Identifying tissues implicated in Anorexia Nervosa using Transcriptomic Imputation

Author List:

Laura M. Huckins, PhD 1,2,3,4,5, Amanda Dobbyn, PhD 1,2,4, Whitney McFadden, MD 1,2,3, Douglas Ruderfer, PhD 6, Weiqing Wang, BSc 1,2, Eric Gamazon, PhD 6,7, Virpi Leppä, Phd 8, Roger Adan, PhD 9,10, Tetsuya Ando, MD, PhD 11, Jessica Baker, PhD 12, Andrew Bergen, PhD 13, Wade Berrettini, MD, PhD 14, Andreas Birgegård, PhD 15,16, Claudette Boni, PhD 17, Vesna Boraska Perica, PhD 18, Harry Brandt, MD 19, Roland Burghardt, MD 20, Matteo Cassina, MD 21, Carolyn Cesta, 22, Maurizio Clementi, MD 21, Joni Coleman, MSc 23, Roger Cone, PhD 24, Philippe Courtet, MD 25, Steven Crawford, MD 26, Scott Crow, MD 27, James Crowley, PhD 28,29, Unna Danner, PhD 10, Oliver Davis, MSc, PhD 30, Martina de Zwaan, MD 31, George Dedoussis, PhD 32, Daniela Degortes, PhD 21, Janiece DeSocio, PhD, RN, PMHNP-BC 33, Danielle Dick, PhD 34, Dimitris Dikeos, MD 35, Monika Dmitrzak-Weglarz, PhD 36, Elisa Docampo, MD, PhD 37,38,39, Karin Egberts, MD 40, Stefan Ehrlich, MD 41,42, Geòrgia Escaramís, PhD 37,38,43, Tõnu Esko, PhD 44, Xavier Estivill, MD, PhD 45,37,38,43, Angela Favaro, MD, PhD 21, Fernando Fernández-Aranda, PhD, FAED 46, Manfred Fichter, MD, Dipl-Psych 47, Chris Finan, PhD 48, Krista Fischer, PhD 49, Manuel Föcker, MD 50,51, Lenka Foretova, MD, PhD 52, Monica Forzan, PhD 53, Christopher Franklin, PhD 48, Héléna Gaspar, PhD 23, Fragiskos Gonidakis, MD 54, Philip Gorwood, MD, PhD 55, Monica Gratacos, MD, PhD 37,38,43, Sébastien Guillaume, MD, PhD 25, Yiran Guo, PhD 56, Hakon Hakonarson, MD, PhD 56,57, Katherine Halmi, MD 58, Konstantinos Hatzikotoulas, MD, PhD 48, Joanna Hauser, MD, PhD 36, Johannes Hebebrand, MD 59, Sietske Helder, PhD 60,61, Judith Hendriks, BSc 62, Beate Herpertz-Dahlmann, MD 63, Wolfgang Herzog, MD 64, Christopher Hilliard, BS 65, Anke Hinney, PhD 59, James Hudson, MD, ScD 66,67, Julia Huemer, MD 68, Hartmut Imgart, MD 69, Hidetoshi Inoko, PhD 70, Susana Jiménez-Murcia, PhD 46, Craig Johnson, PhD 71, Jenny Jordan, PhD 72,73, Anders Juréus, PhD 74, Gursharan Kalsi, PhD 23, Debora Kaminska, PhD 75, Allan Kaplan, MSc, MD, FRCP(C) 76, Jaakko Kaprio, MD, PhD 77, Leila Karhunen, PhD 78, Andreas Karwautz, MD, FAED 68, Martien Kas, PhD 79, Walter Kaye, MD 80, James Kennedy, MD, FRCP(C) 76, Martin Kennedy, PhD 72, Anna Keski-Rahkonen, MD, PhD, MPH 81, Kirsty Kiezebrink, BSc (Hons), PGDip, PhD, FHEA, RNutr 82, Youl-Ri Kim, MD, PhD 83, Kelly Klump, PhD 84, Gun Peggy

Knudsen, PhD 85, Bobby Koeleman, PhD 9, Doris Koubek, MD 68, Maria La Via, MD 65, Mikael Landén, MD, PhD 86, Robert Levitan, MD 76, Dong Li, PhD 56, Paul Lichtenstein, PhD 22, Lisa Lilenfeld, PhD 87, Jolanta Lissowska, PhD 88, Pierre Magistretti, PhD 89, Mario Maj, MD, PhD 90, Katrin Mannik, PhD 91, Nicholas Martin, PhD 92, Sara McDevitt, MB, MD, MRCPsych, MMedED 93, Peter McGuffin, MD 94, Elisabeth Merl, MD 68, Andres Metspalu, PhD, MD 49, Ingrid Meulenbelt, PhD 95, Nadia Micali, MD, PhD 96, James Mitchell, MD 97, Karen Mitchell, PhD 98, Palmiero Monteleone, MD 99, Alessio Maria Monteleone, MD 90, Preben Mortensen, MD, DrMedSc 100, Melissa Munn-Chernoff, PhD 65, Benedetta Nacmias, PhD 101, Ida Nilsson, PhD 102,103, Claes Norring, PhD 104, Ioanna Ntalla, PhD 32, Julie O'Toole, MD 105, Jacques Pantel, PhD 106, Hana Papezova, MD, PhD 75, Richard Parker, 92, Raquel Rabionet, PhD 107, Anu Raevuori, MD, PhD 81, Andrzej Rajewski, MD, PhD 36, Nicolas Ramoz, PhD 108, N.William Rayner, PhD 48,109,110, Ted Reichborn-Kjennerud, MD 111, Valdo Ricca, MD 101, Stephan Ripke, MD, PhD 112, Franziska Ritschel, MSc 113, Marion Roberts, PhD 23,182, Alessandro Rotondo, MD 114, Filip Rybakowski, MD, PhD 115, Paolo Santonastaso, MD 21, André Scherag, PhD 116, Ulrike Schmidt, MD, PhD 23, Nicholas Schork, PhD 117, Alexandra Schosser, PhD 68, Jochen Seitz, MD 63, Lenka Slachtova, PhD 75, P. Eline Slagboom, PhD 95, Margarita Slof-Op 't Landt, PhD 118, Agnieszka Slopien, MD 119, Tosha Smith, PhD 65, Sandro Sorbi, MD 101, 120, Eric Strengman, BS 121, Michael Strober, PhD 122, Patrick Sullivan, MD, FRANZCP 28,29, Jin Szatkiewicz, PhD 65, Neonila Szeszenia-Dabrowska, MD, PhD 123, Ioanna Tachmazidou, PhD 48, Elena Tenconi, MD 21, Laura Thornton, PhD 65, Alfonso Tortorella, MD 90,124, Federica Tozzi, MD 125, Janet Treasure, PhD, FRCP, FRCPsych 23, Artemis Tsitsika, MD, PhD 126, Konstantinos Tziouvas, MD, MSc 127, Annemarie van Elburg, MD, PhD 128,129, Eric van Furth, PhD 130, Tracey Wade, PhD 131, Gudrun Wagner, Dr, MSc, DPO 68, Esther Walton, Dr. rer. nat., PhD 132,133, Hunna Watson, PhD 134,135,136, D.Blake Woodside, MD 137, Shuyang Yao, MSc, BSc 138, Zeynep Yilmaz, PhD 65, Eleftheria Zeggini, PhD 48, Stephanie Zerwas, PhD 65, Stephan Zipfel, MD 139, Alfredsson Lars, PhD 22, Andreassen Ole, MD, PhD 140,141, Harald Aschauer, MD 142, Jeffrey Barrett, PhD 143, Vladimir Bencko, MD, PhD 144, Laura Carlberg, MD 68, Sven Cichon, PhD 145, Sarah Cohen-Woods, PhD 146, Christian Dina, PhD 147, Bo Ding, PhD 148, Thomas Espeseth, PhD 140,141, James Floyd, PhD 149, Steven Gallinger, MD 76, Giovanni

Gambaro, MD, PhD 150, Ina Giegling, PhD 151, Stefan Herms, PhD 152, Vladimir Janout, PhD 153, Antonio Julià, PhD 154, Lars Klareskog, MD 22, Stephanie Le Hellard, PhD 155, Marion Leboyer, MD, PhD 156, Astri J. Lundervold, PhD 157, Sara Marsal, MD, PhD 154, Morten Mattingsdal, PhD 158, Marie Navratilova, MUDr., PhD 52, Roel Ophoff, PhD 159, Aarno Palotie, MD, PhD 160,161,162,163,164, Dalila Pinto, PhD 165,166, Samuli Ripatti, PhD 81, Dan Rujescu, MD 151,167, Stephen Scherer, PhD, FRSC 168, Laura Scott, PhD 169, Robert Sladek, MD 170,171, Nicole Soranzo, PhD 172,173,174, Lorraine Southam, BSc 48,110, Vidar Steen, MD, PhD 155, Wichmann H-Erich, PhD 175, Elisabeth Widen, MD, PhD 176, Bernie Devlin, PhD 177, Solveig K. Sieberts, PhD 178, Nancy Cox, PhD 179, Hae Kyung Im, PhD 180,179, Gerome Breen, PhD 23, Pamela Sklar, MD, PhD 1,5,2,181, Cynthia Bulik, PhD 28,29, Eli A. Stahl, PhD 1,5,

1 Pamela Sklar Division for Precision Psychiatry, Icahn School of Medicine at Mount Sinai, USA

2 Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, USA

3 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA

4 Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, USA

5 Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, USA

6 Vanderbilt University Medical Center, Nashville, TN, USA

7 Section of Genetic Medicine, Department of Medicine, University of Chicago, Chicago, Illinois, USA

8 CEDI – Centre for Eating Disorders Innovation, Department of Medical Epidemiology and Biostatistics (MEB), C8, Karolinska Institutet, Nobels väg 12A, 171 77 Solna, Sweden,

9 University Medical Center Utrecht, Netherlands

10 Altrecht Eating Disorders Rintveld, Netherlands

11 National Institute of Mental Health, Japan

12 University of North Carolina at Chapel Hill, UNC

13 Biorealm Research, Culver City, CA, USA

14 Perelman School of Medicine at the University of Pennsylvania, USA

15 Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Sweden

16 Stockholm Health Care Services, Stockholm County Council, Sweden

17 Centre of Psychiatry and Neuroscience, France

18 Wellcome Trust Sanger Institute, University of Split School of Medicine, UK

19 The Center for Eating Disorders at Sheppard Pratt, Baltimore, USA

20 Klinikum Frankfurt/Oder, Germany

21 University of Padova, Italy

22 Karolinska Institutet, Sweden

23 King's College London, UK

24 University of Michigan, USA

25 CHRU Montpellier, University of Montpellier, France

26 The Center for Eating Disorders at Sheppard Pratt, USA

27 University of Minnesota, USA

28 University of North Carolina at Chapel Hill, USA,

29 Karolinska Institutet, Sweden,

30 University of Bristol, UK

31 Hannover Medical School, Germany

32 Harokopio University, Greece

33 Seattle University College of Nursing, USA

34 Virginia Commonwealth University, USA

35 Athens University Medical School, Greece

36 Poznan University of Medical Sciences, Poland

37 The Barcelona Institute of Science and Technology, Spain

38 Universitat Pompeu Fabra, Spain

39 CIBER Epidemiología y Salud Pública, Spain

40 University Hospital of Würzburg, Germany

41 Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Germany, Germany

42 Eating Disorders Research and Treatment Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, TU Dresden, Germany, Germany

43 Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública, Spain

44 University of Tartu, Broad Institute, Estonia

45 Centre for Genomic Regulation (CRG), Spain

46 University Hospital of Bellvitge-IDIBELL and CIBEROBN, University of Barcelona, Spain

47 Ludwig-Maximilians-University Munich, Schön Klinik Roseneck, Germany

48 Wellcome Trust Sanger Institute, UK

49 University of Tartu, Estonia

50 Department of Child and Adolescent Psychiatry, University Hospital Essen, Germany

51 University of Duisburg-Essen, Essen, Germany

52 Masaryk Memorial Cancer Institute, Czech Republic

53 University Hospital of Padova, Italy

54 National and Kapodistrian University of Athens, Greece

55 INSERM U984, Sainte-Anne Hospital, University of Paris-Descartes, France

56 Children's Hospital of Philadelphia, USA

57 University of Pennsylvania, USA

58 Weill Cornell Medical College, USA

59 Department of Child and Adolescent Psychiatry, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

60 Zorg op Orde, Netherlands,

61 King's College London, UK,

62 University Utrecht, Netherlands

63 RWTH Aachen, Germany

64 Heidelberg University, Germany

65 University of North Carolina at Chapel Hill, USA

66 McLean Hospital, USA

67 Harvard Medical School, USA

68 Medical University of Vienna, Austria

69 Parkland-Klinik, Germany

70 Tokai University School of Medicine, Japan

147 71 Eating Recovery Center, USA
148 72 University of Otago, New Zealand
149 73 Canterbury District Health Board, New Zealand
150 74 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm,
151 Sweden,
152 75 Charles University, Czech Republic
153 76 University of Toronto, Canada
154 77 University of Helsinki, National Institute for Health and Welfare, Finland
155 78 University of Eastern Finland, Finland
156 79 University of Groningen, University Medical Center Utrecht, Netherlands
157 80 University of California, San Diego, USA
158 81 University of Helsinki, Finland
159 82 University of Aberdeen, UK
160 83 Inje University, South Korea
161 84 Michigan State University, USA
162 85 Norwegian Institute of Public Health, Norway
163 86 Karolinska Institutet, Gothenburg University, Sweden
164 87 American School of Professional Psychology at Argosy University, Washington DC, USA
165 88 M. Sklodowska-Curie Cancer Center and Institute of Oncology, Poland
166 89 Brain Mind Institute, EPFL, Center for Psychiatric Neuroscience, Department of Psychiatry -
167 CHUV/UNIL, Switzerland
168 90 University of Campania "Luigi Vanvitelli", Naples
169 91 University of Tartu, University of Lausanne, Estonia
170 92 QIMR Berghofer Medical Research Institute, Australia
171 93 University College Cork, Health Service Executive South, Ireland
172 94 Kings College London, UK
173 95 Leiden University Medical Centre, Netherlands
174 96 University of Geneva, Switzerland
175 97 University of North Dakota School of Medicine and Health Sciences, USA

98 VA Boston Healthcare System, Boston University School of Medicine, USA

99 University of Salerno, Italy

100 Aarhus University, Denmark

101 Department Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Italy

102 Department of Molecular Medicine and Surgery, Karolinska Institutet, Sweden

103 Center for Molecular Medicine, Karolinska University Hospital, Sweden

104 Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, & Stockholm Health Care Services, Stockholm County Council, Sweden

105 Kartini Clinic, USA

106 Centre de Psychiatrie et Neurosciences - Inserm U894, USA

107 Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Universitat Pompeu Fabra, Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública, Spain

108 Centre de Psychiatrie et Neurosciences - Inserm U894, France

109 Oxford Centre for Diabetes, Endocrinology and Metabolism, UK

110 Wellcome Trust Centre for Human Genetics, UK

111 Norwegian Institute of Public Health, University of Oslo, Norway

112 Charité Universtätsmedizin Berlin,

113 Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Germany, Eating Disorders Research and Treatment Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, TU Dresden, Germany,

114 University of Pisa, Italy

115 Institute of Psychiatry and Neurology, University of Social Sciences and Humanities, Poland

116 Jena University Hospital, Germany

117 J. Craig Venter Institute, USA

118 Rivierduinen Eating Disorders Ursula, Leiden University Medical Centre, Netherlands

119 Uniwersytet Medyczny im. Karola Marcinkowskiego, Poland

120 IRCSS Fondazione Don Gnocchi, Florence, Italy

121 Department of Pathology, University Medical Center Utrecht, The Netherlands, Netherlands

122 University of California at Los Angeles , USA

123 Nofer Institute of Occupational Medicine, Department of Environmental Epidemiology, Poland

124 University of Perugia, Italy

125 University of Cyprus, UK

126 University of Athens "P. & A. Kyriakou" Children's Hospital, Greece

127 "P. & A. Kyriakou" Children's Hospital, PICU, Greece

128 Center for Eating Disorders Rintveld, Netherlands

129 University of Utrecht, Netherlands

130 Rivierduinen Eating Disorders Ursula, Leiden University Medical Center, Netherlands

131 Flinders University, Australia

132 Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Germany,

133 Eating Disorders Research and Treatment Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, TU Dresden, Germany,

134 University of North Carolina at Chapel Hill,

135 School of Paediatrics and Child Health, Faculty of Medicine, Dentistry, and Life Sciences, The University of Western Australia, Australia,

136 School of Psychology and Speech Pathology, Faculty of Health Sciences, Curtin University, Australia,

137 University of Toronto, Toronto General Hospital, Canada

138 Karolinksa Institutet, Sweden

139 University Medical Hospital Tuebingen, Germany

140 University of Oslo, Norway

141 Oslo University Hospital, Norway

142 Biopsychosocial Corporation, Austria

143 Sanger Institute, UK

144 Charles University, First Faculty of Medicine, Institute of Hygiene and Epidemiology, Czech Republic
145 University Hospital Basel, Switzerland
146 Finders University, AU
147 University of Nantes, France
148 University of California at San Diego, USA
149 Wellcome Trust Sanger Institute, Genomics PLC, UK
150 Columbus-Gemelli University Hospital, Italy
151 Martin Luther University of Halle-Wittenberg, Germany
152 University of Basel, Switzerland
153 Ostrava University, Czech Republic
154 Vall d'Hebron Hospital Research Institute, Spain
155 University of Bergen, Haukeland University Hospital, Norway
156 Université Paris-Est-Créteil (UPEC), France
157 University of Bergen, K. G. Jebsen Center for Neuropsychiatric Disorders , Noway
158 Oslo University, Norway
159 University of California Los Angeles, University Medical Center Utrecht, Netherlands
160 Massachusetts General Hospital, USA
161 Broad Institute, USA
162 Massachusetts Institute of Technology, USA
163 Harvard, USA
164 Institute for Molecular Medicine, USA
165 Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, USA,
166 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA,
167 Ludwig-Maximilians-University Munich, Germany
168 The Hospital for Sick Children, University of Toronto, Canada
169 Department of Biostatistics, University of Michigan,
170 McGill University, Canada
171 Génome Québec Innovation Centre, Canada

172 Human Genetics, Wellcome Trust Sanger Institute, Genome Campus, Hinxton, CB10 1HH, UK

173 Department of Haematology, University of Cambridge, Hills Rd, Cambridge CB2 0AH, UK

174 The National Institute for Health Research Blood and Transplant Unit (NIHR BTRU) in Donor Health and Genomics at the University of Cambridge, UK

175 Helmholtz Centre Munich - German Research Center for Environmental Health, Germany

176 Institute for Molecular Medicine, Finland

177 Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

178 Systems Biology, Sage Bionetworks, Seattle, WA, USA

179 Section of Genetic Medicine, Department of Medicine, University of Chicago, Chicago, Illinois, USA,

180 Vanderbilt University Medical Center, Nashville, TN,

181 Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, USA

182 University of Auckland, New Zealand

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; $p=8.52x10^{-07}$), and *CUL3*, in the caudate basal ganglia ($p=1.8x10^{-06}$). 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 disorder[1], 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 nervosa[2], as well as a number of promising sub-threshold associations[3–5], 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 point[2]. 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 anxiety[6]. Although aversion to fullness and low appetite could be driven by dysfunction of neurobiological satiety pathways or altered levels of orexigenic hormones[7], 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 disorders[11]. 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 onset[8].

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 controls[2]. Detailed diagnostic criteria used are described in the PGC-ED GWAS of these data[2]. Briefly, cases include individuals with lifetime diagnoses of either AN (including both binge-purge and restrictive subtypes) or "eating disorder not other 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 database[12], 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 PrediXcan[8].

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 METAL[18].

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, $p=2.31\times10^{-7}$).

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 under-estimate 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 group[20].

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-CoJo[21]. 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 FINEMAP[22], 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 package[23], 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 $p<1x10^{-04}$ 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

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

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 portal[26] (Suppl. Table 1).

Descriptions of phenotype curation, quality control, and association models used for the UK BioBank sample are available elsewhere[25]. 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 MetaXcan[27], a summary statistic based software analogous to PrediXcan, to compute gene-tissue associations for genes with $p<1x10^{-04}$ 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 MAGMA[28]. 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], GO[33], REACTOME[34], PANTHER[35,36], BIOCARTA[37], and MGI[38]. 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 ($p<1x10^{-04}$; Suppl. Table 2). The majority of the significant associations (35/37) correspond to the only known genome-wide significant locus for AN[20]. We used FINEMAP[22] 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 ($p=1.86 x10^{-06}$), and increased expression of *WDFY1* and *FAM124B*, in adipose tissue ($p=6.11x10^{-05}$, $6.73x10^{-05}$, 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 ($p=8.34x10^{-07}$), and in the adrenal gland ($p=6.68x10^{-05}$); conditioning *REEP5*-adrenal on *REEP5*-DLPFC completely ameliorates the signal (p=0.085).

Additionally, we identified 22 sub-threshold associations ($p<1x10^{-04}$), 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 ($p<1x10^{-04}$) 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 predixcan[40] ("MetaXcan") to identify gene-tissue associations across all three traits, for all genes reaching $p<1x10^{-04}$ 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; $p<1.28x10^{-07}$), increased weight (~0.135kg/unit of gene expression; $p<5.8x10^{-08}$) in the UK BioBank, and decreased risk of AN in PGC-ED (OR=0.98/unit of gene expression; $p<5x10^{-07}$) (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 ($p<2x10^{-08}$) and decreased AN risk. Three sub-threshold AN genes (*BARX1, MGMT, TRIM38*) are also associated with BMI ($p<2 x10^{-13}$), weight ($p<2x10^{-07}$), and waist circumference ($p=1.35x10^{-08}$), 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 $p=2.39\times10^{-270}$). 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-value<0.05; Table 4). These include multiple calcium-gated voltage channel pathways ($p<0.002$), axon guidance ($p=1.07\times10^{-04}$), Wnt signalling (9.93×10^{-04}), the post-synaptic density (0.003), targets of the FMRP protein[41–45] (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

558 sub-threshold associations across *KLF4*, *BCHE*, *IGF1*, *SPCS2*, *ACHE*, *PCKS1*, and *SPSC3*. Taken
559 together, these associations indicate lower baseline ghrelin expression in individuals with AN
560 than in controls. For example, AN cases have lower GREX of *KLF4*, *SPCS2* and *SPCS3*, all of which
561 stimulate ghrelin secretion[46]. AN cases also have increased expression of *ACHE*, *IGF1*, *PCSK1*,
562 and *BCHE*, which inhibit ghrelin expression[47–49]. We also noted that GREX of ghrelin (GHRL) was
563 lower in AN cases than controls across 11/12 tissues tested.
564
565 Using exclusively brain-gene association statistics as an input to our MAGMA analysis resulted
566 in 51 significantly enriched pathways. 35/51 pathways were from the hypothesis-driven test;
567 these included circadian entrainment ($p=2.6x10^{-04}$), addictive behaviors (nicotine, alcohol,
568 cocaine, and morphine dependence, $p<0.0045$), calcium-gated voltage channels, and a large
569 number of pathways related to processes in the post-synaptic density (Table 4), in line with
570 pathway results from other psychiatric disorders[10,30,50,51]. A further 25 significantly enriched
571 pathways were identified in the agnostic analysis, including further evidence of circadian
572 entrainment ($p=1.39x10^{-06}$), long-term potentiation ($p=4.44x10^{-06}$), as well as multiple pathways
573 implicating ear and neuronal system development in mice ($p<1.2x10^{-04}$). We noted enrichment
574 in cyclic-AMP metabolism pathways ($p<9.3x10^{-05}$). This pathway includes dopamine receptor
575 gene *DRD1* ($p=8.85x10^{-05}$), and *DRD5* ($p=3.5x10^{-04}$), two receptors which are part of the
576 dopaminergic pathways affected by ghrelin in the VTA and nucleus accumbens[52,53], as well as
577 *GCG* (Glucagon; $p=1.3\ x10^{-03}$), and *APOE* ($p=1.0\ x10^{-03}$) which is associated with risk for
578 Alzheimer's disease. CREB phosphorylation through activation of CaMKII pathway was enriched
579 in our results ($p=5.25\ x10^{-05}$). This pathway includes *AKAP9* ($p=2.1x10^{-04}$), which regulates levels
580 of cAMP activity in the brain, and co-localizes with NMDA receptor NR1 which in certain brain
581 regions is involved in appetite and weight regulation[54–56], as well as *GRIN2B* ($p=5.1x10^{-04}$), which
582 is associated with neurite outgrowth and risky decision making[57,58].
583
584 Excluding brain-gene associations statistics from our pathway analysis results in only one
585 subthreshold association ($p=3.2x10^{-04}$; fdr-corrected p-value 0.06) in our hypothesis-driven
586 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 ($p=2.32x10^{-08}$).

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, LDScore 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 GWAS[20]. 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, $p=3.6x10^{-04}$), while adipose tissue-genes explain significantly more variance than we would expect (13.9% vs. 4.6%, $p=2x10^{-04}$). This enrichment of signal within adipose tissue is of particular interest given the demonstrated overlap between adiposity and disordered eating patterns[59], 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.

626 However, these calculations are based on the assumption that all gene-tests are independent;
627 in fact, we note high correlation of GREX between tissues, including a large number of co-linear
628 genes and tissues. The number of independent tests carried out is therefore likely to be
629 substantially lower than the number of tests used in our estimate, perhaps explaining why
630 gastrointestinal/digestive genes explain less variance than we would expect.
631
632 Among our gene-tissue associations are a number of genes which may be of particular interest.
633 For example, decreased expression of *REEP5* in the DLPFC is associated with increased risk of
634 AN. *REEP*5 is a receptor accessory protein which promotes expression of olfactory receptors[65].
635 Reep5, together with RTP1 and RTP2, is required for cell surface expression of odorants, and is
636 primarily expressed in olfactory neurons. The DLPFC has a high localized concentration of
637 olfactory neurons, and DLPFC volume is decreased in anosmic individuals[66]. Olfaction is of
638 particular interest in eating disorders given its role in taste and desire for food, as well as in a
639 number of neurological disorders such as Alzheimer's and Parkinson's[67,68]. Individuals with AN
640 have high rates of reported hyposmia and anosmia[67,69–72], and perform poorly in odor
641 discrimination tests, compared to healthy controls. Importantly, odor discrimination ability and
642 hyposmic status correlates more strongly with BMI than with any specific disordered eating
643 behavior, even among individuals with AN[73]. Previous studies have also demonstrated
644 differential expression of olfactory genes following eight restoration in individuals with
645 Anorexia Nervosa[74]. In line with this, we identified a direct correlation between *REEP5*
646 expression and body weight in the UK BioBank; each additional unit of gene expression
647 corresponds to ~140 g additional body weight, and an AN OR of 0.85. Taken together these
648 results suggest that *REEP5* may have a general role in body size and BMI through altered
649 olfactory cues, and may be of interest to researchers studying appetite and satiety, as well as
650 obesity, normal variation in BMI, and AN. *REEP5* has also been implicated in major depressive
651 disorder and antidepressant response in previous studies[75].

652 We identified four significantly associated genes within our complex chromosome 12 locus.
653 Three of these genes (*SUOX, RPS26, RDH16*) are significantly associated with AN across a range
654 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 ratio[76]. 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 pseudohypoaldosteronism[77], a disorder characterized by sodium imbalance in the body and often presenting with low body weight. Mutations in *CUL3* are associated with schizophrenia[78], autism[79] and non-response to anti-depressants[80]. Variants lying near to *CUL3* were identified in the first GWAS of AN, although these did not reach genome-wide significance[81].

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]).

683 Our pathway analysis identified a large number of significantly enriched pathways. In particular,
684 multiple pathways indicate a role for the post-synaptic density (including PSD95, targets of the
685 FMRP protein, glutamate receptor genes, among others), which has previously been implicated
686 in other psychiatric disorders. Four pathways are associated with addiction and addictive
687 behaviours, including nicotine addiction, alcoholism, cocaine addiction, and amphetamine
688 addiction. Illicit drug use is significant enriched among individuals with eating disorders, in
689 particular AN[105], although this is, to our knowledge, the first study identifying shared genetic
690 risk factors.
691
692 Circadian entrainment and clock genes are highly enriched among our data. Longstanding
693 hypotheses implicated disrupted circadian rhythms in a range of mood disorders, particularly
694 depression and bipolar disorder[106–108]. Further, behavioural patterns in individuals with AN (for
695 example excessive exercise[109–111] and lack of sleep) have long provided epidemiological
696 evidence for circadian rhythm disruption in AN. Circadian rhythms may also have a role is
697 regulating appetite and satiety pathways[7,112,113].
698
699 Our analysis also implicates pathways concerning taste and olfactory transduction, as well as
700 ghrelin secretion. Ghrelin is an orexigenic hormone with a documented role in appetite and
701 satiety[114–118] as well as in gut motility[117–119]. Our results suggest that individuals with AN may
702 have decreased circulating ghrelin levels due to increased genetically regulated expression of
703 ghrelin inhibitors, and decreased GREX of Ghrelin stimulators. Ghrelin enhances appetite and
704 increases food intake in humans; lowered baseline circulating ghrelin levels may begin to
705 explain decreased hunger and desire for food in individuals with AN. Previous studies have
706 documented dysregulation of ghrelin, leptin and glucagon in individuals with AN[120]. However,
707 these studies are by definition performed after long periods of starvation or food restriction,
708 meaning that causation is difficult to disentangle from consequences of eating disordered
709 behaviours; it is likely that the increased ghrelin levels seen in these studies is a consequence of
710 long-term fasting, rather than causative. In this study, we assess only genetically regulated gene
711 expression (GREX), meaning that any associations identified are not affected by diet or

712 environment. Instead, these results may indicate an altered "baseline" level of circulating
713 ghrelin in individuals with AN.
714 There are a number of limitations that should be taken into account. First, the sample size of
715 our study is small, especially compared to GWAS sample sizes in other psychiatric
716 disorders[121,122]. It is likely that increasing sample size substantially will yield many new insights
717 into the aetiology of anorexia nervosa, and that current sub-threshold associations may lose
718 significance as sample size increases. Similarly, transcriptomic imputation approaches rely on
719 large, well-curated reference panels in order to build GREX predictor models; here, we have
720 used reference panels constructed from GTeX[8,14] and CommonMind Consortium data[10,13],
721 including the largest collections of publicly available post-mortem brain tissues. We have shown
722 previously that there is a significant correlation between the sample sizes used to construct
723 these predictors and the number of genes included in each predictor database, and that a
724 number of these databases are therefore likely underpowered[10].
725
726 Our analysis highlights the need for greater investigation into the complex aetiology of anorexia
727 nervosa. Transcriptomic Imputation allows us to identify significant gene-tissue associations
728 with anorexia nervosa, and indicates an excess of signal in adipose tissue. It is clear from these
729 results that both psychiatric and metabolic risk factors play a role in AN risk; these factors
730 should be carefully considered in the design of future studies, as well as in how AN is perceived
731 and considered by clinicians treating individuals with AN.
732

References

1. Bulik, C. M., Slof-Op't Landt, M. C. T., van Furth, E. F. & Sullivan, P. F. The genetics of anorexia nervosa. *Annu. Rev. Nutr.* **27,** 263–275 (2007).
2. 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).
3. Boraska, V. *et al.* A genome-wide association study of anorexia nervosa. *Mol. Psychiatry* **19,** (2014).
4. Huckins, L. M. *et al.* Investigation of common, low-frequency and rare genome-wide variation in anorexia nervosa. *Mol. Psychiatry* (2017). doi:10.1038/mp.2017.88
5. Hinney, A. *et al.* Evidence for three genetic loci involved in both anorexia nervosa risk and variation of body mass index. *Mol. Psychiatry* **22,** (2017).
6. Avena, N. M. & Bocarsly, M. E. Dysregulation of brain reward systems in eating disorders: neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology* **63,** 87–96 (2012).
7. Fabbri, A. D. *et al.* Ghrelin and eating disorders. *Arch. Clin. Psychiatry (São Paulo)* **42,** 52–62 (2015).
8. Gamazon, E. R. *et al.* A gene-based association method for mapping traits using reference transcriptome data. *Nat. Genet.* **47,** 1091–8 (2015).
9. Gusev, A. *et al.* Integrative approaches for large-scale transcriptome-wide association studies. *Nat. Genet.* **48,** 245–52 (2016).
10. Huckins, L. M. *et al.* Gene expression imputation across multiple brain regions reveals schizophrenia risk throughout development. *bioRxiv* 222596 (2017). doi:10.1101/222596
11. De Marco, M. C. *et al.* Assessment of the capacity to express informed consent for organ donation in patients with schizophrenia. *J. Forensic Sci.* **55,** 669–676 (2010).
12. Laura M. Huckins. Gene expression imputation across multiple brain regions reveals schizophrenia risk throughout development. *Nat. Genet.*
13. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* **19,** 1442–1453 (2016).
14. Ardlie, K. G. *et al.* The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science (80-.).* **348,** 648–660 (2015).
15. Watson, T. L. & Andersen, A. E. A critical examination of the amenorrhea and weight criteria for diagnosing anorexia nervosa. *Acta Psychiatr. Scand.* **108,** 175–182 (2003).
16. Gendall, K. A. *et al.* The psychobiology and diagnostic significance of amenorrhea in patients with anorexia nervosa. *Fertil. Steril.* **85,** 1531–1535 (2006).
17. Garfinkel, P. E. *et al.* Should amenorrhoea be necessary for the diagnosis of anorexia nervosa? Evidence from a Canadian community sample. *Br. J. Psychiatry* **168,** 500–506 (1996).
18. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26,** 2190–2191 (2010).
19. Mele, M. *et al.* The human transcriptome across tissues and individuals. *Science (80-.).* **348,** 660–665 (2015).
20. Duncan, L. *et al.* Genome-Wide Association Study Reveals First Locus for Anorexia Nervosa and Metabolic Correlations. *bioRxiv* (2016).

21. 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).
22. Benner, C. *et al.* FINEMAP: Efficient variable selection using summary data from genome-wide association studies. *Bioinformatics* **32,** 1493–1501 (2016).
23. Warnes, A. G. R. *et al.* Package ' gplots '. (2016).
24. Lab), (Rivas. Global Biobank Engine. *Stanford, CA* (2017). at <http://gbe.stanford.edu>
25. Nealelab. UK_Biobank_GWAS. (2017).
26. BioBank), (UK. UK BioBank search. (2017). at <http://biobank.ctsu.ox.ac.uk/crystal/search.cgi>
27. Barbeira, A. *et al.* MetaXcan: Summary Statistics Based Gene-Level Association Method Infers Accurate PrediXcan Results. *bioRxiv* (2016).
28. 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).
29. Kirov, G. *et al.* De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol. Psychiatry* **17,** 142–53 (2012).
30. Pardiñas, A. F. *et al.* Common schizophrenia alleles are enriched in mutation-intolerant genes and maintained by background selection. *bioRxiv* 68593 (2016). doi:10.1101/068593
31. Kanehisa, M. *et al.* Data, information, knowledge and principle: back to metabolism in KEGG. *Nucleic Acids Res.* **42,** D199-205 (2014).
32. Kanehisa, M. & Goto, S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* **28,** 27–30 (2000).
33. The Gene Ontology Consortium. Gene Ontology Consortium: going forward. *Nucleic Acids Res.* **43,** D1049-1056 (2014).
34. Croft, D. *et al.* The Reactome pathway knowledgebase. *Nucleic Acids Res.* **42,** D472-7 (2014).
35. Thomas, P. D. *et al.* PANTHER: a library of protein families and subfamilies indexed by function. *Genome Res.* **13,** 2129–2141 (2003).
36. Mi, H., Muruganujan, A. & Thomas, P. D. PANTHER in 2013: modeling the evolution of gene function, and other gene attributes, in the context of phylogenetic trees. *Nucleic Acids Res.* **41,** D377-86 (2013).
37. BioCarta. MSigDB Collections. (2017).
38. MGI-About the Mouse Genome Informatics database resource. at <http://www.informatics.jax.org/mgihome/projects/aboutmgi.shtml>
39. (GTex Consortium). GTEx Portal. (2015). at <http://gtexportal.org/home/documentationPage>
40. Barbeira, A. N. *et al.* Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat. Commun.* **In Press,** (2018).
41. Darnell, J. C. *et al.* FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. *Cell* **146,** 247–61 (2011).
42. Ascano, M. *et al.* FMRP targets distinct mRNA sequence elements to regulate protein expression. *Nature* **492,** 382–6 (2012).

43. Callan, M. A. & Zarnescu, D. C. Heads-up: new roles for the fragile X mental retardation protein in neural stem and progenitor cells. *Genesis* **49,** 424–40 (2011).
44. Fromer, M. *et al.* De novo mutations in schizophrenia implicate synaptic networks. *Nature* **506,** 179–184 (2014).
45. Iossifov, I. *et al.* De novo gene disruptions in children on the autistic spectrum. *Neuron* **74,** 285–99 (2012).
46. Lee, H. J. *et al.* KLF4 positively regulates human ghrelin expression. *Biochem. J.* **420,** 403–411 (2009).
47. Murtuza, M. I. & Isokawa, M. Endogenous ghrelin-O-acyltransferase (GOAT) acylates local ghrelin in the hippocampus. *J. Neurochem.* (2017). doi:10.1111/jnc.14244
48. Chen, V. P., Gao, Y., Geng, L. & Brimijoin, S. Butyrylcholinesterase regulates central ghrelin signaling and has an impact on food intake and glucose homeostasis. *Int. J. Obes.* **41,** 1413–1419 (2017).
49. Broglio, F. *et al.* Acetylcholine Regulates Ghrelin Secretion in Humans. *J. Clin. Endocrinol. Metab.* **89,** 2429–2433 (2004).
50. Kirov, G. *et al.* De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol. Psychiatry* **17,** 142–53 (2012).
51. Huckins, L. *et al.* Transcriptomic Imputation of Bipolar Disorder and Bipolar subtypes reveals 29 novel associated genes. *bioRxiv* 222786 (2017). doi:10.1101/222786
52. Naleid, A. M., Grace, M. K., Cummings, D. E. & Levine, A. S. Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. *Peptides* **26,** 2274–2279 (2005).
53. Brunetti, L. *et al.* Effects of ghrelin and amylin on dopamine, norepinephrine and serotonin release in the hypothalamus. *Eur. J. Pharmacol.* **454,** 189–192 (2002).
54. Piggott, L. A., Bauman, A. L., Scott, J. D. & Dessauer, C. W. The A-kinase anchoring protein Yotiao binds and regulates adenylyl cyclase in brain. (2008).
55. Lin, J. W. *et al.* Yotiao , a Novel Protein of Neuromuscular Junction and Brain That Interacts with Specific Splice Variants of NMDA Receptor Subunit NR1. **18,** 2017–2027 (2017).
56. Wu, Q., Clark, M. S. & Palmiter, R. D. Deciphering a neuronal circuit that mediates appetite. *Nature* **483,** 594–597 (2012).
57. Chen, L. T., Gilman, A. G. & Kozasa, T. A Candidate Target for G Protein Action in Brain *. **274,** 26931–26938 (1999).
58. Ness, V. *et al.* Variations in the GRIN2B gene are associated with risky decision-making. *Neuropharmacology* **61,** 950–956 (2011).
59. Reed, Z. E., Micali, N., Bulik, C. M., Smith, G. D. & Wade, K. H. Assessing the causal role of adiposity on disordered eating in childhood, adolescence, and adulthood: A Mendelian randomization analysis. *Am. J. Clin. Nutr.* **106,** 764–772 (2017).
60. Barker, E. T. & Galambos, N. L. Body Dissatisfaction of Adolescent Girls and Boys: *J. Early Adolesc.* **23,** 141–165 (2003).
61. Rosenblum, G. D. & Lewis, M. The relations among body image, physical attractiveness, and body mass in adolescence. *Child Dev.* **70,** 50–64
62. Presnell, K., Bearman, S. K. & Stice, E. Risk factors for body dissatisfaction in adolescent

boys and girls: A prospective study. *Int. J. Eat. Disord.* **36,** 389–401 (2004).
63. Bodell, L. P. & Mayer, L. E. S. Percent body fat is a risk factor for relapse in anorexia nervosa: a replication study. *Int. J. Eat. Disord.* **44,** 118–23 (2011).
64. El Ghoch, M., Calugi, S., Chignola, E., Bazzani, P. V & Dalle Grave, R. Body mass index, body fat and risk factor of relapse in anorexia nervosa. *Eur. J. Clin. Nutr.* **70,** 194–198 (2016).
65. Saito, H., Kubota, M., Roberts, R. W., Chi, Q. & Matsunami, H. RTP Family Members Induce Functional Expression of Mammalian Odorant Receptors. *Cell* **119,** 679–691 (2004).
66. Bitter, T. *et al.* Anosmia Leads to a Loss of Gray Matter in Cortical Brain Areas. *Chem. Senses* **35,** 407–415 (2010).
67. Valdes-Socin, H. *et al.* Reproduction, smell, and neurodevelopmental disorders: genetic defects in different hypogonadotropic hypogonadal syndromes. *Front. Endocrinol. (Lausanne).* **5,** 109 (2014).
68. Martin, G. N. *The Neuropsychology of Smell and Taste*. (Taylor & Francis, 2013).
69. Schecklmann, M. *et al.* Olfaction in child and adolescent anorexia nervosa. *J. Neural Transm.* **119,** 721–728 (2012).
70. Roessner, V., Bleich, S., Banaschewski, T. & Rothenberger, A. Olfactory deficits in anorexia nervosa. *Eur. Arch. Psychiatry Clin. Neurosci.* **255,** 6–9 (2005).
71. Rapps, N. *et al.* Olfactory deficits in patients with anorexia nervosa. *Eur. Eat. Disord. Rev.* **18,** 385–9 (2010).
72. Dazzi, F., Nitto, S. De, Zambetti, G., Loriedo, C. & Ciofalo, A. Alterations of the olfactory-gustatory functions in patients with eating disorders. *Eur. Eat. Disord. Rev.* **21,** 382–385 (2013).
73. Rapps, N. *et al.* Olfactory deficits in patients with anorexia nervosa. *Eur. Eat. Disord. Rev.* **18,** 385–389 (2010).
74. Kim, Y. *et al.* Assessment of gene expression in peripheral blood using RNAseq before and after weight restoration in anorexia nervosa. *Psychiatry Res.* **210,** 287–293 (2013).
75. Yang, Z. *et al.* Association of APC and REEP5 gene polymorphisms with major depression disorder and treatment response to antidepressants in a Han Chinese population. *Gen. Hosp. Psychiatry* **34,** 571–577 (2012).
76. Fox, C. S. *et al.* Genome-wide association to body mass index and waist circumference: the Framingham Heart Study 100K project. *BMC Med. Genet.* **8 Suppl 1,** S18 (2007).
77. Osawa, M. *et al.* CUL3 gene analysis enables early intervention for pediatric pseudohypoaldosteronism type II in infancy. *Pediatr. Nephrol.* **28,** 1881–1884 (2013).
78. Ripke, S. *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511,** 421–427 (2014).
79. Firth, H. V & Wright, C. F. The Deciphering Developmental Disorders (DDD) study. *Dev. Med. Child Neurol.* **53,** 702–703 (2011).
80. Li, Q. S., Tian, C., Seabrook, G. R., Drevets, W. C. & Narayan, V. A. Analysis of 23andMe antidepressant efficacy survey data: implication of circadian rhythm and neuroplasticity in bupropion response. *Transl. Psychiatry* **6,** e889 (2016).
81. Boraska, V. *et al.* A genome-wide association study of anorexia nervosa. *Mol. Psychiatry* (2014). doi:10.1038/mp.2013.187

82. Spada, J. *et al.* Genome-wide association analysis of actigraphic sleep phenotypes in the LIFE Adult Study. *J. Sleep Res.* **25,** 690–701 (2016).
83. Kamboh, M. I. *et al.* Genome-wide association analysis of age-at-onset in Alzheimer's disease. *Mol. Psychiatry* **17,** 1340–6 (2012).
84. Sprooten, E. *et al.* White matter integrity as an intermediate phenotype: exploratory genome-wide association analysis in individuals at high risk of bipolar disorder. *Psychiatry Res.* **206,** 223–31 (2013).
85. Seshadri, S. *et al.* Genetic correlates of brain aging on MRI and cognitive test measures: a genome-wide association and linkage analysis in the Framingham Study. *BMC Med. Genet.* **8 Suppl 1,** S15 (2007).
86. Li, H. *et al.* Candidate single-nucleotide polymorphisms from a genomewide association study of Alzheimer disease. *Arch. Neurol.* **65,** 45–53 (2008).
87. Jun, G. *et al.* A novel Alzheimer disease locus located near the gene encoding tau protein. *Mol. Psychiatry* **21,** 108–17 (2016).
88. Pankratz, N. *et al.* Copy number variation in familial Parkinson disease. *PLoS One* **6,** e20988 (2011).
89. About KOMP | IMPC.
90. Ayadi, A. *et al.* Mouse large-scale phenotyping initiatives: overview of the European Mouse Disease Clinic (EUMODIC) and of the Wellcome Trust Sanger Institute Mouse Genetics Project. *Mamm. Genome* **23,** 600–610 (2012).
91. van der Weyden, L., White, J. K., Adams, D. J. & Logan, D. W. The mouse genetics toolkit: revealing function and mechanism. *Genome Biol.* **12,** 224 (2011).
92. Heid, I. M. *et al.* Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat. Genet.* **42,** 949–60 (2010).
93. Randall, J. C. *et al.* Sex-stratified genome-wide association studies including 270,000 individuals show sexual dimorphism in genetic loci for anthropometric traits. *PLoS Genet.* **9,** e1003500 (2013).
94. Kathiresan, S. *et al.* A genome-wide association study for blood lipid phenotypes in the Framingham Heart Study. *BMC Med. Genet.* **8 Suppl 1,** S17 (2007).
95. Shungin, D. *et al.* New genetic loci link adipose and insulin biology to body fat distribution. *Nature* **518,** 187–196 (2015).
96. Fox, C. S. *et al.* Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. *PLoS Genet.* **8,** e1002695 (2012).
97. Velez Edwards, D. R. *et al.* Gene-environment interactions and obesity traits among postmenopausal African-American and Hispanic women in the Women's Health Initiative SHARe Study. *Hum. Genet.* **132,** 323–36 (2013).
98. Bonder, M. J. *et al.* The effect of host genetics on the gut microbiome. *Nat. Genet.* **48,** 1407–1412 (2016).
99. Levine, D. M. *et al.* A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. *Nat. Genet.* **45,** 1487–93 (2013).
100. Keane, T. M. *et al.* Mouse genomic variation and its effect on phenotypes and gene regulation. *Nature* **477,** 289–294 (2011).
101. Meigs, J. B. *et al.* Genome-wide association with diabetes-related traits in the

Framingham Heart Study. *BMC Med. Genet.* **8 Suppl 1,** S16 (2007).

102. Scott, L. J. *et al.* A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* **316,** 1341–5 (2007).
103. Elks, C. E. *et al.* Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* **42,** 1077–85 (2010).
104. Pickrell, J. K. *et al.* Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* **48,** 709–17 (2016).
105. Root, T. L. *et al.* Patterns of co-morbidity of eating disorders and substance use in Swedish females. *Psychol. Med.* **40,** 105–15 (2010).
106. Murray, G., Allen, N. B. & Trinder, J. Mood and the circadian system: investigation of a circadian component in positive affect. *Chronobiol. Int.* **19,** 1151–69 (2002).
107. Bellivier, F., Geoffroy, P.-A., Etain, B. & Scott, J. Sleep- and circadian rhythm–associated pathways as therapeutic targets in bipolar disorder. *Expert Opin. Ther. Targets* **19,** 747–763 (2015).
108. Murray, G. *et al.* Nature's clocks and human mood: The circadian system modulates reward motivation. *Emotion* **9,** 705–716 (2009).
109. Davis, C. *et al.* The Prevalence of High-Level Exercise in the Eating Disorders: Etiological Implications.
110. Anorexia nervosa with excessive exercise: A phenotype with close links to obsessive-compulsive disorder. *Psychiatry Res.* **142,** 209–217 (2006).
111. The prevalence of high-level exercise in the eating disorders: Etiological implications. *Compr. Psychiatry* **38,** 321–326 (1997).
112. Herpertz, S. *et al.* Longitudinal changes of circadian leptin, insulin and cortisol plasma levels and their correlation during refeeding in patients with anorexia nervosa. *Eur. J. Endocrinol.* **142,** 373–9 (2000).
113. Arble, D. M., Bass, J., Laposky, A. D., Vitaterna, M. H. & Turek, F. W. Circadian timing of food intake contributes to weight gain. *Obesity* **17,** 2100–2102 (2009).
114. Zhang, L., Yagi, M. & Herzog, H. The role of NPY and ghrelin in anorexia nervosa. *Curr. Pharm. Des.* **18,** 4766–4778 (2012).
115. Helder, S. G. & Collier, D. A. The genetics of eating disorders. *Curr. Top. Behav. Neurosci.* **6,** 157–175 (2011).
116. Kojima, M. & Kangawa, K. Ghrelin: structure and function. *Physiol. Rev.* **85,** 495–522 (2005).
117. Dailey, M. J. & Moran, T. H. Glucagon-like peptide 1 and appetite. *Trends Endocrinol. Metab.* **24,** 85–91 (2013).
118. Holst, J. J. The physiology of glucagon-like peptide 1. *Physiol. Rev.* **87,** 1409–1439 (2007).
119. Hellström, P. M. *et al.* GLP-1 suppresses gastrointestinal motility and inhibits the migrating motor complex in healthy subjects and patients with irritable bowel syndrome. *Neurogastroenterol. Motil.* **20,** 649–659 (2008).
120. Atalayer, D., Gibson, C., Konopacka, A. & Geliebter, A. Ghrelin and eating disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **40,** 70–82 (2013).
121. Sullivan, P. F. The psychiatric GWAS consortium: big science comes to psychiatry. *Neuron* **68,** 182–186 (2010).
122. Sullivan, P. F., Daly, M. J. & O'Donovan, M. Genetic architectures of psychiatric disorders:

the emerging picture and its implications. *Nat. Rev. Genet.* **13,** 537–51 (2012).

This manuscript is dedicated to the memory of Professor Pamela Sklar.

Acknowledgements

Data were generated as part of the CommonMind Consortium supported by funding from Takeda Pharmaceuticals Company Limited, F. Hoffman-La Roche Ltd and NIH grants R01MH085542, R01MH093725, P50MH066392, P50MH080405, R01MH097276, RO1-MH-075916, P50M096891, P50MH084053S1, R37MH057881 and R37MH057881S1, HHSN271201300031C, AG02219, AG05138 and MH06692.

Brain tissue for the study was obtained from the following brain bank collections: the Mount Sinai NIH Brain and Tissue Repository, the University of Pennsylvania Alzheimer's Disease Core Center, the University of Pittsburgh NeuroBioBank and Brain and Tissue Repositories and the NIMH Human Brain Collection Core. CMC Leadership: Pamela Sklar, Joseph Buxbaum (Icahn School of Medicine at Mount Sinai), Bernie Devlin, David Lewis (University of Pittsburgh), Raquel Gur, Chang-Gyu Hahn (University of Pennsylvania), Keisuke Hirai, Hiroyoshi Toyoshiba (Takeda Pharmaceuticals Company Limited), Enrico Domenici, Laurent Essioux (F. Hoffman-La Roche Ltd), Lara Mangravite, Mette Peters (Sage Bionetworks), Thomas Lehner, Barbara Lipska (NIMH).

The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained from the GTEx Portal on 09/05/16. BrainSpan: Atlas of the Developing Human Brain [Internet]. Funded by ARRA Awards 1RC2MH089921-01, 1RC2MH090047-01, and 1RC2MH089929-01.

UK BioBank analyses were carried out using results obtained from the Neale and Rivas Labs. Results were downloaded from the Global Biobank Engine (Global Biobank Engine, Stanford, CA (URL: http://gbe.stanford.edu) [September 30th, 2017]. The authors would like to thank the Rivas lab for making the resource available.

Acknowledgements for the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED)

The Wellcome Trust Wellcome Trust WT088827/Z/09; WT098051;

Swedish Research Council (VR Dnr: 538-2013-8864);

We thank the Price Foundation for their support of recruiting patients, collecting clinical information and providing DNA samples used in this study. We also thank the Klarman Family Foundation for supporting the study. We thank the technical staff at the Center for Applied Genomics (CAG) at CHOP for generating genotypes used for analyses and the nursing, medical assistant and medical staff for their invaluable assistance with sample collection. Yiran Guo was funded by the 2011-2014 Davis Foundation Postdoctoral Fellowship Program in Eating Disorders Research Award. Dong Li was funded by the 2012-2015 Davis Foundation Postdoctoral Fellowship Program in Eating Disorders Research Award. Genome-wide genotyping for CHOP samples was funded by an Institutional Development Fund to CAG from CHOP. The study was additionally funded through the Electronic Medical Records and Genomics (eMERGE) Network (U01 HG006830) by National Human Genome Research Institute of National Institutes of Health, and also funded by donation from the Kurbert Family;

National Institutes of Health: K01MH093750; K01MH106675; K01MH109782; K02AA018755-06, R01AA015416-08, 5U01MH094432-04, 3U01MH094432-03S1; R01 MH109528; D0886501; R01 MH092793;

This work received grants from EC Framework V Factors in Healthy Eating, from INRA/INSERM (4M406D), and from PHRC ENDANO (2008-A01636-49);

European Commission (2008-2011) as an Early Stage Researcher from the Research Training Network INTACT (Individually Tailored Stepped Care for Women with Eating Disorders) in the Marie Curie Program (MRTN-CT-2006-035988);

Gerome Breen acknowledges support from the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Veneto Region Grant BIOVEDA; Contract grant number: DGR 3984/08;

Academy of Finland (28327, 286028); (Dr. Raevuori, grant number 259764);

The German Ministry for Education and Research (National Genome Research Net-Plus 01GS0820 and 01KU0903), the German Research Foundation (DFG; HI865/2-1), the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 245009 and no.262055." We thank the German Ministry for Education and Research for funding the ANTOP-study (project number 01GV0624)
AS was supported by the Federal Ministry of Education and Research (BMBF), Germany, FKZ 01EO1502; German Federal Ministry for Education and Research (BMBF) 01GV0601 and 01GV0624; German Ministry for Education and Research (National Genome Research Net-Plus 01GS0820) and the German Research Foundation (DFG; HI865/2-1); MHT received grant support from the Alexander von Humboldt Foundation, the Helmholtz Alliance ICEMED-Imaging and Curing Environmental Metabolic Diseases, through the Initiative and Networking Fund of the Helmholtz Association, the Helmholtz cross-program topic "Metabolic Dysfunction," and the Deutsche Forschungsgemeinschaft (DFG-TS226/1-1 and TS226/3-1) and the European Research Council Consolidator Grant (HepatpMetaboPath)"

Ministry for Research and Education, Germany; The Helmholtz Alliance ICEMED-Imaging and Curing Environmental Metabolic Diseases, through the Initiative and Networking Fund of the Helmholtz Association, the Helmholtz cross-program topic "Metabolic Dysfunction," and the Deutsche Forschungsgemeinschaft (DFG-TS226/1-1 and TS226/3-1); This work was supported by the Deutsche Forschungsgemeinschaft (EH 367/5-1 and SFB 940) and the Swiss Anorexia Nervosa Foundation;

Andrew Bergen is supported by a Professional Services Agreement with the Regents of the University of California; Resnick Family Chair in Eating Disorders; Klarman Family Foundation;

Research Council of Norway (RCN), and South-East Norway Regional Health Authority (SEN); Bergen Research Foundation, NFR (NORMENT-SFF), NCNG: This sample collection was supported by grants from the Bergen Research Foundation and the University of Bergen, the Dr Einar Martens Fund, the K.G. Jebsen Foundation, the Research Council of Norway, to SLH, VMS and TE; Supported by the Research Council of Norway (#248778, # 223273); The twin program of research at the Norwegian Institute of Public Health was supported by grants from The Norwegian Research Council and The Norwegian Foundation for Health and Rehabilitation;

China Scholarship Council (Shuyang Yao);

Genome Canada, the government of Ontario, the Canadian Institutes of Health Research, University of Toronto McLaughlin Centre; Ontario Mental Health Foundation for funding the recruitment and collection of the DNA samples. Ministry of Health of Ontario AFP Innovation Fund;

1109 Grants 324715 and 480420 from the National Health and Medical Research Council
1110 (NHMRC) to TDW supported this work. Administrative support for data collection was
1111 received from the Australian Twin Registry, which is supported by an Enabling Grant (ID
1112 310667) from the NHMRC administered by the University of Melbourne;
1113 Matthew Flinders Fellowship, Flinders University, South Australia, Australia
1114
1115 Internal Grant Agency of the Ministry of Health of the Czech Republic IGA MZ _R NT 14094-
1116 3/2013;
1117
1118 Research of Korea Centers for Disease Control and Prevention Fund (code# HD16A1351);
1119
1120 Nicole Soranzo's research is supported by the Wellcome Trust (Grant Codes WT098051 and
1121 WT091310), the EU FP7 (EPIGENESYS Grant Code 257082 and BLUEPRINT Grant
1122 Code†HEALTH-F5-2011-282510) and the National Institute for Health Research Blood and
1123 Transplant Research Unit (NIHR BTRU) in Donor Health and Genomics at the University of
1124 Cambridge in partnership with NHS Blood and Transplant (NHSBT). The views expressed are
1125 those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of
1126 Health or NHSBT.
1127
1128 Psychiatry Research Trust (registered charity no. 284286);
1129
1130 Spanish Ministry of Economy and Competitiveness (MINECO) no. SAF2013-49108-R, the
1131 Generalitat de Catalunya AGAUR 2014 SGR-1138, the European Commission 7th Framework
1132 Program (FP7/2007-2013) 262055 (ESGI); Instituto de Salud Carlos III (FIS PI14/290 and
1133 CIBERobn
1134
1135 Supported by MH CZ - DRO (MMCI, 00209805);

1136

1137 An unrestricted grant from the Lundbeck Foundation, iPSYCH (Initiative for Integrative
1138 Psychiatric Research); and by Aarhus University for CIRRAU (Centre of Integrated Register-
1139 Based Research);

1140

1141 This research was supported by a ZonMW VIDI Grant (91786327) from The Netherlands
1142 Organization for Scientific Research (NWO) to Prof. dr. Martien Kas;

1143

1144 This study was supported by EU H2020 grants 692145, 676550, 654248, Estonian Research
1145 Council Grant IUT20-60, NIASC, EIT ñ Health and NIH-BMI Grant No: 2R01DK075787-06A1
1146 and EU through the European Regional Development Fund (Project No. 2014-2020.4.01.15-
1147 0012 GENTRANSMED;

1148

1149 Ulrike Schmidt receives salary report from the National Institute of Health Research Mental
1150 Health Biomedical Research Centre at South London and Maudsley National Health Service
1151 Foundation Trust and King's College London.

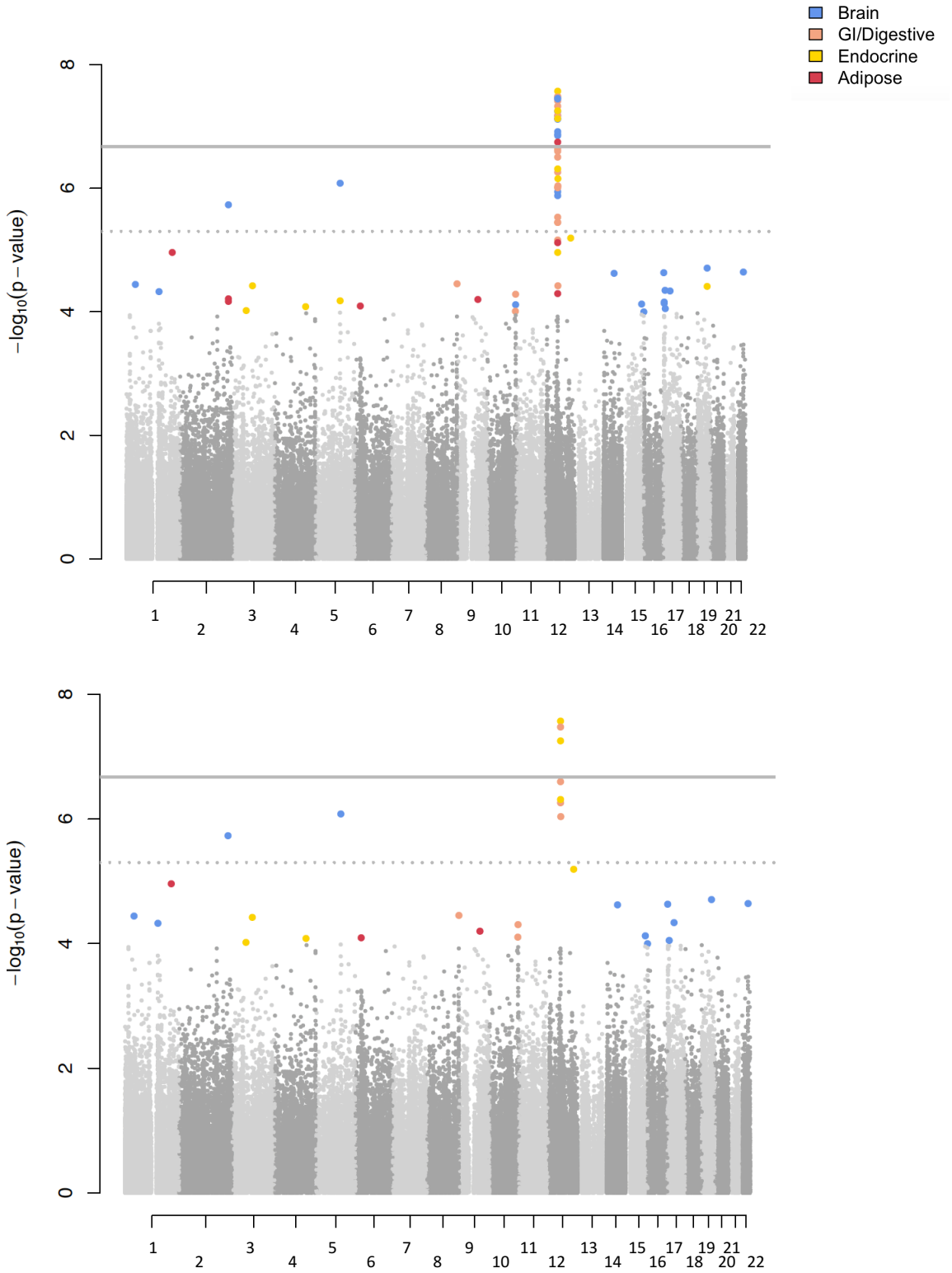

Figure 1: Genic associations in Anorexia Nervosa
A) We identify 37 significant gene-tissue associations across brain, GI/digestive, endocrine, and adipose tissues
B) 14 gene-tissue associations remain significant after applying CoCo and FINEMAP.

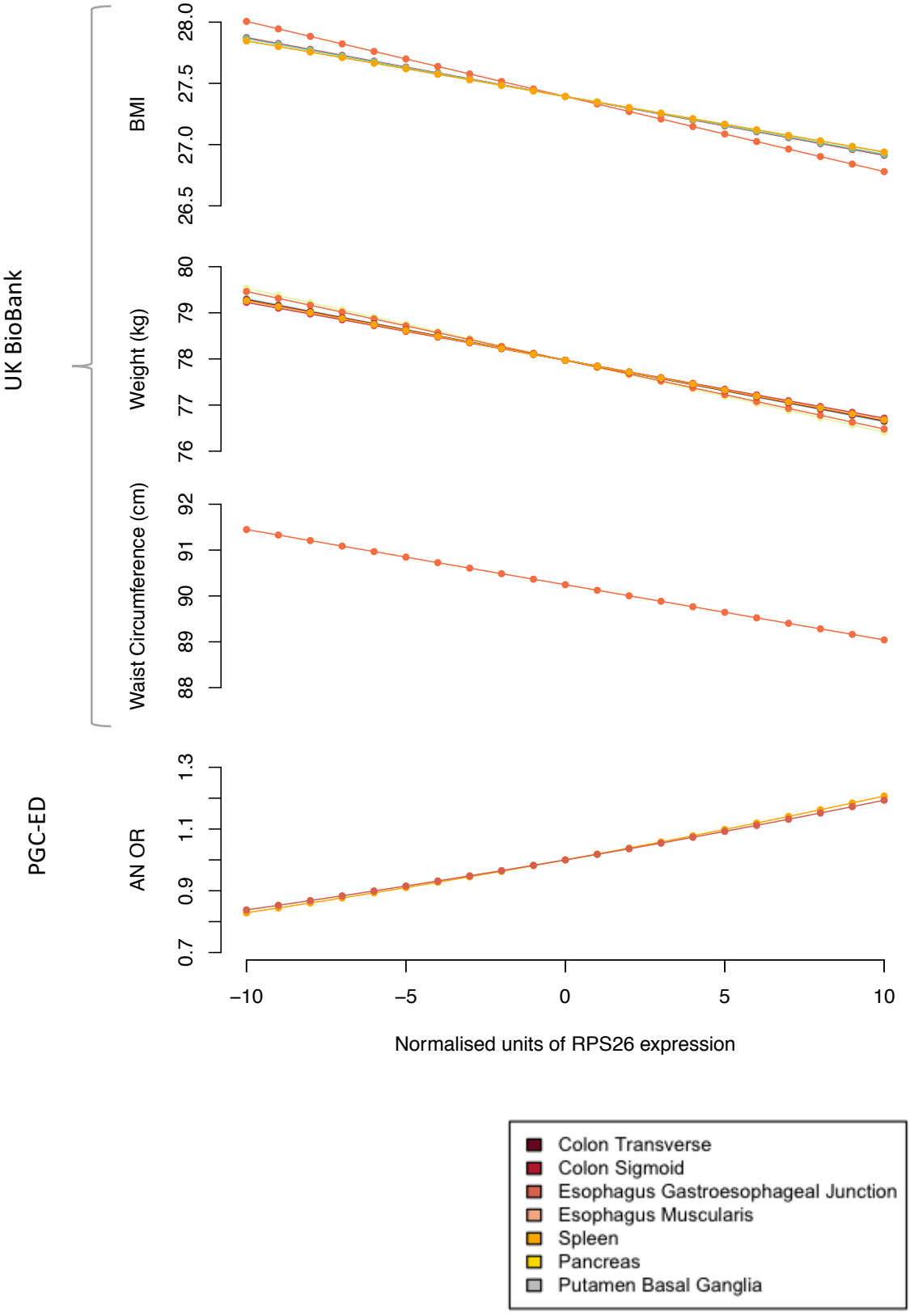

Figure 2A: Genetically regulated expression of *RPS26* is significantly associated with BMI, weight and waist circumference in the UK BioBank, and with AN in PGC-ED

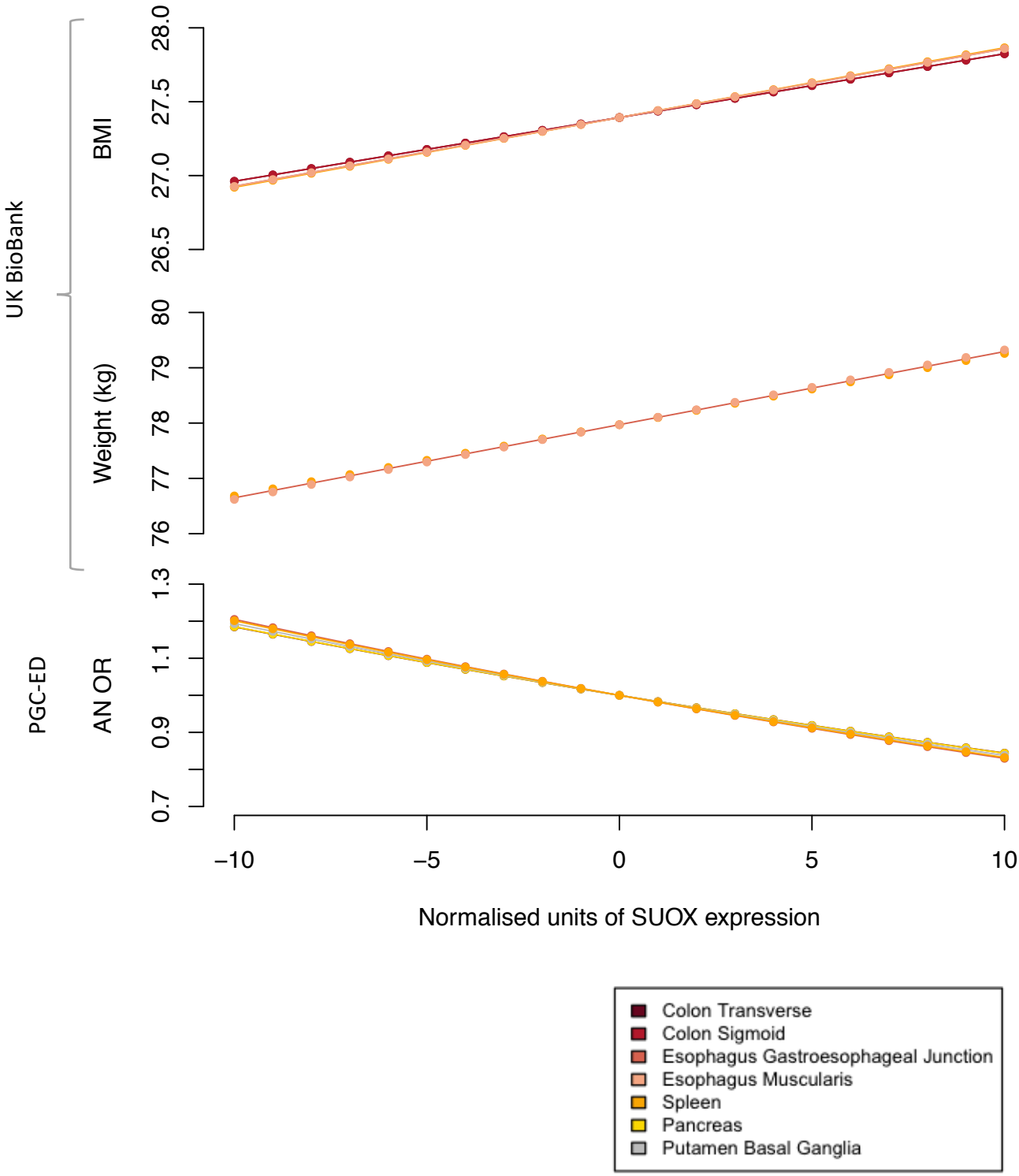

Figure 2B: Genetically regulated expression of *SUOX* is significantly associated with BMI and weight in the UK BioBank, and with AN in PGC-ED

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
ENSG000001	CITED4	Putamen Bas	0.021	0.0051	3.63E-05	+++++--+++-+
ENSG000001	LYSMD1	Cerebellar He	-0.068	0.0166	4.78E-05	+--+--------
ENSG000001	VASH2	Adipose Sub	-0.152	0.0345	1.10E-05	--+--+--+-+-
ENSG000000	CUL3	Caudate Basa	0.072	0.0151	1.86E-06	+-+++++++++
ENSG000001	ADAMTS9	Adrenal Glan	0.078	0.02	9.56E-05	++--+--+-+++
ENSG000001	ARL13B	Pancreas	0.382	0.0929	3.84E-05	++-++-+++++-
ENSG000001	INPP4B	Pancreas	-0.160	0.0407	8.30E-05	------+--+--
ENSG000001	REEP5	DLPFC	-0.160	0.0325	8.34E-07	---------++-
ENSG000001	TRIM38	Adipose Sub	0.091	0.0231	8.05E-05	++++++-++-+-
ENSG000001	FBXL6	Liver	-0.133	0.0323	3.58E-05	-+++-+-+----
ENSG000001	BARX1	Adipose Subc	0.085	0.0211	6.38E-05	+--+++-+++-+
ENSG000001	FOXI2	Colon Transv	-0.650	0.1667	9.73E-05	--+-------+-
ENSG000001	MGMT	Small Intestir	-0.031	0.0076	5.22E-05	-----++-----
ENSG000001	RPS26	Spleen	0.120	0.0215	2.70E-08	++++++-++++
ENSG000001	SUOX	Esophagus G	-0.059	0.0107	3.41E-08	------+-----
ENSG000001	SUOX	Spleen	-0.053	0.0098	5.61E-08	-----++-+---
ENSG000001	SUOX	Putamen Bas	-0.077	0.0147	1.42E-07	-----+------
ENSG000001	RPS26	Esophagus G	0.141	0.0274	2.54E-07	++++++-++++
ENSG000001	SUOX	Pancreas	-0.035	0.007	4.95E-07	------+-----
ENSG000001	SUOX	Colon Transv	-0.059	0.0117	5.47E-07	------+-----
ENSG000001	RDH16	Small Intestir	0.098	0.0199	9.09E-07	++-++--+++++
ENSG000001	C12orf49	Thyroid	0.352	0.0779	6.49E-06	-+--+-++-+++
ENSG000001	FURIN	Putamen Bas	0.114	0.0287	7.64E-05	+++-++-++++-
ENSG000000	CTNS	Hippocampu	0.028	0.0071	6.90E-05	+++-++++++--
ENSG000000	NTN1	Nucleus Accu	0.395	0.1008	8.88E-05	++-+++-+--++
ENSG000001	TMEM108	Cortex	0.602	0.1475	4.47E-05	++--+--++-++
ENSG000001	YWHAE	Hypothalamu	0.050	0.0119	2.37E-05	++++++-++++
ENSG000000	ZNF207	Anterior Cing	-0.026	0.0063	4.55E-05	----+-+-----
ENSG000002	ZNF225	Spleen	0.104	0.0252	3.92E-05	++++++++-++
ENSG000001	ZNF235	Frontal Corte	0.433	0.1014	1.96E-05	++-+++-+-+++
ENSG000001	SMDT1	Cerebellar He	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

Trait	Gene	Gene Name
Body_mass_index_(BMI)	ENSG000001	BARX1
Body_mass_index_(BMI)	ENSG000001	BARX1
Body_mass_index_(BMI)	ENSG000001	RDH16
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	RPS26
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	SUOX
Body_mass_index_(BMI)	ENSG000001	TRIM38
Body_mass_index_(BMI)	ENSG000001	TRIM38
Waist_circumference	ENSG000001	BARX1
Waist_circumference	ENSG000001	BARX1
Waist_circumference	ENSG000001	RPS26
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT
Weight	ENSG000001	MGMT

Weight	ENSG000001 RDH16
Weight	ENSG000001 REEP5
Weight	ENSG000001 REEP5
Weight	ENSG000001 REEP5
Weight	ENSG000001 REEP5
Weight	ENSG000001 REEP5
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 RPS26
Weight	ENSG000001 SUOX
Weight	ENSG000001 SUOX
Weight	ENSG000001 SUOX
Weight	ENSG000001 SUOX
Weight	ENSG000001 SUOX
Weight	ENSG000001 SUOX
Weight	ENSG000001 SUOX
Weight	ENSG000001 TRIM38
Weight	ENSG000001 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

SYSTEM	SOURCE
All Tissues	Drug targets
All Tissues	Drug targets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	GWAS gene sets
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven
All Tissues	Hypothesis Driven

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 Region	Drug targets
Brain Region	Drug targets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	GWAS gene sets
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven

Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven
Brain Region	Hypothesis Driven

Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic
Brain Region	Agnostic

Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic
Brain Region Agnostic

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 uopn Ca2+ infux through NMDA receptor	16
morphogenesis of embryonic epithelium	127
abnormal embryonic tissue morphology	638
Metabotropic glutamate receptor group I pathway	22
5HT1 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