A genome-wide association study of anorexia nervosa suggests a risk locus implicated in dysregulated leptin signaling

Dong Li, Xiao Chang, John J. Connolly, Lifeng Tian, Yichuan Liu, Elizabeth J. Bhoj, Nora Robinson, Debra Abrams, Yun R. Li, Jonathan P. Bradford, Cecilia E. Kim, Jin Li, Fengxiang Wang, James Snyder, Maria Lemma, Cuiping Hou, Zhi Wei, Yiran Guo, Haijun Qiu, Frank D. Mentch, Kelly A. Thomas, Rosetta M. Chiavacci, Roger Cone, Bingshan Li, Patrick A. Sleeiman, Eating Disorders Working Group of the Psychiatric Genomics Consortium*, Price Foundation Collaborative Group* & Hakon Hakonarson

We conducted a genome-wide association study (GWAS) of anorexia nervosa (AN) using a stringently defined phenotype. Analysis of phenotypic variability led to the identification of a specific genetic risk factor that approached genome-wide significance (rs929626 in EBF1 (Early B-Cell Factor 1); $P = 2.04 \times 10^{-7}$; OR = 0.7; 95% confidence interval (CI) = 0.61–0.8) with independent replication ($P = 0.04$), suggesting a variant-mediated dysregulation of leptin signaling may play a role in AN. Multiple SNPs in LD with the variant support the nominal association. This demonstrates that although the clinical and etiologic heterogeneity of AN is universally recognized, further careful sub-typing of cases may provide more precise genomic signals. In this study, through a refinement of the phenotype spectrum of AN, we present a replicable GWAS signal that is nominally associated with AN, highlighting a potentially important candidate locus for further investigation.

Anorexia nervosa (AN) is a complex and often chronic eating disorder characterized by inability to maintain a normal healthy body weight and a persistent fear of weight gain, resulting in extreme emaciation and even death in some cases. Previous genetic and epidemiological studies have indicated a multifactorial etiology, where both genetic and environmental factors contribute to disease risk. As sample sizes have increased, genome-wide association studies (GWASs) of AN have begun to identify risk variants. To further elucidate the genetic architecture of AN, we performed a GWAS using data from our previously published study consisting of 1,033 AN cases by excluding 212 patients with AN who experienced diagnostic crossover during the course of their illness. Specifically, we excluded patients who migrated from or to binge-eating disorder (BED) or bulimia nervosa (BN) as assessed with the Structured Interview for Anorexic and Bulimic Disorders. Although a previous study indicated women with BN were rarely to cross over to AN, we observed ~43% of AN/BN crossover cases falls into this category in our cohort, suggestive of a confounding factor. We hypothesized that this reduction in phenotypic heterogeneity, despite the fact that AN and BN may share some genetic risk factors, would enhance gene discovery.

Results
Our discovery cohort included a total of 692 female AN cases of non-Hispanic European (NHE) descent. Cases were included if they were diagnosed with restricting type and binge eating/purging type of AN as defined by

1 Center for Applied Genomics, Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 2 Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN, USA. 3 Department of Human Genetics, Children’s Hospital of Philadelphia, Philadelphia, PA, USA. 4 Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. 5 Present address: Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI, USA. Dong Li and Xiao Chang contributed equally to this work. *A comprehensive list of consortium members appears at the end of the paper. Correspondence and requests for materials should be addressed to D.L. (email: lid2@email.chop.edu) or H.H. (email: hakonarson@chop.edu)
Both types are characterized by below-normal weight and restricted food intake. Individuals diagnosed as restricting type do not experience binge-eating episodes and do not engage in purging, such as vomiting or use of laxatives. Standard quality controls measures were applied, specifically, excluding potential cryptic relatedness and checking for population stratification (details described elsewhere). The average age of onset of the case subjects was 16.3 years with a standard deviation (SD) of 3 years (Interquartile Range; IQR = 16(14–18)). The control group included 3,570 female matched healthy adolescents of NHE ancestry that had an average age of 18.3 years at the time of data analysis (SD = 5.7; IQR = 19(13–23)) (Supplementary Table 1). Associations were assessed with 507,999 SNPs genotyped on either Illumina HumanHap550 or Human610-Quad BeadChips in an additive model using logistic regression analyses with principal components adjustment, based on the principal component analysis of cases and controls (Supplementary Figure 1), resulting in significantly low level of genomic control inflation factor of 1.03 (Supplementary Figure 2). The analysis yielded one SNP (rs929626) with a P value of $2.04 \times 10^{-7}$ and 4 other SNPs with marginally larger P values that are in strong linkage disequilibrium ($r^2 > 0.8$); these SNPs were selected for further analysis (Supplementary Figure 3; Supplementary Table 2).

Using imputation analysis based on data from the 1000 Genomes Project (Phase I integrated variant set, v2, March 2012), we subsequently tested associations with SNPs (imputed info > 0.5, minor allele frequency (MAF) > 0.05) located in a 200-kb window centered on the SNP rs929626. We observed association with a series of markers around this region, of which 34 SNPs supported suggestive associations (P < 1.0 × 10^{-6}) with both imputed and genotyped SNPs, which were in high LD with AN (Fig. 1; Supplementary Table 3). This suggests that the single markers demonstrating nominal association in the GWAS are likely to be true positives.

We further explored this finding using the meta-analysis results from 15 previously reported AN cohorts. Interestingly, two SNPs were also nominally significant (rs929626 with P = 0.037 and rs17543752 with P = 0.05) in the same direction as in the GWAS (Table 1). Meta-analysis results in a P value of 1.52 × 10^{-7}.

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We next used the ENCODE project data to predict possible functional effect of the SNPs identified in this study. The top SNP, rs929626, and other significant markers located in the 6th intron of the EBF1 gene (Early B-Cell Factor 1) as well as two SNPs (rs113252656 and rs1081071) flanking the top SNP rs929626 at $r^2 > 0.5$ function as binding sites for EBF1 itself (HaploReg v4.1; ref. 15). This suggests that these genetic variants may modulate the expression of EBF1. Indeed, we observed a positive correlation with the rs929626 C allele carriers compared with TT homozygotes on the EBF1 expression level in nine independent subjects (the FPKM

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**Table 1.** Association results for the lead genotyped SNP. Abbreviations: MA, minor allele; OR, odds ratio; SE, standard error; L95, lower 95% confidence interval; U95, upper 95% confidence interval; P, P-value.

| SNP     | Study | MA  | OR   | SE  | L95     | U95     | P       |
|---------|-------|-----|------|-----|---------|---------|---------|
| rs929626| CHOP  | C   | 0.7004 | 0.06855 | 0.6123 | 0.8011 | 2.04E-07 |
|         | PGC-ED| C   | 0.938252 | 0.027953 | 0.883465 | 0.966437 | 0.037887 |

**Figure 1.** Region of genome-wide nominal association at 5q33.3. Regional plot of the EBF1-associated interval for the imputation analysis. Foreground shows scatter plot of the $-\log_{10} P$ values plotted against physical position of human reference hg19. Background shows estimated recombination rates plotted to reflect the local LD structure. The color of the dots represents the strength of LD between the top SNP (rs929626) and its proxies (red, $r^2 \geq 0.8$; orange, $0.8 > r^2 > 0.6$; green, $0.6 > r^2 > 0.4$; blue and navy; $r^2 < 0.4$). Genes, position of exons, and direction of transcription from UCSC genome browser (http://genome.ucsc.edu) are noted.
value for TT homozygotes (3 subjects) versus C allele carriers (6 individuals) is 5.0 versus 6.4) with both whole genome sequencing data of blood and corresponding RNA-Seq data of heart right ventricle selected from the Pediatric Cardiac Genomics Consortium cohort (dbGaP Study Accession: phs000571.v3.p2). By using the Genotype-Tissue Expression Portal database (http://www.gtexportal.org), we also observed nominally significant expression quantitative trait loci (eQTLs) association ($P = 0.0024$, tested in 97 samples) in the putamen for rs929626 in the same direction. A few comorbid psychiatric disorders have been linked with the function of the putamen, such as anxiety, obsessive-compulsive disorder and attention deficit-hyperactivity disorder$^{16-18}$. Taken together, these suggest the minor allele C carriers have relatively higher EBF1 expression.

Discussion

EBF1 encodes a transcription factor that originally thought to function as necessary for the development of the immune system$^{19}$, but it has since been shown to regulate the development of both osteoblast and adipocyte lineages$^{20-22}$. Two EBF1 variants, rs11953630- T and rs9313772- T, showed significant association at genome-wide level ($P < 5 \times 10^{-8}$) in a study testing blood pressure in European whites$^{23,24}$. In addition, rs17056278- C was also identified as a metabolic risk allele, interacting with psychosocial stress to contribute to increased hip circumference ($P = 3 \times 10^{-4}$)$^{25}$. However none of these is in LD with any markers in our identified locus. In animal studies, Ebf1−/− mice showed increased adipose tissue within marrow, whereas peripheral white adipose tissue was severely reduced. Circulating levels of leptin, a hormone released by adipocytes and one of the major players in food intake regulation, were also decreased in Ebf1−/− mice compared with controls$^{26}$. This concurs with the reported generalized loss of accumulation of subcutaneous and visceral adipose accompanied by significant increases in yellow marrow in AN patients$^{27,28}$. Also notable is the finding that circulating levels of leptin are very low in AN patients$^{29,30}$ and a decline in levels of circulating leptin can lead to changes in brain activity in areas involved in regulatory, emotional, and cognitive control of appetite.

Understanding the genetics of AN is currently a major within-field initiative, in parallel to other neuropsychiatric/neurodevelopmental disorders such as schizophrenia, bipolar disorder, and autism spectrum disorders. Although the clinical and etiologic heterogeneity is universally recognized, in practice, many studies still failed to account for sample heterogeneity. In this study, by focusing on individuals with AN who have not crossed over to BN or BED, we have identified a marginally replicating GWAS signal that approached genome-wide significance. One limitation of our study is that all participants may not yet have experienced the full course of their eating disorder (The average duration of follow-up was 8.6 years with a SD of 7.0 years in the discovery cohort, while the average crossover time was 2.8 years with a SD of 2.6 years for the excluded AN patients), and a portion of the sample may develop BN or BED at later stages of illness. This would represent a conservative bias and underscores the importance of further investigation of this locus in the future focusing on individuals with lifetime AN who have never crossed over to other eating disorder presentations.

Methods

Discovery data set and quality control. We conducted a GWAS using data from our previously published study$^{6}$ consisting of 1,033 AN cases by excluding 212 patients with AN who experienced diagnostic crossover during the course of their illness (i.e. migrated from or to binge-eating disorder (BED) or bulimia nervosa (BN) as assessed with the Structured Interview for Anorexic and Bulimic Disorders$^{11}$) plus 100 patients without such information. A total of 692 female AN cases and 3,570 female matched controls that were carefully selected from Center for Applied Genomics (CAG) data sets were included in the analysis after Standard quality controls, namely, excluding potential cryptic relatedness and checking for population stratification by using the PLINK software$^{31}$ version 1.90a. The Research Ethics Board of CHOP and other participating centers approved the study. Informed consent was obtained from all adult participants and from a parent or legal guardian in the case of children and all work followed was in accordance with an IRB-approved protocol.

Association tests. For the genome-wide association analysis for SNPs, we utilized the PLINK software$^{31}$ version 1.90a, through Cochran–Armitage trend test.

Expression studies. The extended locus around associated SNP was then defined by identification of all SNPs showing $r^2 > 0.5$. Linkage disequilibrium (LD) was defined with the HaploReg v4.1 (ref. 15) based on Phase I of the 1000 Genomes project. Variants showing evidence of LD with associated AN variants were explored for impact on gene function via regulatory function (including eQTLs) by HaploReg v4.1, which both collate data from the Encyclopedia of DNA Elements (ENCODE)$^{14}$. We also referred to the Genotype-Tissue Expression Portal database (http://www.gtexportal.org) for eQTLs analysis.

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D.L. and H.H. were leading contributors in the design, analysis and writing; D.L., X.C., Y.L., J.P.B. and P.S contributed to data analysis; J.C., L.T., N.R., D.A., Y.R.L. contributed samples and phenotypes. C.E.K., J.L., F.W., J.S., M.L., C.H., Z.W., Y.G., H.Q., F.M., K.T., R.C., B.L., and R.C. provided assistance with samples and data processing. Eating Disorders Working Group of the Psychiatric Genomics Consortium and Price Foundation Collaborative Group provided data for the replication and helped with the discussion; D.L. drafted the manuscript. D.L., J.J.C., E.J.B. and H.H. revised the manuscript. All authors approved final version of manuscript.

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Consortia
Eating Disorders Working Group of the Psychiatric Genomics Consortium
Vesna Boraska Perić6,7, Christopher S. Franklin5, James A. B. Floyd6,8, Laura M. Thornton9,
Laura M. Huckins4, Lorraine Southam4, N. William Rayner6,10,11, Ioanna Tachmazidou4, Kelly
L. Klump12, Janet Treasure13, Ulrike Schmidt13, Federica Tozzi13, Kirsty Kiezebrink14, Johannes
Hebebrand15, Philip Gorwood16,17, Roger A. H. Adan18,19, Martien J. H. Kas18 Angela Favaro20,
Paolo Santonastaso20, Fernando Fernández-Aranda21,22, Monica Gratacos23,24,25,26, Filip
Rybakovski23, Monika Dmitriacz-Weglarcz28, Jaakko Kaprio29,30,31, Anna Keski-Rahkonen29,
Anu Raeuvori-Helkamaa28,32, Eric F. Van Fruh33,34, Margarita C. T. Slof Op’t Landt33,35,
James I. Hudson36, Ted Reichborn-Kjennerud37,38, Gun Peggy S. Knudsen37, Palmiro
Monteleone39,40, Allan S. Kaplan41,42, Andreas Karwautz35, Wade H. Berrettini44, Nicholas J.
Schork45, Tetsuya Ando46, Hidotsuho Inoko47, Tôn Ooku48, Krista Fischer48, Katrin Männik49,50,
Andres Metspalu48,49, Jessica H. Baker4, Janice E. De Socio51, Christopher E. Hilliard9, Julie
K. O’Toole52, Jacques Pantel53, Jin P. Szatkiewicz54, Stephanie Zerwas5, Oliver S. P. Davis5,56,
Siets Helder54, Katharina Bührken57, Roland Burghardt58, Martina de Zwaan59,60, Karin
Egberts61, Stefan Ehrlich62,63, Beate Herpertz-Dahlmann64, Wolfgang Herzog65,8, Hartmut
Imag66, André Scherag67, Stephan Zipfel68, Claudette Boni69, Nicolas Ramoz70,71, Audrey
Versini72, Unna N. Danner73, Judith Hendriks74, Bobby P. C. Koelemann69, Roel A. Offhoff70,71,
Eric Strengman75, Annemarie A. van Elburg76,77, Alice Bruson78, Maurizio Clementi75,
Daniela Degortes79, Monica Forzan79, Elena Tenconi80, Elisa Docamo23,24,25,26, Georgiá
Escaramis23,24,25,26, Susana Jiménez-Murcia21,22, Jolanta Lisowska74, Andrzej Rajewski75,
Neoníla Szeszenia-Dabrowska75, Agnieszka Słopien28, Joanna Hauser28, Leila Karhunen76,
Ingrid Meulenbelt35, P. Eline Slagboom29, Alfonso Tortorella39, Mario Maj35, George
Dedoussis35, Dimitris Dikeos79, Fragiskos Goniadakis80, Konstantinos Tziouvas78, Artemis
Tsitsika81, Hana Papezova6, Lenka Slachtová83, Debora Martaskova82, James L. Kennedy41,42,
Robert D. Levitan41,42, Zeynep Yilmaz49, Julia Huemer43, Doris Koubek43, Elisabeth Merli44,
Gudrun Wagner44, Paul Lichtenstein85,4, Gerome Breen44, Sarah Cohen-Woods85, Anne
Farmer55, Peter McGuinness54, Sven Cichon86,87, Ina Giegling88, Stefan Herms85,87, Dan
Rujescu89, Stefan Schreiber89, H-Erich Wichmann90,91, Christian Dina92, Rob Sladek93, Giovanna
Gamborino94,95, Nicole Soranzo96, Antonio Julia96, Sara Marsal97, Raquel Rabionet97,98,99, Valérie
Gaborieau100, Danièle M. Dick97, Aarno Palotie100,101, Samuli Ripatti98,99, Elisabeth Widén98,99,100,
Ole A. Andreassen101, Thomas Espeseth101,102, Astri Lundervold103,104,105, Ivar Reinvang106,
Vidar M. Steen106,107, Stephanie Le Hellard106,107, Morton Mattingsdal105, Ina Ntalla78,
Vladimir Bencko108, Lenka Foretova109, Vladimir Janout110, Marie Navratilova109, Steven
Gallinger111, Dalila Pinto112, Stephen W. Scherer113, Harald Aschauer114, Laura Carlberg114,
Alexandra Schosser114, Lars Alfredsson115, Bo Ding115, Lars Klareskog116, Leonid Padyukov116,
Chris Finan117, Gursharan Kalsi117, Marion Roberts55, Jeff C. Barrett118, Xavier Estivill121,23,24,25,26, Anke
Hinney119, Patrick F. Sullivan55,111, Eleftheria Zeggini18 & Cynthia M. Bulik59,117

14Health Services Research Unit, University of Aberdeen, Aberdeen, UK. 15Wellcome Trust Sanger Institute,
Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. 16University of Split School of Medicine, Split, Croatia.
17William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of
London, John Vane Science Centre, Charterhouse Square, London, UK. 18Department of Psychiatry, University of
North Carolina at Chapel Hill, Chapel Hill, NC, USA. 19Wellcome Trust Centre for Human Genetics (WTCHG),
University of Oxford, Oxford, UK. 20Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), Oxford,
UK. 21Department of Psychology, Michigan State University, East Lansing, MI, USA. 22Section of Eating Disorders,
Institute of Psychiatry, King’s College London, London, UK. 23Department of Child and Adolescent Psychiatry,
Psychosomatics and Psychotherapy, Universitätsklinikum Essen, University of Duisburg-Essen, Essen, Germany.
24INSERM U894, Centre de Psychiatry and Neurosciences Psychiatrie et Neurologie, Paris, France. 25Sainte-Anne Hospital (CMME), University of
Paris-Descartes, Paris, France. 26Brain Center Rudolf Magnus, Department of Translational Neuroscience,
University Medical Center Utrecht, Utrecht, The Netherlands. 27Altrecht Eating Disorders Rintved, Zeist, The
Netherlands. 28Department of Neurosciences, University of Padova, Padova, Italy. 29Department of Psychiatry and
CIBERON, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain. 30Department of Clinical Sciences, School of
Medicine, University of Barcelona, Barcelona, Spain. 31Genomics and Disease Group, Centre for Genomic
Regulation (CRG), Barcelona, Spain. 32Universitat Pompeu Fabra (UPF), Barcelona, Spain. 33Centro de Investigación
Biomédica en Red en Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. 34Hospital del Mar Medical
Research Institute (IMIM), Barcelona, Spain. 35Department of Child and Adolescent Psychiatry, Institute of
Psychiatry and Neurology, Warsaw, Poland. 36Department of Child and Adolescent Psychiatry, Department of
Psychiatry, Poznan University of Medical Sciences, Poznan, Poland. 37Hjelt Institute, University of Helsinki, Helsinki,
Finland. 38Institute of Molecular Medicine, University of Helsinki, Helsinki, Finland. 39Department of Mental Health

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for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway.
32Department of Psychiatry, University of Naples SUN, Naples, Italy. 66Chair of Psychology, University of Salerno, Salerno, Italy. 42Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada. 44Department of Psychiatry, University of Toronto, Toronto, Canada.
47Eating Disorders Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria.
49Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. 46Department of Molecular and Experimental Medicine and The Scripps Translational Science Institute, The Scripps Research Institute, La Jolla, CA, USA. 46Department of Psychosomatic Research, National Institute of Mental Health, NCNP, Tokyo, Japan.
50Department of Molecular Life Sciences, Tokai University School of Medicine, Kanagawa, Japan. 48Estonian Genome Center, University of Tartu, Tartu, Estonia. 49Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia.
53Centre for Integrative Genomics, University of Lausanne, Lausanne, Switzerland. 52Seattle University College of Nursing, Seattle, WA, USA. 53Kartini Clinic, Portland, OR, USA. 51Centre de Psychiatrie et Neurosciences – Inserm U894, Paris, France. 52Department of Genetics, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
55Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, London, UK.
58UC Genetics Institute, Department of Genetics, Evolution and Environment, University College London, London, UK.
59Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Clinics RWTH Aachen, Aachen, Germany. 59Department of Psychosomatic Medicine and Psychotherapy, Charité, Berlin, Germany. 59Department of Psychosomatic Medicine and Psychotherapy, Hannover Medical School, Hannover, Germany. 59Department of Psychosomatic Medicine and Psychotherapy, University of Erlangen-Nuremberg, Erlangen, Germany. 59Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Medical Hospital Würzburg, Würzburg, Germany. 59Department of Child and Adolescent Psychiatry, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany. 55Massachusetts General Hospital/Harvard Medical School, Athinoula A. Martinos Center for Biomedical Imaging, Psychiatric Neuroimaging Research Program, Charlestown, MA, USA. 61Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Clinics RWTH Aachen, Aachen, Germany. 60Departments of Psychosocial and Internal Medicine, Heidelberg University, Heidelberg, Germany. 61Parklandklinik, Bad Wildungen, Germany.
62Institute for Medical Informatics, Biometry and Epidemiology, Universitätssätklinikum Essen, University of Duisburg-Essen, Essen, Germany. 63Department of Internal Medicine VI, Psychosomatic Medicine and Psychotherapy, University Medical Hospital Tübingen, Tübingen, Germany. 60Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands. 70Department of Neuropsychological Behavioral Research, University of California, Los Angeles, Los Angeles, CA, USA. 83Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands.
71Department of Social Sciences, Utrecht University, Utrecht, The Netherlands. 71Clinical Genetics Unit, Department of Woman and Child Health, University of Padova, Padova, Italy. 72M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland. 72Department of Epidemiology, Institute of Occupational Medicine, Department of Epidemiology, Lodz, Poland. 72Department of Clinical Nutrition, Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland.
77Netherlands Consortium for Healthy Ageing, Leiden University Medical Center, Leiden, The Netherlands. 78Department of Nutrition and Dietetics, Harokopio University, Athens, Greece. 79Department of Psychiatry, Athens University Medical School, Athens, Greece. 80Eating Disorders Unit, 1st Department of Psychiatry, Athens University Medical School, Athens, Greece. 81Adolescent Health Unit (AHU), 2nd Department of Pediatrics – Medical School, University of Athens’ P & A Kyriakou Children’s Hospital, Athens, Greece. 82Department of Psychiatry, 1st Faculty of Medicine, Charles University, Prague, Czech Republic. 83Department of Pediatrics, 1st Faculty of Medicine, Charles University, Prague, Czech Republic. 84Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. 85Institute of Human Genetics, Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. 86Institute of Neurosciences and Medicine (INM-1), Research Center Jülich, Jülich, Germany. 87Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland. 88Martin-Luther-Universität Halle-Wittenberg, Klinikum der Medizinischen Fakultät, Halle/Saale, Germany. 89Institute of Clinical Molecular Biology, University of Kiel, Kiel, Germany. 89Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. 89Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany. 90CNRS 8090-Institute of Biology, Pasteur Institute, Lille, France. 91McGill University and Genome Quebec Innovation Centre, Montreal, QC, Canada. 91Division of Nephrology, Department of Internal Medicine and Medical Specialties, Columbus-Gemeinschafts Hospitals, Catholic University, Rome, Italy. 92Unitat de Recerca de Reumatologia (URR), Institut de Recerca Hospital Universitari Vall d’Hebron, Barcelona, Spain. 95Genetic Epidemiology Group, International Agency for Research on Cancer (IARC), Lyon, France. 97Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Virginia, VA, USA. 98The Finnish Institute of Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. 99The Program for Human and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, MA, USA.
100Finnish Institute of Occupational Health, Province of Southern Finland, Helsinki, Finland. 101NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway. 102Department of Psychology, University of Oslo, Oslo, Norway. 103Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway.
100KG Jebsen Centre for Research on Aging and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway. 100KG Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway.
Psychosis Research, Norwegian Centre For Mental Disorders Research (NORMENT), Department of Clinical Science, University of Bergen, Bergen, Norway. 107 Dr Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway. 108 Institute of Hygiene and Epidemiology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic. 109 Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic. 110 Palacky University, Olomouc, Czech Republic. 111 University Health Network and Mount Sinai Hospital, Toronto General Hospital, and Samuel Lunenfeld Research Institute, Toronto, ON, Canada. 112 Departments of Psychiatry, and Genetics and Genomic Sciences, Seaver Autism Center, and the Mindich Child Health and Development Institute, Mount Sinai School of Medicine, New York, NY, USA. 113 The Centre for Applied Genomics and Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada. 114 Department of Psychiatry and Psychotherapy, Medical University Vienna, Vienna, Austria. 115 The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. 116 Rheumatology Unit, Department of Medicine at the Karolinska University Hospital, Solna, Sweden. 117 Department of Nutrition, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

Price Foundation Collaborative Group

Harry Brandt118, Steve Crawford118, Scott Crow119, Manfred M. Fichter120,121, Katherine A. Halmi122, Craig Johnson123, Allan S. Kaplan124,125, Maria C. La Via9, James Mitchell126,127, Michael Strober128, Alessandro Rotondo129, Janet Treasure130, D. Blake Woodside42,124,125, Cynthia M. Bulik9, Pamela K. Keel131, Kelly L. Klump12, Lisa Lilenfeld132, Laura M. Thornton9, Andrew W. Bergen133, Wade Berrettini134, Walter Kaye135 & Pierre Magistretti136

118 Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA. 119 Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA. 120 Rosenheim Hospital for Behavioral Medicine, Prien, Germany. 121 Department of Psychiatry, University of Munich (LMU), Munich, Germany. 122 New York Presbyterian Hospital, Westchester Division, Weill Medical College of Cornell University, White Plains, NY, USA. 123 Laureate Psychiatric Clinic and Hospital, Tulsa, OK, USA. 124 Center for Addiction and Mental Health, Toronto, Canada. 125 Department of Psychiatry, Toronto General Hospital, University Health Network, Toronto, Canada. 126 Neuropsychiatric Research Institute, Fargo, ND, USA. 127 Department of Clinical Neuroscience, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND, USA. 128 Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. 129 Neuropsychiatric Research Biotechnologies, University of Pisa, Pisa, Italy. 130 Eating Disorders Section, Institute of Psychiatry, King’s College, University of London, London, England. 131 Department of Psychology, Florida State University, Tallahassee, FL, USA. 132 Department of Psychology, Georgia State University, Atlanta, GA, USA. 133 Center for Health Sciences, SRI International, Menlo Park, CA, USA. 134 Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. 135 Department of Psychiatry, University of California at San Diego, San Diego, CA, USA. 136 Department of Psychiatry, Brain Mind Institute EPFL—Lausanne, Center for Psychiatric Neuroscience, University of Lausanne Medical School, Lausanne, Switzerland.