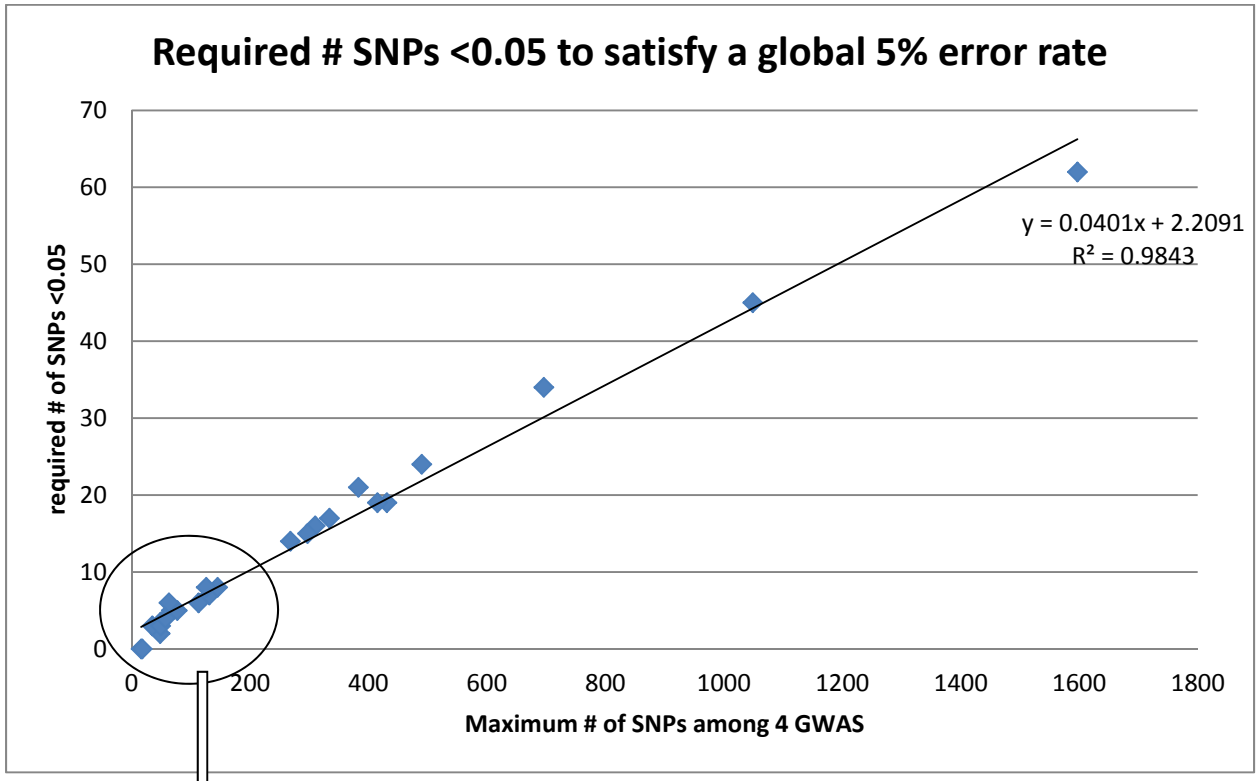
Supplementary Online Content

Nurnberger JI Jr, Koller DL, Jung J, et al; Psychiatric Genomics Consortium Bipolar Group. Identification of pathways for bipolar disorder: a meta-analysis. *JAMA Psychiatry*. Published online April 9, 2014. doi:10.1001/jamapsychiatry.2014.176.

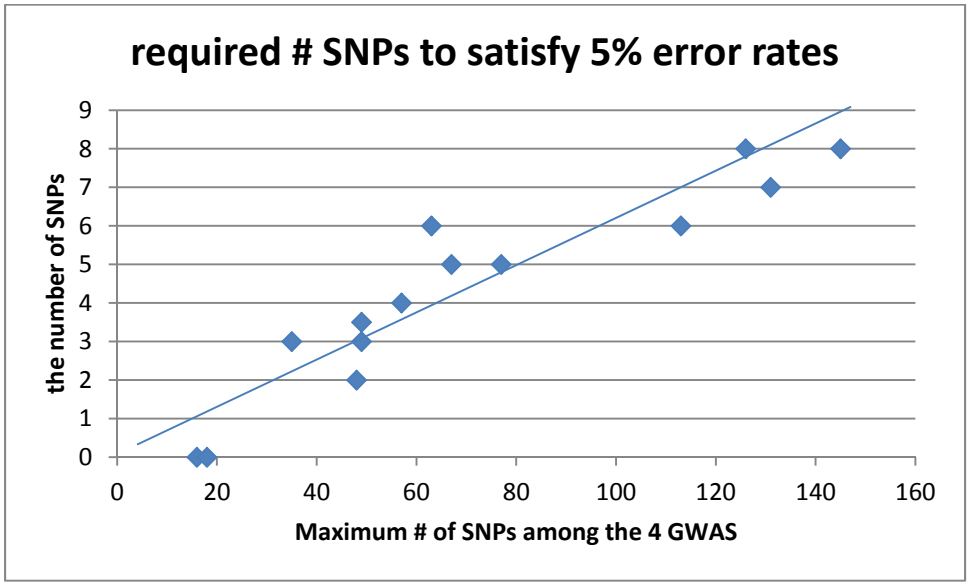
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Threshold for Study Entry Is Related to Gene Size

A



B

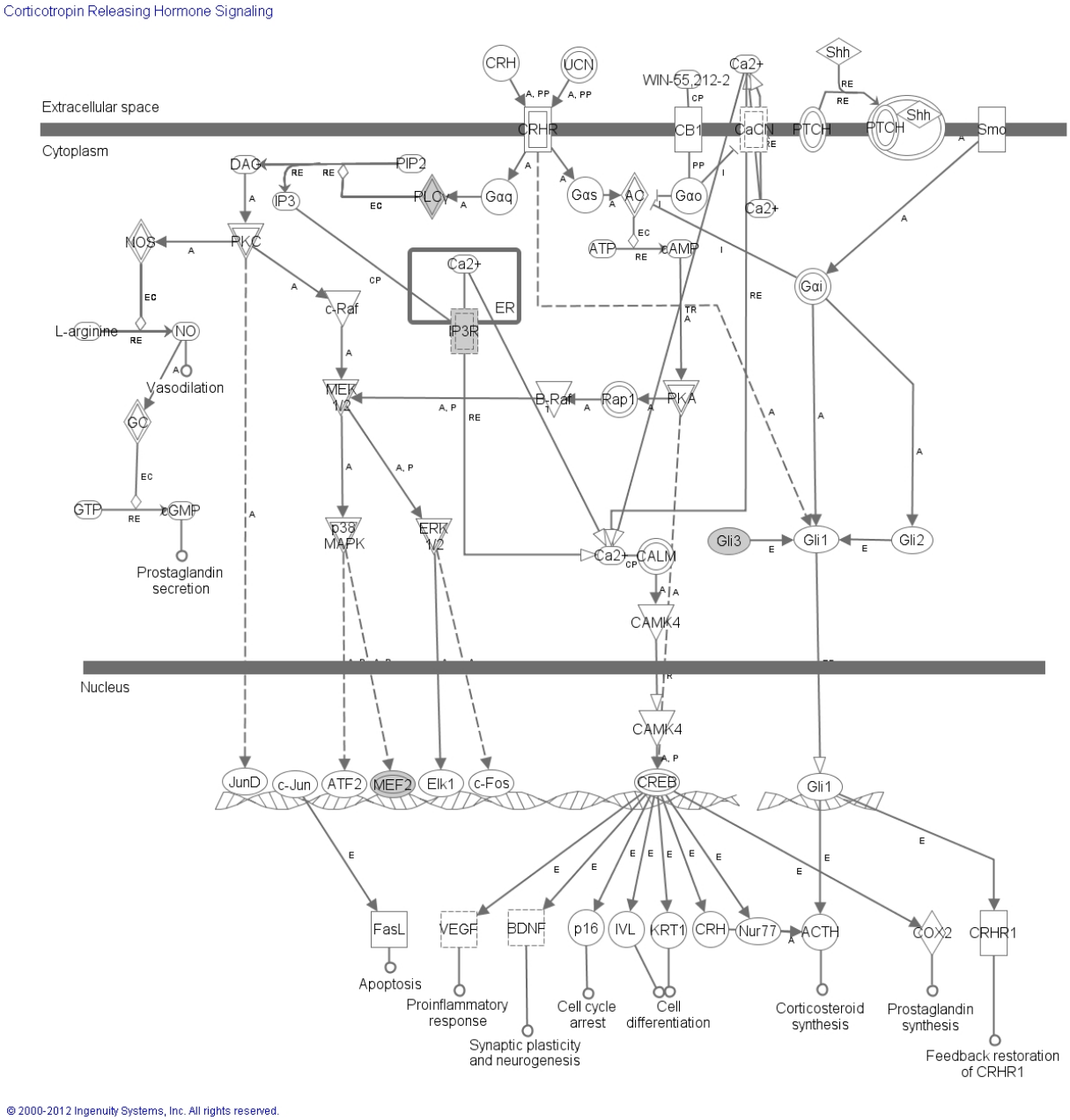


eFigure 1A shows the derivation of a regression equation to determine the empirical p value threshold for each gene entered into the pathway analysis. Four GWAS studies were simulated using 10,000

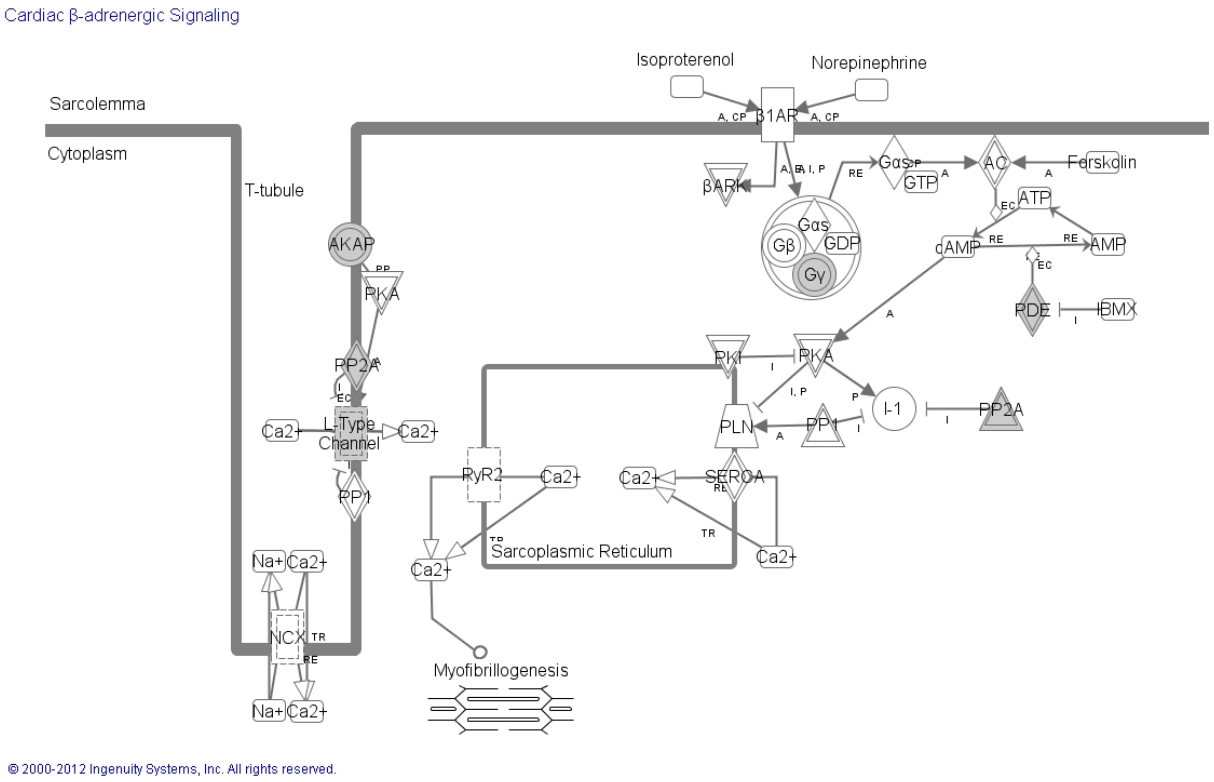
replications per study and permuting case and control status. The number of times that SNPs from a particular gene were found to reach a nominal p value of $\leq$ .05 in 3 out of 4 GWAS datasets was found to be directly related to the maximum number of SNPs tested in that gene in any GWAS (an indirect measure of gene size). The relationship between maximum number of SNPs tested in a gene and the number of SNPs at nominal $p \leq .05$ necessary to achieve an empirical $p \leq .05$ is given by the regression line. eFigure 1B provides an expansion of that relationship to more precisely define the threshold for smaller genes.

eFigures 2-7. These figures show the Canonical Pathway Diagrams for each of the selected pathways, as designated in Ingenuity Systems. The shaded molecules in each diagram indicate the specific genes, or gene-families, tagged by genes in the list of 226 in the Box of the present report.

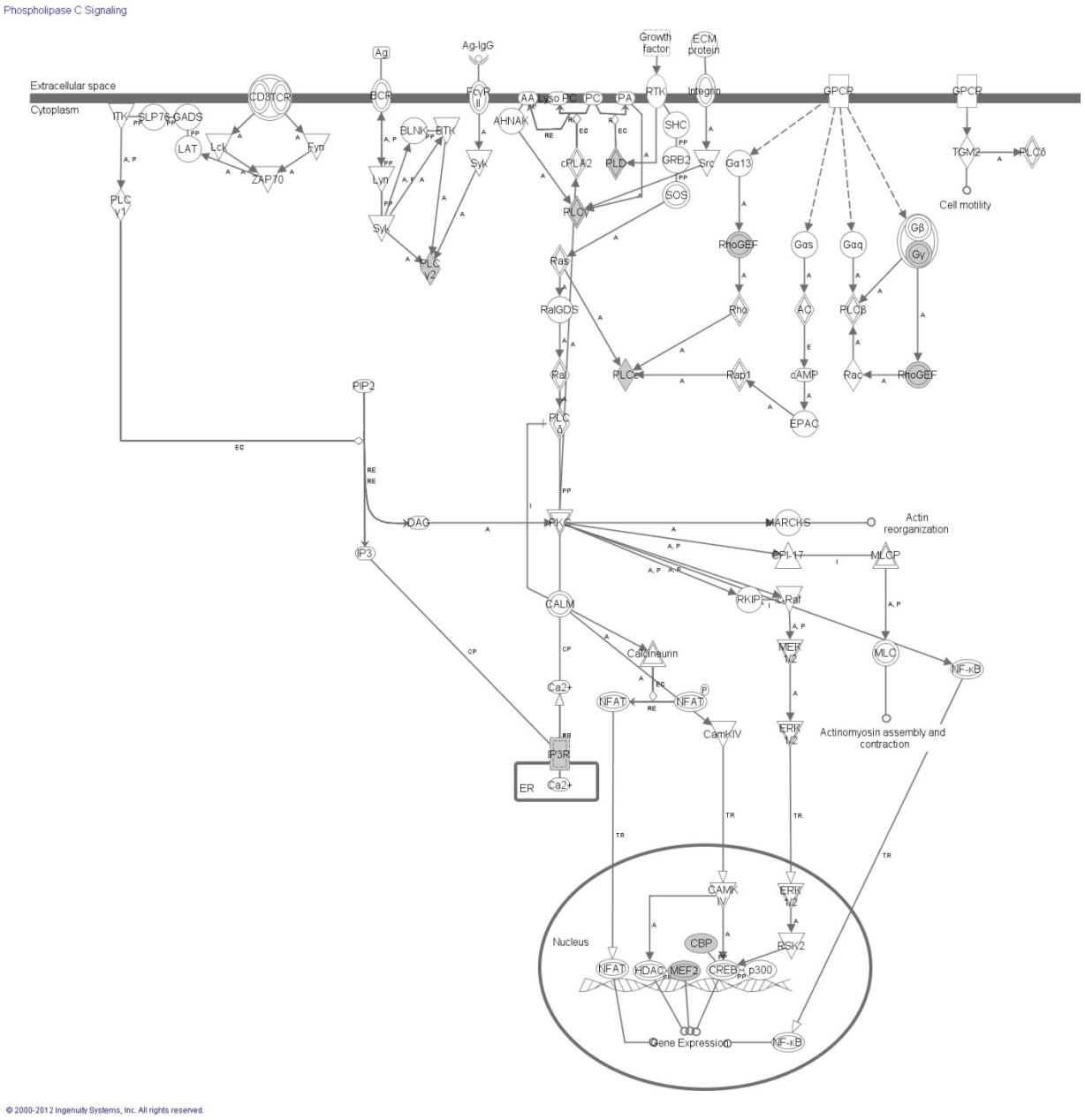
eFigure 2. Corticotropin-Releasing Hormone Signaling



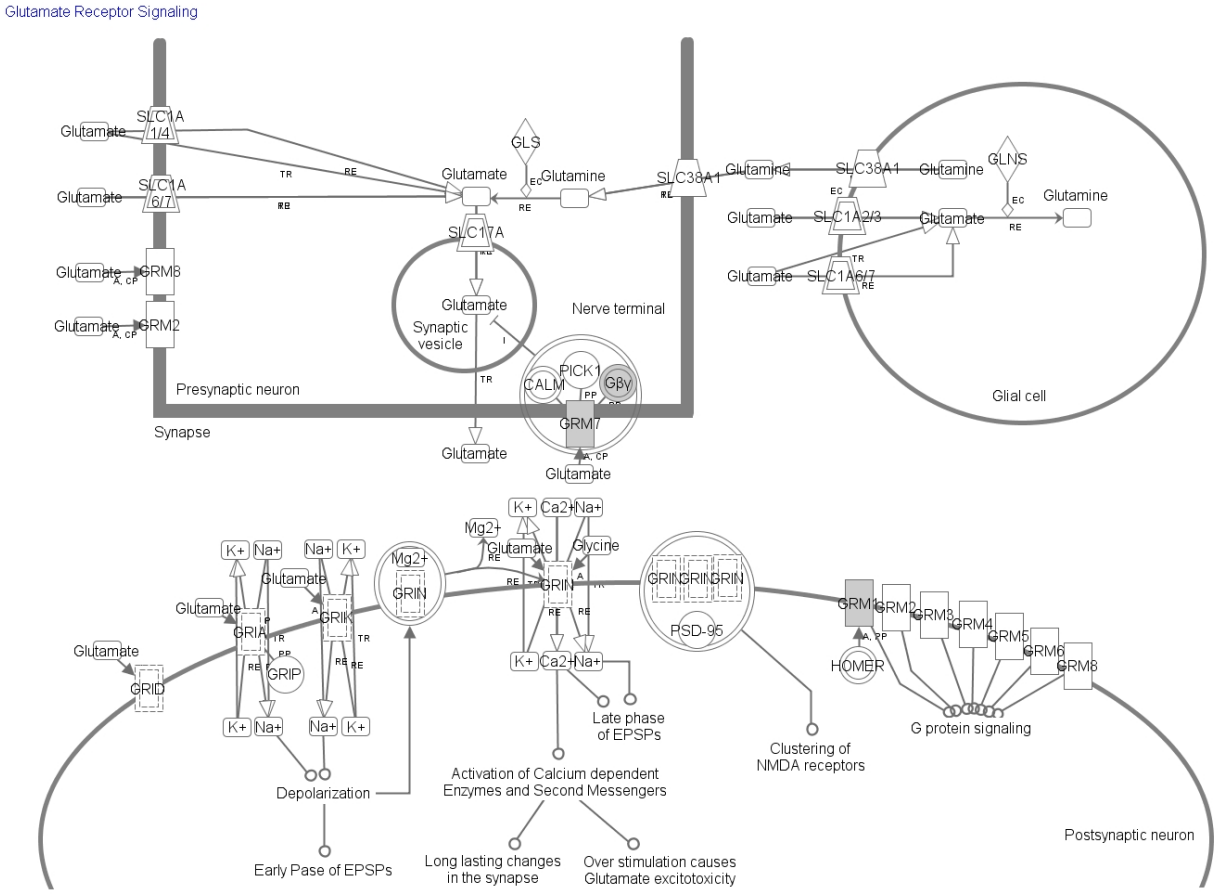
eFigure 3. Cardiac β-Adrenergic Signaling



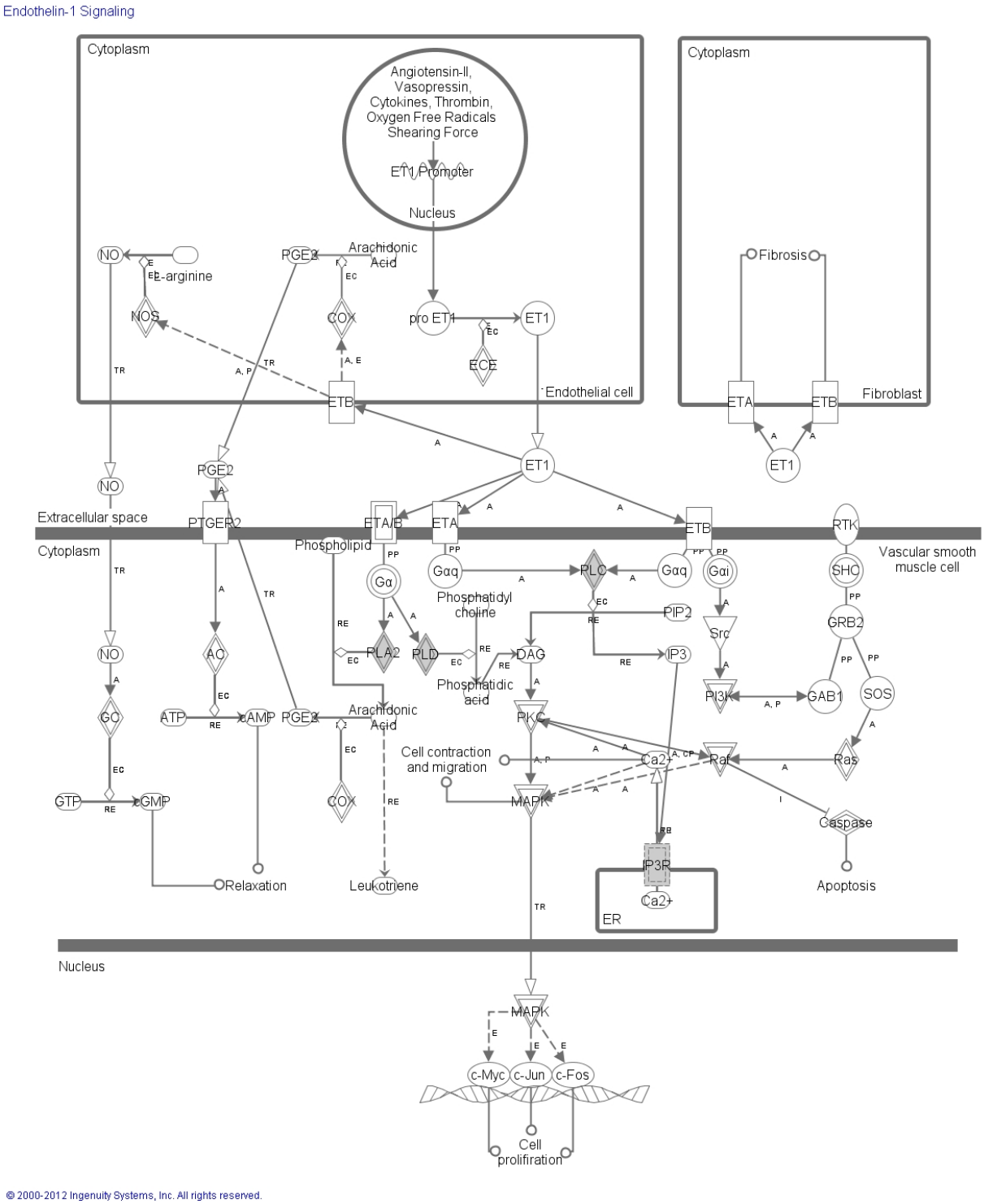
eFigure 4. Phospholipase C Signaling



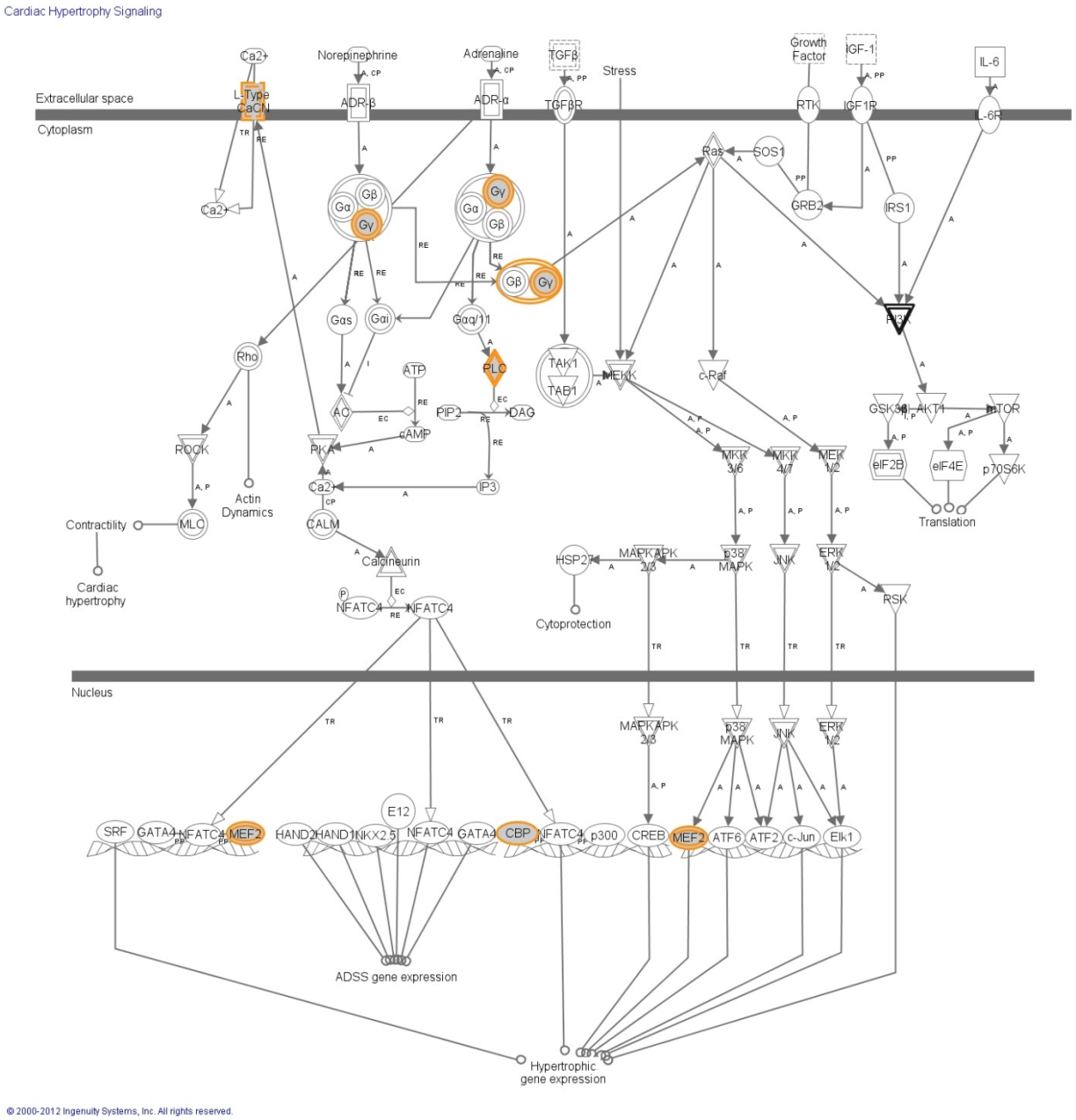
eFigure 5. Glutamate Receptor Signaling



eFigure 6. Endothelin 1 Signaling



eFigure 7. Cardiac Hypertrophy Signaling



eTable. Characteristics of 25 Genes Included in Simulation to Determine the Relationship Between Gene Size and Empirical *P* Value

Gene	GAIN	STEP	Wellcome	German	GENE_SIZE(bp)	mean # of SNPs among 4 GWAS	Maximum # of SNPs among 4 GWAS	the required # of SNPs <0.05 for a global 5% FPE
A2BP1	1049	544	614	856	1,694,208	766	1049	45
ADCY2	131	74	82	116	433,851	101	131	7
CNTNAP2	696	372	438	558	2,304,637	516	696	34
CSMD1	1420	685	793	1597	2,059,453	1124	1597	62
DLG2	383	206	233	366	2,172,259	297	383	21
GRM7	334	182	210	300	880,416	257	334	17
KCNMA1	310	178	203	217	768,218	227	310	16
NPAS3	431	209	235	370	864,923	311	431	19
OPCML	415	192	222	413	1,117,528	311	415	19
PARK2	490	247	283	456	1,380,244	369	490	24
PTPRG	268	137	170	236	733,330	203	268	14
SLIT3	297	160	177	267	635,062	225	297	15
CDK6	49	25	33	42	231,706	37	49	3.5
DDEF2/ ASAP2	48	26	38	31	198,918	36	48	2
FER1L3/ MYOF	67	33	59	63	175,888	56	67	5
TP53I11	35	20	26	33	18,709	29	35	3
C15ORF53	16	8	8	9	3,440	10	16	1
CHST8	49	33	38	46	151,553	42	49	3
FBN2	77	43	53	71	280,134	61	77	5
LGMN	18	7	9	18	44,895	13	18	1
MYLK4	63	38	38	56	87,291	49	63	6
NCAM1	145	94	103	93	317,163	109	145	8
NTNG1	113	55	80	81	341,846	82	113	6
PLA2R1	57	38	47	45	121,109	47	57	4
PRKCB	126	69	88	97	384,632	95	126	8

eBox. Summary of Steps in Pathway Analysis

1) We derived a list of 966 genes with 2 SNPs at p <0.05 in 3 out of four GWAS datasets (N = 5253 cases and 6874 controls).

2) We used 10,000 permutations of phenotype in the four GWAS datasets in order to extract 226 genes from the 966 that were each empirically significant at p<0.05.

3) We ran the 226 genes through an Ingenuity pathway analysis and obtained 16 pathways.

4) We ran the 16 pathways in a separate GWAS dataset (PGC2, an independent set of several thousand cases and controls). 6/16 pathways showed p<.05 and FDR<.05.

5) We compared gene-level results from a multicenter gene expression analysis (N=919 genes) with the gene-level results from our own analysis (N=226 genes), observing an overlap of 9 genes, three of which were among the genes driving the pathway results (chi-square p < 0.005).

eAppendix. Psychiatric Genomics Consortium Bipolar Group Members and Affiliations

Pamela Sklar, MD, PhD[1,2]; Stephan Ripke, MD[3,4]; Laura J. Scott, PhD[5]; Ole A. Andreassen, MD, PhD[6,7]; Sven Cichon, PhD[8-11]; Nick Craddock, PhD[12]; Howard J. Edenberg, PhD[13]; John I. Nurnberger Jr, MD, PhD[14,15]; Marcella Rietschel, MD[16]; Douglas Blackwood, MD, PhD[17,18]; Aiden Corvin, MD, PhD[19]; Matthew Flickinger, MS[5]; Weihua Guan, PhD[5]; Morten Mattingsdal, PhD[6,20]; Andrew McQuillin, PhD[21]; Phoenix Kwan, MS[5]; Thomas F. Wienker, MD[22]; Mark Daly, PhD[3,4]; Frank Dudbridge, PhD[23]; Peter A. Holmans, PhD[12,24]; Danyu Lin, PhD[25]; Margit Burmeister, PhD[26]; Tiffany A. Greenwood, PhD[27]; Marian L. Hamshere, PhD[12,24]; Pierandrea Muglia, MD[28]; Erin N. Smith, PhD[29]; Peter P. Zandi, PhD[30]; Caroline M. Nievergelt, PhD[27]; Rebecca McKinney, BA[27]; Paul D. Shilling, PhD[27]; Nicholas J. Schork, PhD[31]; Cinnamon S. Bloss, PhD[29]; Tatiana Foroud, PhD[13]; Daniel L. Koller, PhD[13]; Elliot S. Gershon, MD[32]; Chunyu Liu, PhD[32]; Judith A. Badner, MD, PhD[32]; William A. Scheftner, MD[33]; William B. Lawson, MD, PhD[34]; Evaristus A. Nwulia, MD[34]; Maria Hipolito, MD[34]; William Coryell, MD[35]; John Rice, PhD[36]; William Byerley, MD[37]; Francis J. McMahon, MD[38]; Thomas G. Schulze, MD[16,38,39]; Wade Berrettini, MD, PhD[40]; Falk W. Lohoff, MD[40]; James B. Potash, MD[30]; Pamela B. Mahon, PhD[30]; Melvin G. McInnis, MD[41]; Sebastian Zöllner, MD[5,41]; Peng Zhang, PhD[5,41]; David W. Craig, PhD[42]; Szabocls Szelinger, MD[42]; Thomas B. Barrett, MD[43]; René Breuer[16]; Sandra Meier[16]; Jana Strohmaier, PhD[16]; Stephanie H. Witt, PhD[16]; Federica Tozzi, MD[28]; Anne Farmer, MD[44]; Peter McGuffin, MD[44]; John Strauss, MD[45]; Wei Xu[46]; James L. Kennedy, MD[47]; John B. Vincent, PhD[45]; Keith Matthews, MD[48]; Richard Day, MD[48]; Manuel A. Ferreira, PhD[2,4,49]; Colm O'Dushlaine, PhD[3,4]; Roy Perlis, MD[2,4]; Soumya Raychaudhuri, MD, PhD[2,4]; Douglas Ruderfer, PhD[2,4]; Phil H. Lee, PhD[2]; Jordan W. Smoller, MD[2,4]; Jun Li, PhD[48]; Devin Absher, PhD[51]; William E. Bunney, MD[52]; Jack D. Barchas, MD[53]; Alan F. Schatzberg, MD[54]; Edward G. Jones, MD[55]; Fan Meng, PhD[56]; Robert C. Thompson, PhD[56]; Stanley J. Watson, MD[56]; Richard M. Myers, MD[51]; Huda Akil, PhD[56]; Michael Boehnke, PhD[5]; Kimberly Chambert, MSc[4]; Jennifer L. Moran, PhD[4]; Edward M. Scolnick, MD[4]; Srdjan Djurovic, PhD[6,57]; Ingrid Melle, MD, PhD[6,7]; Gunnar Morken, MD, PhD[58,59]; Michael Gill, MD[19]; Derek Morris, PhD[19]; Emma Quinn, MSc[19]; Thomas W. Mühleisen[8,9]; Franziska A. Degenhardt, PhD[8,9]; Manuel Mattheisen, MD, PhD[60,61,62]; Johannes Schumacher[8]; Wolfgang Maier, MD[63]; Michael Steffens, PhD[22]; Peter Propping, MD, PhD[8]; Markus M. Nöthen, MD[8,9]; Adebayo Anjorin, MBChB, MSc, MRCPsych[21]; Nick Bass, MD, MRCPsych[21]; Hugh Gurling, MD, FRCPsych[21]; Radhika Kandaswamy, PhD[21]; Jacob Lawrence, MBBS, MRCPsych[21]; Kevin McGhee, PhD[17,18]; Andrew M. McIntosh, MD[17,18]; Alan W. McLean, PhD[17,18]; Walter J. Muir, DSc[17,18]; Benjamin S. Pickard, PhD[17,18]; Gerome Breen, MSc[44,63]; David St. Clair, MD[64]; Sian Caesar[65]; Katherine Gordon-Smith, PhD[12,65]; Lisa Jones, PhD, MBPsS[65]; Christine Fraser[12]; Elaine K. Green, PhD[12]; Detelina Grozeva, MSc[12]; Ian R. Jones, MRCPsych, PhD[12]; George Kirov, PhD[12]; Valentina Moskvina[12,24]; Ivan Nikolov, MD[12]; Michael C. O'Donovan, PhD, FRCPsych[12]; Michael J. Owen, PhD[12]; David A. Collier, PhD[44]; Amanda Elkin[44]; Richard Williamson[**44**]; Allan H. Young, MD[48,66]; I. Nicol Ferrier, MD[48]; Kari Stefansson, MD[67]; Hreinn Stefansson, PhD[67]; Þorgeir E. Þorgeirsson, PhD[67]; Stacy Steinberg[67]; Ómar Gustafsson, PhD[67]; Sarah E. Bergen, PhD[2,4]; Vishwajit Nimgaonkar, MD, PhD[68]; Christina Hultman, PhD[69]; Mikael Landén, MD, PhD[69,70]; Paul Lichtenstein, PhD[69]; Patrick F. Sullivan, MD[71], Martin Schalling, MD, PhD[72]; Urban Osby, MD, PhD[72]; Lena Backlund, MD, PhD[73]; Louise Frisén, MD, PhD[72]; Niklas Langstrom, MD[70]; Stéphane Jamain, PhD[74,75,76,77]; Marion Leboyer, MD[74,75,76,77]; Bruno Etain, MD, PhD[74-77]; Frank Bellivier, MD, PhD[74,75,76,77]; Hannes Petursson, PhD[78]; Engilbert Sigurðsson, MD, PhD[78]; Bertram Müller-Mysok, MD, PhD[79]; Susanne Lucae, MD, PhD[79]; Markus Schwarz, MD[80]; Janice M. Fullerton, PhD[81,82]; Peter R. Schofield, MD[81,82]; Nick Martin, PhD[49]; Grant W. Montgomery, PhD[49]; Mark Lathrop, PhD[83]; Högni Óskarsson, MD[84]; Michael Bauer, MD, PhD[85]; Adam Wright[86]; Philip B. Mitchell, MB, BS, MD[86]; Martin Hautzinger, PhD[87]; Andreas Reif, MD[88]; John R. Kelsoe, MD[27,89]; Shaun M. Purcell, PhD[1,2,4]

[1]Division of Psychiatric Genomics, Department of Psychiatry, Mount Sinai School of Medicine, New York, New York
[2]Center for Human Genetic Research, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts
[3]Analytical and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts
[4]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts
[5]Department of Biostatistics and Center for Statistical Genetics, School of Public Health, University of Michigan, Ann Arbor, Michigan
[6]NORMENT, KG Jebsen Center, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[7]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[8]Institute of Human Genetics, University of Bonn, Bonn, Germany
[9]Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany
[10]Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany
[11]Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland
[12]MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
[13]Department of Biochemistry and Molecular Biology, Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana
[14]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana
[15]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana
[16]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health Mannheim, University of Heidelberg, Mannheim, Germany
[17]Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK
[18]The Institute of Genetics and Molecular Medicine, University of Edinburgh Molecular Medicine Centre, Western General Hospital, Edinburgh, UK
[19]Neuropsychiatric Genetics Research Group, Department of Psychiatry and Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland
[20]Sorlandet Hospital HF, Kristiansand, Norway
[21]Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London, UK
[22]Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany
[23]London School of Hygiene and Tropical Medicine, University of London, London, UK
[24]Biostatistics and Bioinformatics Unit, Cardiff University School of Medicine, Cardiff, UK
[25]Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina
[26]Department of Human Genetics, Department of Psychiatry, Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, Michigan
[27]Department of Psychiatry, University of California, San Diego, La Jolla, California
[28]Neurosciences Centre of Excellence in Drug Discovery, GlaxoSmithKline Research and Development, Verona, Italy
[29]The Scripps Translational Science Institute and Scripps Health, La Jolla, California
[30]Department of Mental Health, Johns Hopkins University and Hospital, Baltimore, Maryland
[31]J. Craig Venter Institute, La Jolla, California
[32]Department of Psychiatry, University of Chicago, Chicago, Illinois
[33]Rush University Medical Center, Chicago, Illinois
[34]Department of Psychiatry and Behavioral Sciences, Howard University College of Medicine, Washington, DC
[35]Department of Psychiatry, University of Iowa, Iowa City, Iowa
[36]Washington University School of Medicine, St Louis, Missouri
[37]Department of Psychiatry, University of California, San Francisco School of Medicine, San Francisco, California
[38]National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland
[39]Department of Psychiatry, University Göttingen, Göttingen, Germany
[40]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania
[41]Department of Psychiatry, University of Michigan, Ann Arbor, Michigan
[42]The Translational Genomics Research Institute, Phoenix, Arizona
[43]Portland Veterans Affairs Medical Center, Portland, Oregon
[44]Social, Genetic and Developmental Psychiatry (SGDP) Centre, The Institute of Psychiatry, King's College London, London, UK

[45]Molecular Neuropsychiatry and Development Laboratory, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[46]Department of Biostatistics, Princess Margaret Hospital, Toronto, Ontario, Canada
[47]Psychiatric Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[48]Division of Neuroscience, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK
[49]QIMR Berghofer Medical Research Institute, Brisbane, Australia
[50]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan
[51]HudsonAlpha Institute for Biotechnology, Huntsville, Alabama
[52]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, California
[53]Department of Psychiatry, Weill Medical College, Cornell University, New York, New York
[54]Psychiatry and Behavioral Science, Stanford University School of Medicine, Palo Alto, California
[55]Department of Psychiatry and Behavioral Sciences, Center for Neuroscience, University of California, Davis, Davis, California
[56]Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, Michigan
[57]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway
[58]Department of Psychiatry, St Olavs Hospital, Trondheim, Norway
[59]Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway
[60]Department of Biomedicine, Aarhus University, Aarhus, Denmark
[61]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus and Copenhagen, Denmark
[62]Centre for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark
[63]Department of Psychiatry, University of Bonn, Bonn, Germany
[64]University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, UK
[65]Department of Psychiatry, School of Clinical and Experimental Medicine, Birmingham University, Birmingham, UK
[66]University of British Columbia Institute of Mental Health, Vancouver, British Columbia, Canada
[67]deCODE genetics, Reykjavík, Iceland
[68]Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania
[69]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[70]Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden
[71]Department of Genetics, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina
[72]Department of Molecular Medicine, Karolinska Institutet, Stockholm, Sweden
[73]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[74]INSERM, U955, Psychiatrie Génétique, Créteil, France
[75]Université Paris Est, Faculté de Médecine, Créteil, France
[76]Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital H. Mondor–A. Chenevier, Département de Psychiatrie, Créteil, France
[77]ENBREC Group, Fondation FondaMental, Créteil, France
[78]Division of Psychiatry, Landspitali University Hospital, University of Iceland, Reykjavik, Iceland
[79]Max Planck Institute of Psychiatry, Munich, Germany
[80]Psychiatric Center Nordbaden, Wiesloch, Germany
[81]Neuroscience Research Australia, Sydney, Australia
[82]University of New South Wales, Sydney, Australia
[83]Centre National de Génotypage, Evry, France
[84]Therapeia, Reykjavik, Iceland
[85]Department of Psychiatry and Psychotherapy, ENBREC Group, University Hospital Carl Gustav Carus, Dresden, Germany
[86]School of Psychiatry, University of New South Wales and Black Dog Institute, Sydney, New South Wales, Australia
[87]Department of Clinical and Developmental Psychology, Institute of Psychology, University of Tübingen, Tübingen, Germany
[88]Department of Psychiatry, University of Würzburg, Würzburg, Germany
[89]Department of Psychiatry, Special Treatment and Evaluation Program (STEP), Veterans Affairs San Diego Healthcare System, San Diego, California