01685573
1	0.0014176	0.02860257
1	0.0015625	0.02860257
1	0.0016647	0.02860257
1	0.0019511	0.03072983
0.99898	0.0021656	0.03148449
1	0.0024029	0.03243915
1	0.0031707	0.03895763
0.94846	0.003298	0.03895763
1	0.0045245	0.04857897
1	0.0046422	0.04857897
1	0.0048836	0.04857897
1	0.005179	0.04894155
0.99999	0.0063647	0.05688814
0.85231	0.0066219	0.05688814
0.99986	0.0073367	0.06028853
1	0.0077512	0.0610407
1	0.0089817	0.06790165
0.99929	0.0093868	0.06823482
1	0.010253	0.07015275
1	0.010393	0.07015275

0.89702	0.011027	0.07186562
1	0.011959	0.0753417
1	0.014531	0.08859223
1	0.01544	0.09060545
1	0.01582	0.09060545
1	0.016661	0.09261556
1	0.018149	0.0980046
0.99713	1.39E-06	0.00906001
0.98723	2.12E-06	0.00906001
0.99988	4.44E-06	0.0094967
0.99384	3.77E-06	0.0094967
0.99983	8.43E-06	0.01201703
1	7.57E-06	0.01201703
0.99976	9.98E-06	0.01218925
0.99995	1.72E-05	0.0143912
0.99998	1.68E-05	0.0143912
0.99995	1.72E-05	0.0143912
0.99998	1.85E-05	0.0143912
0.47858	2.13E-05	0.01517981
1	2.31E-05	0.01521966
1	3.34E-05	0.02037954
1	3.94E-05	0.0224352
0.88099	4.92E-05	0.02626988
0.66681	5.25E-05	0.02640441
1	5.68E-05	0.02695815
1	6.50E-05	0.02926935
1	8.80E-05	0.03584404
0.99999	8.62E-05	0.03584404
1	9.30E-05	0.03616223
1	0.00012491	0.04449919
0.85806	0.00012411	0.04449919
0.88138	0.00013926	0.04762692
1	0.00015287	0.05027071
0.99999	0.00020155	0.06382417
0.95278	0.00021	0.064125
1	0.00026817	0.07225017
1	0.00027041	0.07225017
0.94933	0.00025314	0.07225017
0.99204	0.00026744	0.07225017
1	0.00028995	0.07279226
0.99946	0.00029798	0.07279226

0.99576	0.00029221	0.07279226
0.99955	0.00030681	0.07286738
0.99996	0.00034877	0.0804555
0.86126	0.00035758	0.0804555
1	0.00039331	0.08186923
0.97551	0.00041174	0.08186923
0.9824	0.00039927	0.08186923
1	0.00037751	0.08186923
0.99994	0.00040289	0.08186923
0.0082276	0.00048983	0.09157941
0.99972	0.00047394	0.09157941
1	0.00049294	0.09157941
0.25191	0.00051413	0.09157941
0.25191	0.00051413	0.09157941
1	0.00056017	0.09684585
0.99967	0.00056635	0.09684585

SYSTEM	SOURCE
Gastro-Intestinal and Peripheral Tissue	Drug targets
Gastro-Intestinal and Peripheral Tissue	GWAS gene s
Gastro-Intestinal and Peripheral Tissue	Hypothesis D
Gastro-Intestinal and Peripheral Tissue	Agnostic
Gastro-Intestinal and Peripheral Tissue	Agnostic
Gastro-Intestinal and Peripheral Tissue	Agnostic

SET	NGENES	SELF P	COMP P
ANABOLIC STEROIDS	34	0.56804	0.00026816
Schizophrenia, schizoaffective disorder or bipolar disorder	32	0.66707	0.00029124
CLOCK-CONTROLLED PERVA...	121	1	0.00032294
hyaluronic acid binding	20	0.95248	2.32E-08
KEGG PATHWAYS IN CANCER	310	1	1.87E-05
abnormal nervous system development	736	1	1.55E-05

FDR

0.0388832

0.04135608

0.06103566

0.00019827

0.05352215

0.05352215