

SUPPLEMENTARY DATA

Index of contents

- Author contributions
- Acknowledgements
- Consortium authors and affiliations:
 - DIAGRAM Consortium authors and affiliations
 - GIANT Consortium authors and affiliations
 - MuTHER Consortium authors and affiliations
 - CARDIoGRAM Consortium authors and affiliations
 - C4D Consortium authors and affiliations
- Supplementary Methods
- Supplementary Methods references
- Supplementary Tables
 - Supplementary Table 1: Cohort information (Excel)
 - Supplementary Table 2: SNPs with suggestive evidence of association that did not reach genome-wide significance on follow-up
- Supplementary Figures
 - Supplementary Figure 1: The proinsulin processing pathway
 - Supplementary Figure 2: Conditions in which circulating proinsulin levels may be altered out of proportion to changes in fasting insulin
 - Supplementary Figure 3: Flow chart detailing the study design
 - Supplementary Figure 4: Meta-analyses demonstrating the sex-specific association at *DDX31*
 - Supplementary Figure 5: Regional plots of top proinsulin-associated loci after imputation using the 1000 Genomes CEU reference panel
 - Supplementary Figure 6: Expression profiles of biologically plausible genes within significant association signals across a range of human tissue types
- Gene Box

SUPPLEMENTARY DATA

Author contributions:

Writing group:

Rona J. Strawbridge, Josée Dupuis, Inga Prokopenko, Adam Barker, Emma Ahlqvist, John R. Petrie, George V. Dedoussis, Valeriya Lyssenko, James B. Meigs, Inês Barroso, Richard M. Watanabe, Erik Ingelsson, Claudia Langenberg, Anders Hamsten and Jose C. Florez

Project design, management and coordination:

BotniaPPP - Leif Groop

DGI - Leif Groop

Ely - Nicholas J. Wareham

Fenland - Ruth J.F. Loos, Nicholas J. Wareham

FHS - James B. Meigs, Jose C. Florez

GHRAS - George V. Dedoussis

Helsinki Birth Cohort Study - Tom J. Forsen

Hertfordshire - Cyrus C. Cooper

METSIM - Mike Boehnke, Francis S. Collins, Markku Laakso

PIVUS - Erik Ingelsson, Lars Lind

PROCARDIS - Robert Clarke, Maria Grazia Franzosi, Anders Hamsten, Udo Sedorf, Hugh Watkins

RISC - Ele Ferrannini

SEGOVIA - Manuel Serrano Ríos

Stockholm Diabetes Prevention Program - Claes-Göran Östenson

ULSAM - Erik Ingelsson

Sample collection and phenotyping:

BotniaPPP - Leif Groop, Bo Isomaa, Tiinamaija Tuomi

DGI - Leif Groop, Bo Isomaa, Tiinamaija Tuomi

Ely - Nicholas J. Wareham

Fenland - Nicholas J. Wareham

FHS - Caroline S. Fox, James B. Meigs

GHRAS - Stavroula Kanoni, Konstantinos Makrilakis

Helsinki Birth Cohort Study - Tom J. Forsen, Eero Kajantie, Clive Osmond

Hertfordshire - Cyrus C. Cooper, Elaine M. Dennison, Karen A. Jameson, Avan A. Sayer

METSIM - Markku Laakso, Teemu Kuulasmaa, Johanna Kuusisto, Alena Stancakova

PIVUS - Lars Lind, Björn Zethelius

PROCARDIS - Maria Nastase Mannila, Angela Silveira

RISC - Mark Walker

Stockholm Diabetes Prevention Program - Harvest Gu

ULSAM - Björn Zethelius

Genotyping:

BotniaPPP - Emma Ahlqvist, Valeriya Lyssenko, Fabiola Turrini

DGI - Valeriya Lyssenko

Ely - Nicholas J. Wareham, Inês Barroso, Claudia Langenberg, Felicity Payne

Fenland - Ruth J.F. Loos, Nicholas J. Wareham, Claudia Langenberg

FHS - James B. Meigs, Josée Dupuis, Caroline S. Fox

SUPPLEMENTARY DATA

GHRAS – Panos Deloukas, Kathy Stirrups

Hertfordshire - Inês Barroso, Claudia Langenberg, Felicity Payne, Nicholas J. Wareham

METSIM - Narisu Narisu, Amy J. Swift

PIVUS - Ann-Christine Syvänen

PROCARDIS - Ann-Christine Syvänen

RISC - Laura Pascoe, Mark Walker

ULSAM - Ann-Christine Syvänen

Statistical analysis:

BotniaPPP - Emma Ahlqvist, Valeriya Lyssenko

DGI - Valeriya Lyssenko, Emma Ahlqvist, Peter Almgren, Benjamin F. Voight

Ely - Claudia Langenberg, Adam Barker

ENGAGE - Momoko Horikoshi, Inga Prokopenko

Fenland - Claudia Langenberg, Daniel Barnes, Jian'an Luan

FHS - Caroline S. Fox, Josée Dupuis, Chen Han, Alisa K. Manning, Denis Rybin

GHRAS – Stavroula Kanoni

Hertfordshire - Claudia Langenberg, Adam Barker

METSIM - Anne U. Jackson, Richard M. Watanabe

PIVUS - Erik Ingelsson, Stefan Gustafsson

PROCARDIS - Anuj Goel, John Öhrvik, John F. Peden, Bengt Sennblad, Rona J. Strawbridge

RISC - Timothy M. Frayling, Michael N. Weedon, Weijia Xie

ULSAM - Erik Ingelsson, Stefan Gustafsson

Expression analysis:

Lille - Nabila Bouatia-Naji, Elodie Eury, Philippe Froguel, Julie Kerr-Conte, François Pattou

Oxford - Anna L. Gloyn, Paul Johnson, Mary Travers

eQTL analysis:

eQTL - MuTHER - Antigone S. Dimas, Alexandra C. Nica, Emmanouil T. Dermitzakis

eQTL - Sweden - Per Eriksson, Lasse Folkersen, Ferdinand M. van 't Hooft

Copy number variant analysis:

Eleanor Wheeler, Inês Barroso

SUPPLEMENTARY DATA

ACKNOWLEDGEMENTS

General - We acknowledge the Wellcome Trust Case Control Consortium for making available data about SNP tagging of common CNVs (http://www.wtccc.org.uk/wtcccplus_cnv/supplemental.shtml). We thank Zoe Paschkis of the Center for Human Genetic Research at the Massachusetts General Hospital for excellent editorial assistance.

Botnia - The Botnia PPP study was supported by grants from the Signe and Ane Gyllenberg Foundation, Swedish Cultural Foundation in Finland, Finnish Diabetes Research Society, the Sigrid Juselius Foundation, Folkhälsan Research Foundation, Foundation for Life and Health in Finland, Jakobstad Hospital, Medical Society of Finland, Närpes Research Foundation and the Vasa and Närpes Health centers, the European Community's Seventh Framework Programme (FP7/2007-2013), the European Network for Genetic and Genomic Epidemiology (ENGAGE), the Collaborative European Effort to Develop Diabetes Diagnostics (CEED/2008-2012), and the Swedish Research Council, including a Linné grant (No.31475113580). Human islets were provided by the Nordic network for clinical islets transplantation by the courtesy of Dr. Olle Korsgren, Uppsala, Sweden. We thank the patients for their participation and the Botnia Study Group for clinically studying the patients.

DGI - The DGI study was supported by a grant from Novartis.

Ely - IB acknowledges funding from the Wellcome Trust grant 077016/Z/05/Z and Cambridge NIHR Comprehensive Biomedical Research Centre. We are grateful to the Wellcome Trust Sanger Institute for genotyping support.

eQTL - Liver, Sweden 3 -The ASAP eQTL study was supported by the Swedish Heart-Lung Foundation, the Swedish Research Council, the European Commission (FAD, Health-F2-2008- 200647), the Danish Agency for Science, Technology and Innovation and a donation by Fredrik Lundberg.

eQTL via A. Dimas - MuTHER Consortium, Louis-Jeantet Foundation, Swiss National Science Foundation and NIH.

Expression – Lille - We acknowledge funding from Contrat-Plan-Etat-Région Nord-Pas-De-Calais 2010-2012: R3P12 SANTE-DIABETE entitled "Genome-wide association studies of pre-diabetes phenotypes in the French prospective D.E.S.I.R. study" and the Juvenile Diabetes Research Foundation (E.C.I.T. grant 31-2008-416) and the Inserm, NB-N's employer.

Expression – Oxford - Medical Research Council (MRC) Grant 81696. ALG is an MRC New Investigator.

Fenland - The Fenland Study is funded by the Wellcome Trust and the Medical Research Council. We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study Investigators, Fenland Study Co-ordination team and the Epidemiology Field, Data and Technical teams. Biochemical assays were performed by the National Institute for Health Research, Cambridge Biomedical Research Centre, Core Biochemistry Assay Laboratory, and the Cambridge University Hospitals NHS Foundation Trust, Department of Clinical Biochemistry.

FHS - This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of

SUPPLEMENTARY DATA

Medicine at Boston University School of Medicine and Boston Medical Center. Also supported by National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) R01 DK078616 to Drs. Meigs, Dupuis and Florez, NIDDK K24 DK080140 to Dr. Meigs, and a Doris Duke Charitable Foundation Clinical Scientist Development Award to Dr. Florez.

GHRAS - GHRAS, Greek Health Randomized Aging Study, would like to thank all the field investigators for samples and data collection and all of the people who participated in the studies. This work was supported by the Wellcome Trust.

HBCS - We would like to thank all participating subjects. We are grateful to the HBCS research staff. Financial support was received from the Academy of Finland, Samfundet Folkhälsan, Finnish Diabetes Research Foundation, Finska Läkaresällskapet, Finnish Foundation for Cardiovascular Research; Yrjö Jahnsson Foundation, Foundation Liv och Hälsa.

Hertfordshire - The Hertfordshire Cohort Study was funded by the Medical Research Council and Arthritis Research Campaign. Genotyping is supported by an MRC-GSK grant to the MRC Epidemiology Unit, Cambridge, UK. IB acknowledges funding from the Wellcome Trust grant 077016/Z/05/Z and Cambridge NIHR Comprehensive Biomedical Research Centre. We are grateful to the Wellcome Trust Sanger Institute for genotyping support.

METSIM - The METSIM study was funded by the Academy of Finland (grant no. 77299 and 124243). METSIM genotyping and data analysis was supported by NIH grant DK062370 (to M.B.) and intramural project number 1Z01 HG000024 (to F.S.C.).

PIVUS - Genotyping was performed by the SNP Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University and the Knut and Alice Wallenberg Foundation. E.I. is supported by grants from the Swedish Research Council and the Swedish Heart-Lung Foundation. B.Z. is supported by grants from the family foundations of Thureus, Ernfors, Thuring, Sehlander, and Ake Wiberg, by the Swedish Diabetes Association Research Fund and Uppsala University.

PROCARDIS - PROCARDIS was funded by the European Commission (LSHM-CT-2007-037273), the British Heart Foundation, AstaZeneca, the Swedish Research Council (8691), the Knut and Alice Wallenberg Foundation, the Swedish Heart-Lung Foundation and the Torsten and Ragnar Söderberg Foundation.

RISC - Wellcome Trust grant: 083270/Z/07/Z, MRC grant: G0601261

SDPP - SDPP had funding from the Stockholm County Council, the Swedish Medical Research Council and the Swedish Diabetes Foundation

Segovia - Supported by grant FISS 03/1618 from Fondo de Investigaciones Sanitarias and a grant from Instituto de Salud Carlos III - RETIC RD06 (RD06/0015/0012). This work was also partially supported by an Educational Grant from Eli Lilly Laboratories, Spain. CIBER de Diabetes y Enfermedades Metabólicas Asociadas is an ISCIII project, Spain. We thank Milagros Pérez-Barba and Carmen Obiang-Ansue for dedicated and careful technical assistance, and Dr. Cristina Fernández, Dr. Arturo Corbatón and CEGEN (Centro Nacional de Genotipado) for their assistance with genotyping.

ULSAM - Genotyping was performed by the SNP Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University and the Knut and Alice Wallenberg Foundation. E.I. is supported by grants from the Swedish Research Council and the Swedish Heart-Lung Foundation. B.Z. is supported by grants from the family foundations of Thureus, Ernfors, Thuring, Sehlander, and Ake Wiberg, by the Swedish Diabetes Association Research Fund and Uppsala University.

SUPPLEMENTARY DATA

For **Acknowledgements** specific to the DIAGRAM, GIANT, CARDIoGRAM, C4D and MuTHER consortia, please consult the original publications (references 29, 30, 37 and 38 in the main text, and supplementary reference 6, respectively).

Disclosures:

Dr. Meigs currently has a research grant from GlaxoSmithKline and serves on a consultancy board for Interleukin Gene. Dr. Florez has received consulting fees from Daiichi-Sankyo and AstraZeneca. Dr. Barroso and her spouse own stock in the companies GlaxoSmithKline (GSK) and Incyte (INCY).

SUPPLEMENTARY DATA

DIAGRAM Consortium authors and affiliations

Benjamin F Voight^{1-3,100}, Laura J Scott^{4,100}, Valgerdur Steinthorsdottir^{5,100}, Andrew P Morris^{6,100}, Christian Dina^{7,8,100}, Ryan P Welch⁹, Eleftheria Zeggini^{6,10}, Cornelia Huth^{11,12}, Yurii S Aulchenko¹³, Gudmar Thorleifsson⁵, Laura J Mcculloch¹⁴, Teresa Ferreira⁶, Harald Grallert^{11,12}, Najaf Amin¹³, Guanming Wu¹⁵, Cristen J Willer⁴, Soumya Raychaudhuri^{1,2,16}, Steve A Mccarroll^{1,17}, Claudia Langenberg¹⁸, Oliver M Hofmann¹⁹, Josée Dupuis^{20,21}, Lu Qi²²⁻²⁴, Ayellet V Segrè^{1,2,17}, Mandy van Hoek²⁵, Pau Navarro²⁶, Kristin Ardlie¹, Beverley Balkau^{27,28}, Rafn Benediktsson^{29,30}, Amanda J Bennett¹⁴, Roza Blagieva³¹, Eric Boerwinkle³², Lori L Bonnycastle³³, Kristina Bengtsson Boström³⁴, Bert Bravenboer³⁵, Suzannah Bumpstead¹⁰, Noisël P Burt¹, Guillaume Charpentier³⁶, Peter S Chines³³, Marilyn Cornelis²⁴, David J Couper³⁷, Gabe Crawford¹, Alex S F Doney^{38,39}, Katherine S Elliott⁶, Amanda L Elliott^{1,17,40}, Michael R Erdos³³, Caroline S Fox^{21,41}, Christopher S Franklin⁴², Martha Ganser⁴, Christian Gieger¹¹, Niels Grarup⁴³, Todd Green^{1,2}, Simon Griffin¹⁸, Christopher J Groves¹⁴, Candace Guiducci¹, Samy Hadjadj⁴⁴, Neelam Hassanali¹⁴, Christian Herder⁴⁵, Bo Isomaa^{46,47}, Anne U Jackson⁴, Paul R V Johnson⁴⁸, Torben Jørgensen^{49,50}, Wen H L Kao^{51,52}, Norman Klopp¹¹, Augustine Kong⁵, Peter Kraft^{22,23}, Johanna Kuusisto⁵³, Torsten Lauritzen⁵⁴, Man Li⁵¹, Aloysius Lieverse⁵⁵, Cecilia M Lindgren⁶, Valeriya Lyssenko⁵⁶, Michel Marre^{57,58}, Thomas Meitinger^{59,60}, Kristian Midthjell⁶¹, Mario A Morcken³³, Narisu Narisu³³, Peter Nilsson⁵⁶, Katharine R Owen¹⁴, Felicity Payne¹⁰, John R B Perry^{62,63}, Ann-Kristin Petersen¹¹, Carl Platou⁶¹, Christine Proença⁷, Inga Prokopenko^{6,14}, Wolfgang Rathmann⁶⁴, N William Rayner^{6,14}, Neil R Robertson^{6,14}, Ghislain Rocheleau⁶⁵⁻⁶⁷, Michael Roden^{45,68}, Michael J Sampson⁶⁹, Richa Saxena^{1,2,40}, Beverley M Shields^{62,63}, Peter Shrader^{3,70}, Gunnar Sigurdsson^{29,30}, Thomas Sparsø⁴³, Klaus Strassburger⁶⁴, Heather M Stringham⁴, Qi Sun^{22,23}, Amy J Swift³³, Barbara Thorand¹¹, Jean Tichet⁷¹, Tiinamaija Tuomi^{46,72}, Rob M van Dam²⁴, Timon W van Haeften⁷³, Thijs van Herpt^{25,55}, Jana V van Vliet-Ostaptchouk⁷⁴, G Bragi Walters⁵, Michael N Weedon^{62,63}, Cisca Wijmenga⁷⁵, Jacqueline Witteman¹³, the MAGIC investigators⁹⁹, the GIANT consortium⁹⁹, Richard N Bergman⁷⁶, Stephane Cauchi⁷, Francis S Collins⁷⁷, Anna L Gloyn¹⁴, Ulf Gyllensten⁷⁸, Torben Hansen^{43,79}, Winston A Hide¹⁹, Graham A Hitman⁸⁰, Albert Hofman¹³, David J Hunter^{22,23}, Kristian Hveem^{61,81}, Markku Laakso⁵³, Karen L Mohlke⁸², Andrew D Morris^{38,39}, Colin N A Palmer^{38,39}, Peter P Pramstaller⁸³, Igor Rudan^{42,84,85}, Eric Sijbrands²⁵, Lincoln D Stein¹⁵, Jaakko Tuomilehto⁸⁶⁻⁸⁸, Andre Uitterlinden²⁵, Mark Walker⁸⁹, Nicholas J Wareham¹⁸, Richard M Watanabe^{76,90}, Gonçalo R Abecasis⁴, Bernhard O Boehm³¹, Harry Campbell⁴², Mark J Daly^{1,2}, Andrew T Hattersley^{62,63}, Frank B Hu²²⁻²⁴, James B Meigs^{3,70}, James S Pankow⁹¹, Oluf Pedersen^{43,92,93}, H-Erich Wichmann^{11,12,94}, Inês Barroso¹⁰, Jose C Florez^{1-3,95}, Timothy M Frayling^{62,63}, Leif Groop^{56,72}, Rob Sladek⁶⁵⁻⁶⁷, Unnur Thorsteinsdottir^{5,96}, James F Wilson⁴², Thomas Illig¹¹, Philippe Froguel^{17,97}, Cornelia M van duijn¹³, Kari Stefansson^{5,96}, David Altshuler^{1-3,17,40,95}, Michael Boehnke⁴ & Mark I McCarthy^{6,14,98}

SUPPLEMENTARY DATA

AFFILIATIONS:

1. Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, USA.
2. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA.
3. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
4. Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA.
5. deCODE Genetics, Reykjavik, Iceland.
6. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
7. CNRS-UMR-8090, Institute of Biology and Lille 2 University, Pasteur Institute, Lille, France.
8. INSERM UMR915 CNRS ERL3147, Nantes, France.
9. Bioinformatics Program, University of Michigan, Ann Arbor, Michigan, USA.
10. Wellcome Trust Sanger Institute, Hinxton, UK.
11. Institute of Epidemiology, Helmholtz Zentrum Muenchen, Neuherberg, Germany.
12. Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
13. Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.
14. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.
15. Ontario Institute for Cancer Research, Toronto, Ontario, Canada.
16. Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
17. Department of Molecular Biology, Harvard Medical School, Boston, Massachusetts, USA.
18. Medical Research Council (MRC) Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK.
19. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA.
20. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA.
21. National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA.
22. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA.
23. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
24. Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.
25. Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands.
26. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK.
27. INSERM, CESP Centre for Research in Epidemiology and Population Health, U1018, Epidemiology of Diabetes, Obesity and Chronic Kidney Disease over the Lifecourse, Villejuif, France.
28. University Paris-Sud 11, UMRS 1018, Villejuif, France.
29. Landspítali University Hospital, Reykjavik, Iceland.
30. Icelandic Heart Association, Kopavogur, Iceland.
31. Division of Endocrinology, Diabetes and Metabolism, Ulm University, Ulm, Germany.

SUPPLEMENTARY DATA

32. The Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA.
33. National Human Genome Research Institute, National Institute of Health, Bethesda, Maryland, USA.
34. Research and Development Centre, Skaraborg Primary Care, Skövde, Sweden.
35. Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands.
36. Endocrinology-Diabetology Unit, Corbeil-Essonnes Hospital, Corbeil-Essonnes, France.
37. Department of Biostatistics and Collaborative Studies Coordinating Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.
38. Diabetes Research Centre, Biomedical Research Institute, University of Dundee, Ninewells Hospital, Dundee, UK.
39. Pharmacogenomics Centre, Biomedical Research Institute, University of Dundee, Ninewells Hospital, Dundee, UK.
40. Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA.
41. Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
42. Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK.
43. Hagedorn Research Institute, Gentofte, Denmark.
44. Centre Hospitalier Universitaire de Poitiers, Endocrinologie Diabetologie, CIC INSERM 0801, INSERM U927, Université de Poitiers, UFR, Médecine Pharmacie, Poitiers Cedex, France.
45. Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
46. Folkhälsan Research Center, Helsinki, Finland.
47. Malmiska Municipal Health Center and Hospital, Jakobstad, Finland.
48. Diabetes Research and Wellness Foundation Human Islet Isolation Facility and Oxford Islet Transplant Programme, University of Oxford, Oxford, UK.
49. Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark.
50. Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark.
51. Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA.
52. Department of Medicine and Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, Maryland, USA.
53. Department of Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, Finland.
54. Department of General Medical Practice, University of Aarhus, Aarhus, Denmark.
55. Department of Internal Medicine, Maxima Medical Center, Eindhoven, The Netherlands.
56. Department of Clinical Sciences, Diabetes and Endocrinology Research Unit, University Hospital Malmö, Lund University, Malmö, Sweden.
57. Department of Endocrinology, Diabetology and Nutrition, Bichat-Claude Bernard University Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France.
58. INSERM U695, Université Paris 7, Paris, France.
59. Institute of Human Genetics, Helmholtz Zentrum Muenchen, Neuherberg, Germany.
60. Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität München, München, Germany.
61. Nord-Trøndelag Health Study (HUNT) Research Center, Department of Community Medicine and General Practice, Norwegian University of Science and Technology, Trondheim, Norway.
62. Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical

SUPPLEMENTARY DATA

- School, University of Exeter, Exeter, UK.
63. Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, Exeter, UK.
 64. Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
 65. Department of Human Genetics, McGill University, Montreal, Canada.
 66. Department of Medicine, Faculty of Medicine, McGill University, Montreal, Canada.
 67. McGill University and Genome Quebec Innovation Centre, Montreal, Canada.
 68. Department of Metabolic Diseases, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
 69. Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital National Health Service Trust, Norwich, UK.
 70. General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA.
 71. Institut interrégional pour la Santé (IRSA), La Riche, France.
 72. Department of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland.
 73. Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands.
 74. Molecular Genetics, Medical Biology Section, Department of Pathology and Medical Biology, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands.
 75. Department of Genetics, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands.
 76. Department of Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles, California, USA.
 77. National Institute of Health, Bethesda, Maryland, USA.
 78. Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden.
 79. University of Southern Denmark, Odense, Denmark.
 80. Centre for Diabetes, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
 81. Department of Medicine, The Hospital of Levanger, Levanger, Norway.
 82. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA.
 83. Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy.
 84. Croatian Centre for Global Health, Faculty of Medicine, University of Split, Split, Croatia.
 85. Institute for Clinical Medical Research, University Hospital 'Sestre Milosrdnice', Zagreb, Croatia.
 86. Department of Public Health, University of Helsinki, Helsinki, Finland.
 87. South Ostrobothnia Central Hospital, Seinäjoki, Finland.
 88. Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, Madrid, Spain.
 89. Diabetes Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK.
 90. Department of Preventative Medicine, Keck Medical School, University of Southern California, Los Angeles, California, USA.
 91. Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, USA.
 92. Department of Biomedical Science, Panum, Faculty of Health Science, University of

SUPPLEMENTARY DATA

Copenhagen, Copenhagen, Denmark.

93. Faculty of Health Science, University of Aarhus, Aarhus, Denmark.
94. Klinikum Grosshadern, Munich, Germany.
95. Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
96. Faculty of Medicine, University of Iceland, Reykjavík, Iceland.
97. Genomic Medicine, Imperial College London, Hammersmith Hospital, London, UK.
98. Oxford National Institute for Health Research Biomedical Research Centre, Churchill Hospital, Oxford, UK.
99. A full list of members is provided in the supplementary Note of the original publication.
100. These authors contributed equally

GIANT Consortium authors and affiliations

Elizabeth K. Speliotes*^{1,2}, Cristen J. Willer*³, Sonja I. Berndt*⁴, Keri L. Monda*⁵, Gudmar Thorleifsson*⁶, Anne U. Jackson³, Hana Lango Allen⁷, Cecilia M. Lindgren^{8,9}, Jian'an Luan¹⁰, Reedik Mägi⁸, Joshua C. Randall⁸, Sailaja Vedantam^{1,11}, Thomas W. Winkler¹², Lu Qi^{13,14}, Tsegaselassie Workalemahu¹³, Iris M. Heid^{12,15}, Valgerdur Steinthorsdottir⁶, Heather M. Stringham³, Michael N. Weedon⁷, Eleanor Wheeler¹⁶, Andrew R. Wood⁷, Teresa Ferreira⁸, Robert J. Weyant³, Ayellet V. Segre^{17,18,19}, Karol Estrada^{20,21,22}, Liming Liang^{23,24}, James Nemesh¹⁸, Ju-Hyun Park⁴, Stefan Gustafsson²⁵, Tuomas O. Kilpeläinen¹⁰, Jian Yang²⁶, Nabila Bouatia-Naji^{27,28}, Tõnu Esko^{29,30,31}, Mary F. Feitosa³², Zoltán Kutalik^{33,34}, Massimo Mangino³⁵, Soumya Raychaudhuri^{18,36}, Andre Scherag³⁷, Albert Vernon Smith^{38,39}, Ryan Welch³, Jing Hua Zhao¹⁰, Katja K. Aben⁴⁰, Devin M. Absher⁴¹, Najaf Amin²⁰, Anna L. Dixon⁴², Eva Fisher⁴³, Nicole L. Glazer⁴⁴, Michael E. Goddard^{45,46}, Nancy L. Heard-Costa⁴⁷, Volker Hoesel⁴⁸, Jouke-Jan Hottenga⁴⁹, Åsa Johansson^{50,51}, Toby Johnson^{33,34,52,53}, Shamika Ketkar³², Claudia Lamina^{15,54}, Shengxu Li¹⁰, Miriam F. Moffatt⁵⁵, Richard H. Myers⁵⁶, Narisu Narisu⁵⁷, John R.B. Perry⁷, Marjolein J. Peters^{21,22}, Michael Preuss⁵⁸, Samuli Ripatti^{59,60}, Fernando Rivadeneira^{20,21,22}, Camilla Sandholt⁶¹, Laura J. Scott³, Nicholas J. Timpson⁶², Jonathan P. Tyrer⁶³, Sophie van Wingerden²⁰, Richard M. Watanabe^{64,65}, Charles C. White⁶⁶, Fredrik Wiklund²⁵, Christina Barlassina⁶⁷, Daniel I. Chasman^{68,69}, Matthew N. Cooper⁷⁰, John-Olov Jansson⁷¹, Robert W. Lawrence⁷⁰, Niina Pellikka^{59,60}, Inga Prokopenko^{8,9}, Jianxin Shi⁴, Elisabeth Thiering¹⁵, Helene Alavere²⁹, Maria T. S. Alibrandi⁷², Peter Almgren⁷³, Alice M. Arnold^{74,75}, Thor Aspelund^{38,39}, Larry D. Atwood⁴⁷, Beverley Balkau^{76,77}, Anthony J. Balmforth⁷⁸, Amanda J. Bennett⁹, Yoav Ben-Shlomo⁷⁹, Richard N. Bergman⁶⁵, Sven Bergmann^{33,34}, Heike Biebermann⁸⁰, Alexandra I.F. Blakemore⁸¹, Tanja Boes³⁷, Lori L. Bonnycastle⁵⁷, Stefan R. Bornstein⁸², Morris J. Brown⁸³, Thomas A. Buchanan^{65,84}, Fabio Busonero⁸⁵, Harry Campbell⁸⁶, Francesco P. Cappuccio⁸⁷, Christine Cavalcanti-Proença^{27,28}, Yii-Der Ida Chen⁸⁸, Chih-Mei Chen¹⁵, Peter S. Chines⁵⁷, Robert Clarke⁸⁹, Lachlan Coin⁹⁰, John Connell⁹¹, Ian N.M. Day⁶², Martin den Heijer^{92,93}, Jubao Duan⁹⁴, Shah Ebrahim^{95,96}, Paul Elliott^{90,97}, Roberto Elosua⁹⁸, Gudny Eiriksdottir³⁸, Michael R. Erdos⁵⁷, Johan G. Eriksson^{99,100,101,102,103}, Maurizio F. Facheris^{104,105}, Stephan B. Felix¹⁰⁶, Pamela Fischer-Posovszky¹⁰⁷, Aaron R. Folsom¹⁰⁸, Nele Friedrich¹⁰⁹, Nelson B. Freimer¹¹⁰, Mao Fu¹¹¹, Stefan Gaget^{27,28}, Pablo V. Gejman⁹⁴, Eco J.C. Geus⁴⁹, Christian Gieger¹⁵, Anette P. Gjesing⁶¹, Anuj Goel^{8,112}, Philippe Goyette¹¹³, Harald Grallert¹⁵, Jürgen Gräßler¹¹⁴, Danielle M. Greenawalt¹¹⁵, Christopher J. Groves⁹, Vilmundur Gudnason^{38,39}, Candace Guiducci¹, Anna-Liisa Hartikainen¹¹⁶, Neelam Hassanali⁹, Alistair S. Hall⁷⁸, Aki S. Havulinna¹¹⁷, Caroline Hayward¹¹⁸, Andrew C. Heath¹¹⁹, Christian Hengstenberg^{120,121}, Andrew A. Hicks¹⁰⁴, Anke Hinney¹²², Albert Hofman^{20,22}, Georg Homuth¹²³, Jennie Hui^{70,124,125}, Wilmar Igl⁵⁰, Carlos Iribarren^{126,127}, Bo Isomaa^{102,128}, Kevin B. Jacobs¹²⁹, Ivonne Jarick¹³⁰, Elizabeth Jewell³, Ulrich John¹³¹, Torben Jørgensen^{132,133}, Pekka Jousilahti¹¹⁷, Antti Jula¹³⁴, Marika Kaakinen^{135,136}, Eero Kajantie^{100,137}, Lee M. Kaplan^{2,69,138}, Sekar Kathiresan^{17,18,139,140,141}, Johannes Kettunen^{59,60}, Leena Kinnunen¹⁴², Joshua W. Knowles¹⁴³, Ivana Kolcic¹⁴⁴, Inke R. König⁵⁸, Seppo Koskinen¹¹⁷, Peter Kovacs¹⁴⁵, Johanna Kuusisto¹⁴⁶, Peter Kraft^{23,24}, Kirsti Kvaløy¹⁴⁷, Jaana Laitinen¹⁴⁸, Olivier Lantieri¹⁴⁹, Chiara Lanzani⁷², Lenore J. Launer¹⁵⁰, Cecile Lecoeur^{27,28}, Terho Lehtimäki¹⁵¹, Guillaume Lettre^{113,152}, Jianjun Liu¹⁵³, Marja-Liisa Lokki¹⁵⁴, Mattias Lorentzon¹⁵⁵, Robert N. Luben¹⁵⁶, Barbara Ludwig⁸², MAGIC¹⁵⁷, Paolo Manunta⁷², Diana Marek^{33,34}, Michel Marre^{158,159}, Nicholas G. Martin¹⁶⁰, Wendy L. McArdle¹⁶¹, Anne McCarthy¹⁶², Barbara McKnight⁷⁴, Thomas Meitinger^{163,164}, Olle Melander¹⁶⁵, David Meyre^{27,28}, Kristian Midthjell¹⁴⁷, Grant W. Montgomery¹⁶⁶, Mario A. Morken⁵⁷, Andrew P. Morris⁸, Rosanda Mulic¹⁶⁷, Julius S. Ngwa⁶⁶, Mari Nelis^{29,30,31}, Matt J. Neville⁹, Dale R. Nyholt¹⁶⁸, Christopher J. O'Donnell^{140,169}, Stephen O'Rahilly¹⁷⁰, Ken K. Ong¹⁰, Ben Oostra¹⁷¹, Guillaume Paré¹⁷², Alex N. Parker¹⁷³, Markus Perola^{59,60}, Irene Pichler¹⁰⁴, Kirsi H. Pietiläinen^{174,175}, Carl G.P. Platou^{147,176}, Ozren Polasek^{144,177}, Anneli Pouta^{116,178}, Suzanne Rafelt¹⁷⁹,

SUPPLEMENTARY DATA

Olli Raitakari¹⁸⁰, Nigel W. Rayner^{8,9}, Martin Ridderstråle¹⁶⁵, Winfried Rief¹⁸¹, Aimo Ruukonen¹⁸², Neil R. Robertson^{8,9}, Peter Rzehak^{15,183}, Veikko Salomaa¹¹⁷, Alan R. Sanders⁹⁴, Manjinder S. Sandhu^{10,16,156}, Serena Sanna⁸⁵, Jouko Saramies¹⁸⁴, Markku J. Savolainen¹⁸⁵, Susann Scherag¹²², Sabine Schipf^{109,186}, Stefan Schreiber¹⁸⁷, Heribert Schunkert¹⁸⁸, Kaisa Silander^{59,60}, Juha Sinisalo¹⁸⁹, David S. Siscovick^{190,191}, Jan H. Smit¹⁹², Nicole Soranzo^{16,35}, Ulla Sovio⁹⁰, Jonathan Stephens^{193,194}, Ida Surakka^{59,60}, Amy J. Swift⁵⁷, Mari-Liis Tammesoo²⁹, Jean-Claude Tardif^{113,152}, Maris Teder-Laving^{30,31}, Tanya M. Teslovich³, John R. Thompson^{195,196}, Brian Thomson¹, Anke Tönjes^{197,198}, Tiinamaija Tuomi^{102,199,200}, Joyce B.J. van Meurs^{20,21,22}, Gert-Jan van Ommen²⁰¹, Vincent Vatin^{27,28}, Jorma Viikari²⁰², Sophie Visvikis-Siest²⁰³, Veronique Vitart¹¹⁸, Carla I. G. Vogel¹²², Benjamin F. Voight^{17,18,19}, Lindsay L. Waite⁴¹, Henri Wallaschofski¹⁰⁹, G.Bragi Walters⁶, Elisabeth Widen⁵⁹, Susanna Wiegand⁸⁰, Sarah H. Wild⁸⁶, Gonneke Willemssen⁴⁹, Daniel R. Witte²⁰⁴, Jacqueline C. Witteman^{20,22}, Jianfeng Xu²⁰⁵, Qunyuan Zhang³², Lina Zgaga¹⁴⁴, Andreas Ziegler⁵⁸, Paavo Zitting²⁰⁶, John P. Beilby^{124,125,207}, I. Sadaf Farooqi¹⁷⁰, Johannes Hebebrand¹²², Heikki V. Huikuri^{208,208}, Alan L. James^{125,209}, Mika Kähönen²¹⁰, Douglas F. Levinson²¹¹, Fabio Macciardi^{67,212}, Markku S. Nieminen^{189,189}, Claes Ohlsson¹⁵⁵, Lyle J. Palmer^{70,125}, Paul M. Ridker^{68,69}, Michael Stumvoll^{197,213}, Jacques S. Beckmann^{33,214}, Heiner Boeing⁴³, Eric Boerwinkle²¹⁵, Dorret I. Boomsma⁴⁹, Mark J. Caulfield⁵³, Stephen J. Chanock⁴, Francis S. Collins⁵⁷, L. Adrienne Cupples⁶⁶, George Davey Smith⁶², Jeanette Erdmann¹⁸⁸, Philippe Froguel^{27,28,81}, Henrik Grönberg²⁵, Ulf Gyllensten⁵⁰, Per Hall²⁵, Torben Hansen^{61,216}, Tamara B. Harris¹⁵⁰, Andrew T. Hattersley⁷, Richard B. Hayes²¹⁷, Joachim Heinrich¹⁵, Frank B. Hu^{13,14,23}, Kristian Hveem¹⁴⁷, Thomas Illig¹⁵, Marjo-Riitta Jarvelin^{90,135,136,178}, Jaakko Kaprio^{59,174,218}, Fredrik Karpe^{9,219}, Kay-Tee Khaw¹⁵⁶, Lambertus A. Kiemeny^{40,92,220}, Heiko Krude⁸⁰, Markku Laakso¹⁴⁶, Debbie A. Lawlor⁶², Andres Metspalu^{29,30,31}, Patricia B. Munroe⁵³, Willem H. Ouwehand^{16,193,194}, Oluf Pedersen^{61,221,222}, Brenda W. Penninx^{192,223,224}, Annette Peters¹⁵, Peter P. Pramstaller^{104,105,225}, Thomas Quertermous¹⁴³, Thomas Reinehr²²⁶, Aila Rissanen¹⁷⁵, Igor Rudan^{86,167}, Nilesh J. Samani^{179,195}, Peter E.H. Schwarz²²⁷, Alan R. Shuldiner^{111,228}, Timothy D. Spector³⁵, Jaakko Tuomilehto^{142,229,230}, Manuela Uda⁸⁵, André Uitterlinden^{20,21,22}, Timo T. Valle¹⁴², Martin Wabitsch¹⁰⁷, Gérard Waeber²³¹, Nicholas J. Wareham¹⁰, Hugh Watkins^{8,112} on behalf of Procardis Consortium, James F. Wilson⁸⁶, Alan F. Wright¹¹⁸, M.Carola Zillikens^{21,22}, Nilanjan Chatterjee⁴, Steven A. McCarroll^{17,18,19}, Shaun Purcell^{17,232,233}, Eric E. Schadt^{234,235}, Peter M. Visscher²⁶, Themistocles L. Assimes¹⁴³, Ingrid B. Borecki^{32,236}, Panos Deloukas¹⁶, Caroline S. Fox²³⁷, Leif C. Groop⁷³, Talin Haritunians⁸⁸, David J. Hunter^{13,14,23}, Robert C. Kaplan²³⁸, Karen L. Mohlke²³⁹, Jeffrey R. O'Connell¹¹¹, Leena Peltonen^{16,59,60,232,240}, David Schlessinger²⁴¹, David P. Strachan²⁴², Cornelia M. van Duijn^{20,22}, H.-Erich Wichmann^{15,183,243}, Timothy M. Frayling⁷, Unnur Thorsteinsdottir^{6,244}, Gonçalo R. Abecasis³, Inês Barroso^{16,245}, Michael Boehnke^{*3}, Kari Stefansson^{*6,244}, Kari E. North^{*5,246}, Mark I. McCarthy^{*8,9,219}, Joel N. Hirschhorn^{*1,11,247}, Erik Ingelsson^{*25}, Ruth J.F. Loos^{*10}

*These authors contributed equally to this work.

AFFILIATIONS

1. Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts 02142, USA
2. Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
3. Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA
4. Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, USA

SUPPLEMENTARY DATA

5. Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514, USA
6. deCODE Genetics, 101 Reykjavik, Iceland
7. Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, EX1 2LU, UK
8. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK
9. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, OX3 7LJ, UK
10. MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK
11. Divisions of Genetics and Endocrinology and Program in Genomics, Children's Hospital, Boston, Massachusetts 02115, USA
12. Regensburg University Medical Center, Department of Epidemiology and Preventive Medicine, 93053 Regensburg, Germany
13. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA
14. Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA
15. Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany
16. Wellcome Trust Sanger Institute, Hinxton, Cambridge, CB10 1SA, UK
17. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
18. Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA
19. Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
20. Department of Epidemiology, Erasmus MC, Rotterdam, 3015GE, The Netherlands
21. Department of Internal Medicine, Erasmus MC, Rotterdam, 3015GE, The Netherlands
22. Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA)
23. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA
24. Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, USA
25. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden
26. Queensland Statistical Genetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
27. CNRS UMR8199-IBL-Institut Pasteur de Lille, F-59019 Lille, France
28. University Lille Nord de France, 59000 Lille, France
29. Estonian Genome Center, University of Tartu, Tartu 50410, Estonia
30. Estonian Biocenter, Tartu 51010, Estonia
31. Institute of Molecular and Cell Biology, University of Tartu, Tartu 51010, Estonia
32. Department of Genetics, Washington University School of Medicine, St Louis, Missouri 63110, USA
33. Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland
34. Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland
35. Department of Twin Research and Genetic Epidemiology, King's College London, London, SE1 7EH, UK

SUPPLEMENTARY DATA

36. Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115 USA
37. Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, 45122 Essen, Germany
38. Icelandic Heart Association, Kopavogur, Iceland
39. University of Iceland, Reykjavik, Iceland
40. Comprehensive Cancer Center East, 6501 BG Nijmegen, The Netherlands
41. Hudson Alpha Institute for Biotechnology, Huntsville, Alabama 35806, USA
42. Royal National Hospital for Rheumatic Diseases and University of Bath, Bath, BA1 1RL, UK
43. Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, 14558 Nuthetal, Germany
44. Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington 98101, USA
45. University of Melbourne, Parkville 3010, Australia
46. Department of Primary Industries, Melbourne, Victoria 3001, Australia
47. Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, USA
48. Technical University Munich, Chair of Biomathematics, Boltzmannstrasse 3, 85748 Garching
49. Department of Biological Psychology, VU University Amsterdam, 1081 BT Amsterdam, The Netherlands
50. Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, SE-75185 Uppsala, Sweden
51. Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, N-7489, Norway
52. Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK
53. Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK
54. Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, 6020 Innsbruck, Austria
55. National Heart and Lung Institute, Imperial College London, London SW3 6LY, UK
56. Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, USA
57. National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
58. Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, 23562 Lübeck, Germany
59. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, 00014, Helsinki, Finland
60. National Institute for Health and Welfare, Department of Chronic Disease Prevention, Unit of Public Health Genomics, 00014, Helsinki, Finland
61. Hagedorn Research Institute, 2820 Gentofte, Denmark
62. MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, Oakfield House, Bristol, BS8 2BN, UK
63. Department of Oncology, University of Cambridge, Cambridge, CB1 8RN, UK

SUPPLEMENTARY DATA

64. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California 90089, USA
65. Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA
66. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA
67. University of Milan, Department of Medicine, Surgery and Dentistry, 20139 Milano, Italy
68. Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts 02215, USA
69. Harvard Medical School, Boston, Massachusetts 02115, USA
70. Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia 6009, Australia
71. Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden
72. University Vita-Salute San Raffaele, Division of Nephrology and Dialysis, 20132 Milan, Italy
73. Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden
74. Departments of Biostatistics, University of Washington, Seattle, Washington 98195, USA
75. Collaborative Health Studies Coordinating Center, Seattle, Washington 98115, USA
76. INSERM CESP Centre for Research in Epidemiology and Public Health U1018, Epidemiology of diabetes, obesity and chronic kidney disease over the lifecourse, 94807 Villejuif, France
77. University Paris Sud 11, UMRS 1018, 94807 Villejuif, France
78. Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds LS2 9JT, UK
79. Department of Social Medicine, University of Bristol, Bristol, BS8 2PS, UK
80. Institute of Experimental Paediatric Endocrinology, Charité Universitätsmedizin Berlin, 13353 Berlin, Germany
81. Department of Genomics of Common Disease, School of Public Health, Imperial College London, W12 0NN, London, UK
82. Department of Medicine III, University of Dresden, 01307 Dresden, Germany
83. Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK
84. Division of Endocrinology, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA
85. Istituto di Neurogenetica e Neurofarmacologia del CNR, Monserrato, 09042, Cagliari, Italy
86. Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland
87. University of Warwick, Warwick Medical School, Coventry, CV2 2DX, UK
88. Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA
89. Clinical Trial Service Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford, OX3 7LF, UK
90. Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London, W2 1PG, UK
91. University of Dundee, Ninewells Hospital & Medical School, Dundee, DD1 9SY, UK
92. Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands

SUPPLEMENTARY DATA

93. Department of Endocrinology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
94. Northshore University Healthsystem, Evanston, Illinois 60201, USA
95. The London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK
96. South Asia Network for Chronic Disease
97. MRC-HPA Centre for Environment and Health, London W2 1PG, UK
98. Cardiovascular Epidemiology and Genetics, Institut Municipal D'investigacio Medica and CIBER Epidemiología y Salud Pública, Barcelona, Spain
99. Department of General Practice and Primary health Care, University of Helsinki, Helsinki, Finland
100. National Institute for Health and Welfare, 00271 Helsinki, Finland
101. Helsinki University Central Hospital, Unit of General Practice, 00280 Helsinki, Finland
102. Folkhalsan Research Centre, 00250 Helsinki, Finland
103. Vasa Central Hospital, 65130 Vasa, Finland
104. Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano/Bozen, 39100, Italy. Affiliated Institute of the University of Lübeck, Lübeck, Germany.
105. Department of Neurology, General Central Hospital, Bolzano, Italy
106. Department of Internal Medicine B, Ernst-Moritz-Arndt University, 17475 Greifswald, Germany
107. Pediatric Endocrinology, Diabetes and Obesity Unit, Department of Pediatrics and Adolescent Medicine, 89075 Ulm, Germany
108. Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis Minnesota 55454, USA
109. Institut für Klinische Chemie und Laboratoriumsmedizin, Universität Greifswald, 17475 Greifswald, Germany
110. Center for Neurobehavioral Genetics, University of California, Los Angeles, California 90095, USA
111. Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA
112. Department of Cardiovascular Medicine, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU
113. Montreal Heart Institute, Montreal, Quebec, H1T 1C8, Canada
114. Department of Medicine III, Pathobiochemistry, University of Dresden, 01307 Dresden, Germany
115. Merck Research Laboratories, Merck & Co., Inc., Boston, Massachusetts 02115, USA
116. Department of Clinical Sciences/Obstetrics and Gynecology, University of Oulu, 90014 Oulu, Finland
117. National Institute for Health and Welfare, Department of Chronic Disease Prevention, Chronic Disease Epidemiology and Prevention Unit, 00014, Helsinki, Finland
118. MRC Human Genetics Unit, Institute for Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU, Scotland, UK
119. Department of Psychiatry and Midwest Alcoholism Research Center, Washington University School of Medicine, St Louis, Missouri 63108, USA
120. Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, 93053 Regensburg, Germany
121. Regensburg University Medical Center, Innere Medizin II, 93053 Regensburg, Germany
122. Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, 45147 Essen, Germany
123. Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany

SUPPLEMENTARY DATA

124. PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands, Western Australia 6009, Australia
125. Busselton Population Medical Research Foundation Inc., Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia
126. Division of Research, Kaiser Permanente Northern California, Oakland, California 94612, USA
127. Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California 94107, USA
128. Department of Social Services and Health Care, 68601 Jakobstad, Finland
129. Core Genotyping Facility, SAIC-Frederick, Inc., NCI-Frederick, Frederick, Maryland 21702, USA
130. Institute of Medical Biometry and Epidemiology, University of Marburg, 35037 Marburg, Germany
131. Institut für Epidemiologie und Sozialmedizin, Universität Greifswald, 17475 Greifswald, Germany
132. Research Centre for Prevention and Health, Glostrup University Hospital, 2600 Glostrup, Denmark
133. Faculty of Health Science, University of Copenhagen, 2100 Copenhagen, Denmark
134. National Institute for Health and Welfare, Department of Chronic Disease Prevention, Population Studies Unit, 20720 Turku, Finland
135. Institute of Health Sciences, University of Oulu, 90014 Oulu, Finland
136. Biocenter Oulu, University of Oulu, 90014 Oulu, Finland
137. Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, 00029 HUS, Finland
138. MGH Weight Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
139. Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
140. Framingham Heart Study of the National, Heart, Lung, and Blood Institute and Boston University, Framingham, Massachusetts 01702, USA
141. Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA
142. National Institute for Health and Welfare, Diabetes Prevention Unit, 00271 Helsinki, Finland
143. Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA
144. Andrija Stampar School of Public Health, Medical School, University of Zagreb, 10000 Zagreb, Croatia
145. Interdisciplinary Centre for Clinical Research, University of Leipzig, 04103 Leipzig, Germany
146. Department of Medicine, University of Kuopio and Kuopio University Hospital, 70210 Kuopio, Finland
147. HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, 7600 Levanger, Norway
148. Finnish Institute of Occupational Health, 90220 Oulu, Finland
149. Institut inter-regional pour la sante (IRSA), F-37521 La Riche, France.
150. Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA
151. Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, 33520 Tampere, Finland
152. Department of Medicine, Université de Montréal, Montreal, Quebec, H3T 1J4, Canada
153. Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore
154. Transplantation Laboratory, Haartman Institute, University of Helsinki, 00014, Helsinki, Finland
155. Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden

SUPPLEMENTARY DATA

156. Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR, UK
157. On behalf of the MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium) investigators
158. Department of Endocrinology, Diabetology and Nutrition, Bichat-Claude Bernard University Hospital, Assistance Publique des Hôpitaux de Paris, F-75018 Paris, France
159. Cardiovascular Genetics Research Unit, Université Henri Poincaré-Nancy 1, 54000, Nancy, France
160. Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
161. Avon Longitudinal Study of Parents and Children (ALSPAC) Laboratory, Department of Social Medicine, University of Bristol, Bristol, BS8 2BN, UK
162. Division of Health, Research Board, An Bord Taighde Sláinte, Dublin, 2, Ireland
163. Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universität München, 81675 Munich, Germany
164. Institute of Human Genetics, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany
165. Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden
166. Molecular Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
167. Croatian Centre for Global Health, School of Medicine, University of Split, Split 21000, Croatia
168. Neurogenetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia
169. National, Lung, and Blood Institute, National Institutes of Health, Framingham, Massachusetts 01702, USA
170. University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
171. Department of Clinical Genetics, Erasmus MC, Rotterdam, 3015GE, The Netherlands
172. Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario L8N3Z5, Canada
173. Amgen, Cambridge, Massachusetts 02139, USA
174. Finnish Twin Cohort Study, Department of Public Health, University of Helsinki, 00014, Helsinki, Finland
175. Obesity Research unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland
176. Department of Medicine, Levanger Hospital, The Nord-Trøndelag Health Trust, 7600 Levanger, Norway
177. Gen-Info Ltd, 10000 Zagreb, Croatia
178. National Institute for Health and Welfare, 90101 Oulu, Finland
179. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK
180. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and the Department of Clinical Physiology, Turku University Hospital, 20520 Turku, Finland
181. Clinical Psychology and Psychotherapy, University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany
182. Department of Clinical Sciences/Clinical Chemistry, University of Oulu, 90014 Oulu, Finland
183. Ludwig-Maximilians-Universität, Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, 81377 Munich, Germany

SUPPLEMENTARY DATA

184. South Karelia Central Hospital, 53130 Lappeenranta, Finland
185. Department of Clinical Sciences/Internal Medicine, University of Oulu, 90014 Oulu, Finland
186. Institut für Community Medicine, 17489 Greifswald, Germany
187. Christian-Albrechts-University, University Hospital Schleswig-Holstein, Institute for Clinical Molecular Biology and Department of Internal Medicine I, Schittenhelmstrasse 12, 24105 Kiel
188. Universität zu Lübeck, Medizinische Klinik II, 23562 Lübeck, Germany
189. Division of Cardiology, Cardiovascular Laboratory, Helsinki University Central Hospital, 00029 Helsinki, Finland
190. Cardiovascular Health Research Unit, University of Washington, Seattle, Washington 98101, USA
191. Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington 98195, USA
192. Department of Psychiatry/EMGO Institute, VU University Medical Center, 1081 BT Amsterdam, The Netherlands
193. Department of Haematology, University of Cambridge, Cambridge CB2 0PT, UK
194. NHS Blood and Transplant, Cambridge Centre, Cambridge, CB2 0PT, UK
195. Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK
196. Department of Health Sciences, University of Leicester, University Road, Leicester, LE1 7RH, UK
197. Department of Medicine, University of Leipzig, 04103 Leipzig, Germany
198. Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16-18, 04103 Leipzig, Germany
199. Department of Medicine, Helsinki University Central Hospital, 00290 Helsinki, Finland
200. Research Program of Molecular Medicine, University of Helsinki, 00014 Helsinki, Finland
201. Department of Human Genetics and Center of Medical Systems Biology, Leiden University Medical Center, 2333 ZC Leiden, the Netherlands
202. Department of Medicine, University of Turku and Turku University Hospital, 20520 Turku, Finland
203. INSERM Cardiovascular Genetics team, CIC 9501, 54000 Nancy, France
204. Steno Diabetes Center, 2820 Gentofte, Denmark
205. Center for Human Genomics, Wake Forest University, Winston-Salem, North Carolina 27157, USA
206. Department of Psychiatrics, Lapland Central Hospital, 96101 Rovaniemi, Finland
207. School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia 6009, Australia
208. Department of Internal Medicine, University of Oulu, 90014 Oulu, Finland
209. School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6009, Australia
210. Department of Clinical Physiology, University of Tampere and Tampere University Hospital, 33520 Tampere, Finland;
211. Stanford University School of Medicine, Stanford, California 93405, USA
212. Department of Psychiatry and Human Behavior, University of California, Irvine (UCI), Irvine, California 92617, USA
213. LIFE Study Centre, University of Leipzig, Leipzig, Germany
214. Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, 1011 Lausanne, Switzerland
215. Human Genetics Center and Institute of Molecular Medicine and Division of Epidemiology, University of Texas Health Science Center, Houston, Texas 77030, USA
216. Faculty of Health Science, University of Southern Denmark, 5000 Odense, Denmark

SUPPLEMENTARY DATA

217. New York University Medical Center, New York, New York 10016, USA
218. National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Unit for Child and Adolescent Mental Health, 00271 Helsinki, Finland
219. NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LJ, UK
220. Department of Urology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
221. Institute of Biomedical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark
222. Faculty of Health Science, University of Aarhus, 8000 Aarhus, Denmark
223. Department of Psychiatry, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands
224. Department of Psychiatry, University Medical Centre Groningen, 9713 GZ Groningen, The Netherlands
225. Department of Neurology, University of Lübeck, Lübeck, Germany.
226. Institute for Paediatric Nutrition Medicine, Vestische Hospital for Children and Adolescents, University of Witten-Herdecke, 45711 Datteln, Germany
227. Department of Medicine III, Prevention and Care of Diabetes, University of Dresden, 01307 Dresden, Germany
228. Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, Maryland 21201, USA
229. Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland
230. South Ostrobothnia Central Hospital, 60220 Seinajoki, Finland
231. Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, 1011 Lausanne, Switzerland
232. The Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02142, USA
233. Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA
234. Pacific Biosciences, Menlo Park, California 94025, USA
235. Sage Bionetworks, Seattle, Washington 98109, USA
236. Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri 63110, USA
237. Division of Intramural Research, National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, Massachusetts 01702, USA
238. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York 10461, USA
239. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA
240. Department of Medical Genetics, University of Helsinki, 00014 Helsinki, Finland
241. Laboratory of Genetics, National Institute on Aging, Baltimore, Maryland 21224, USA
242. Division of Community Health Sciences, St George's, University of London, London, SW17 0RE, UK
243. Klinikum Grosshadern, 81377 Munich, Germany
244. Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland
245. University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, CB2 0QQ, Cambridge, UK
246. Carolina Center for Genome Sciences, School of Public Health, University of North Carolina Chapel Hill, Chapel Hill, North Carolina 27514, USA
247. Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA

SUPPLEMENTARY DATA

MuTHER Consortium authors and affiliations

Alexandra C. Nica^{1,2}, Leopold Parts¹, Daniel Glass³, James Nisbet¹, Amy Barrett⁴, Magdalena Sekowska¹, Mary Travers⁴, Simon Potter¹, Elin Grundberg^{1,3}, Kerrin Small^{1,3}, Åsa K. Hedman⁵, Veronique Bataille³, Jordana Tzenova Bell^{3,5}, Gabriela Surdulescu³, Antigone S. Dimas^{2,5}, Catherine Ingle¹, Frank O. Nestle⁶, Paola di Meglio⁶, Josine L. Min⁵, Alicja Wilk¹, Christopher J. Hammond³, Neelam Hassanali⁴, Tsun-Po Yang¹, Stephen B. Montgomery², Steve O'Rahilly⁷, Cecilia M. Lindgren⁵, Krina T. Zondervan⁵, Nicole Soranzo^{1,3}, Inês Barroso^{1,7}, Richard Durbin¹, Kourosh Ahmadi³, Panos Deloukas¹, Mark I. McCarthy^{4,5,8}, Emmanouil T. Dermizakis², Timothy D. Spector³

AFFILIATIONS:

1. Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, UK
2. Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva, Switzerland
3. Department of Twin Research, King's College London, London, UK
4. Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Churchill Hospital, Oxford, UK
5. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
6. St. John's Institute of Dermatology, King's College London, London, UK
7. University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital Cambridge, UK
8. Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford, UK

SUPPLEMENTARY DATA

CARDIoGRAM authors and affiliations

Heribert Schunkert^{1,119*}, Inke R König^{2,119}, Sekar Kathiresan^{3-5,119}, Muredach P Reilly^{6,119}, Themistocles L Assimes^{7,119}, Hilma Holm^{8,119}, Michael Preuss^{1,2}, Alexandre F R Stewart⁹, Maja Barbalic¹⁰, Christian Gieger¹¹, Devin Absher¹², Zouhair Aherrahrou¹, Hooman Allayee¹³, David Altshuler^{5,14}, Sonia S Anand¹⁵, Karl Andersen^{16,17}, Jeffrey L Anderson¹⁸, Diego Ardissino¹⁹, Stephen G Ball^{20,21}, Anthony J Balmforth²², Timothy A Barnes²³, Diane M Becker²⁴, Lewis C Becker²⁴, Klaus Berger²⁵, Joshua C Bis²⁶, S Matthijs Boekholdt^{27,28}, Eric Boerwinkle¹⁰, Peter S Braund²³, Morris J Brown²⁹, Mary Susan Burnett³⁰, Ian Buyschaert^{31,32}, Cardiogenics, John F Carlquist¹⁸, Li Chen³³, Sven Cichon³⁴⁻³⁶, Veryan Codd²³, Robert W Davies³⁷, George Dedoussis³⁸, Abbas Dehghan^{39,40}, Serkalem Demissie^{41,42}, Joseph M Devaney³⁰, Patrick Diemert¹, Ron Do⁴³, Angela Doering¹¹, Sandra Eifert⁴⁴, Nour Eddine El Mokhtari⁴⁵, Stephen G Ellis⁴⁶, Roberto Elosua⁴⁷, James C Engert^{43,48}, Stephen E Epstein³⁰, Ulf de Faire^{49,50}, Marcus Fischer⁵¹, Aaron R Folsom⁵², Jennifer Freyer¹, Bruna Gigante^{49,50}, Domenico Girelli⁵³, Solveig Gretarsdottir⁸, Vilmundur Gudnason^{17,54}, Jeffrey R Gulcher⁸, Eran Halperin⁵⁵⁻⁵⁷, Naomi Hammond⁵⁸, Stanley L Hazen⁵⁹, Albert Hofman³⁹, Benjamin D Horne¹⁸, Thomas Illig¹¹, Carlos Iribarren⁶⁰, Gregory T Jones⁶¹, J Wouter Jukema^{62,63}, Michael A Kaiser²³, Lee M Kaplan⁶⁴, John J P Kastelein⁶⁵, Kay-Tee Khaw⁶⁶, Joshua W Knowles⁷, Genovefa Kolovou⁶⁷, Augustine Kong⁸, Reijo Laaksonen⁶⁸, Diether Lambrechts³², Karin Leander⁶⁹, Guillaume Lettre^{69,70}, Mingyao Li⁷¹, Wolfgang Lieb¹, Christina Loley^{1,2}, Andrew J Lotery^{72,73}, Pier M Mannucci⁷⁴, Seraya Maouche¹, Nicola Martinelli⁵³, Pascal P McKeown⁷⁵, Christa Meisinger¹¹, Thomas Meitinger^{76,77}, Olle Melander⁷⁸, Pier Angelica Merlini⁷⁹, Vincent Mooser⁸⁰, Thomas Morgan⁸¹, Thomas W Mühleisen^{34,35}, Joseph B Muhlestein¹⁸, Thomas Münzel⁸², Kiran Musunuru³⁻⁵, Janja Nahrstaedt^{1,2}, Christopher P Nelson²², Markus M Nöthen^{34,35}, Oliviero Olivieri⁵³, Riyaz S Patel^{83,84}, Chris C Patterson⁷⁵, Annette Peters¹¹, Flora Peyvandi⁸⁵, Liming Qu⁷¹, Arshed A Quyyumi⁸³, Daniel J Rader^{6,86}, Loukianos S Rallidis⁸⁷, Catherine Rice⁵⁸, Frits R Rosendaal⁸⁸⁻⁹⁰, Diana Rubin⁹¹, Veikko Salomaa⁹², M Lourdes Sampietro⁹³, Manj S Sandhu^{94,95}, Eric Schadt^{96,97}, Arne Schäfer⁹⁸, Arne Schillert², Stefan Schreiber⁹⁸, Jürgen Schrezenmeier^{99,100}, Stephen M Schwartz²⁶, David S Siscovick²⁶, Mohan Sivananthan¹⁰¹, Suthesh Sivapalaratnam²⁷, Albert Smith^{17,54}, Tamara B Smith¹⁰², Jaapjan D Snoep⁸⁸, Nicole Soranzo⁵⁸, John A Spertus¹⁰³, Klaus Stark⁵¹, Kathy Stirrups⁵⁸, Monika Stoll¹⁰⁴, W H Wilson Tang⁴⁶, Stephanie Tennstedt¹, Gudmundur Thorgeirsson^{16,17}, Gudmar Thorleifsson⁸, Maciej Tomaszewski^{23,105}, Andre G Uitterlinden^{39,40,106}, Andre M van Rij⁶¹, Benjamin F Voight^{4,5,107}, Nick J Wareham¹⁰⁸, George A Wells³⁷, H-Erich Wichmann^{11,44,109}, Philipp S Wild⁸², Christina Willenborg^{1,2}, Jaqueline C M Witteman^{39,40}, Benjamin J Wright¹¹⁰, Shu Ye¹¹¹, Tanja Zeller⁸², Andreas Ziegler², Francois Cambien¹¹², Alison H Goodall^{23,105}, L Adrienne Cupples^{41,42}, Thomas Quertermous⁷, Winfried März¹¹³⁻¹¹⁵, Christian Hengstenberg⁵¹, Stefan Blankenberg⁸², Willem H Ouwehand^{58,116}, Alistair S Hall²¹, Panos Deloukas⁵⁸, John R Thompson¹¹⁷, Kari Stefansson^{8,17}, Robert Roberts⁹, Unnur Thorsteinsdottir^{8,17}, Christopher J O'Donnell^{42,119}, Ruth McPherson^{9,118,119}, Jeanette Erdmann^{1,119} & Nilesh J Samani^{23,105,119} for the CARDIoGRAM Consortium

SUPPLEMENTARY DATA

AFFILIATIONS:

1. Universität zu Lübeck, Medizinische Klinik II, Lübeck, Germany.
2. Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Lübeck, Germany.
3. Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts, USA.
4. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA.
5. Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA.
6. The Cardiovascular Institute, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
7. Department of Medicine, Stanford University School of Medicine, Stanford, California, USA.
8. deCODE genetics, Reykjavik, Iceland.
9. The John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.
10. University of Texas Health Science Center, Human Genetics Center, Houston, Texas, USA.
11. Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
12. Hudson Alpha Institute, Huntsville, Alabama, USA.
13. Department of Preventive Medicine, University of Southern California, Los Angeles, California, USA.
14. Department of Molecular Biology and Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.
15. Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada.
16. Department of Medicine, Landspítali University Hospital, Reykjavik, Iceland.
17. University of Iceland, Faculty of Medicine, Reykjavik, Iceland.
18. Cardiovascular Department, Intermountain Medical Center, Cardiology Division, University of Utah, Salt Lake City, Utah, USA.
19. Division of Cardiology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy.
20. LIGHT Research Institute, Faculty of Medicine and Health, University of Leeds, Leeds, UK.
21. Division of Cardiovascular and Neuronal Remodelling, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, UK.
22. Division of Cardiovascular and Diabetes Research, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, UK.
23. Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Leicester, UK.
24. The Johns Hopkins University School of Medicine, Division of General Internal Medicine, Baltimore, Maryland, USA.
25. Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany.
26. Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington, USA.
27. Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands.
28. Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands.

SUPPLEMENTARY DATA

29. Clinical Pharmacology Unit, University of Cambridge, Cambridge, UK.
30. Cardiovascular Research Institute, Medstar Health Research Institute, Washington Hospital Center, Washington, DC, USA.
31. Department of Cardiology, University Hospital Gasthuisberg, Leuven, Belgium.
32. Vesalius Research Center, VIB-K.U.Leuven, Leuven, Belgium.
33. Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.
34. Institute of Human Genetics, University of Bonn, Bonn, Germany.
35. Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany.
36. Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany.
37. The Cardiovascular Research Methods, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.
38. Department of Dietetics-Nutrition, Harokopio University, Athens, Greece.
39. Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.
40. Member of Netherlands Consortium for Healthy Aging (NCHA) sponsored by Netherlands Genomics Initiative (NGI), Leiden, The Netherlands.
41. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA.
42. National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA.
43. Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
44. Klinikum Grosshadern, Munich, Germany.
45. Klinik für Innere Medizin, Kreiskrankenhaus Rendsburg, Rendsburg, Germany.
46. Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA.
47. Cardiovascular Epidemiology and Genetics Group, Institut Municipal d'Investigació Mèdica, Ciber Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
48. Department of Medicine, McGill University, Montreal, Canada.
49. Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.
50. Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden.
51. Klinik und Poliklinik für Innere Medizin II, Regensburg, Germany.
52. University of Minnesota School of Public Health, Division of Epidemiology and Community Health, School of Public Health (A.R.F.), Minneapolis, Minnesota, USA.
53. Department of Medicine, University of Verona, Verona, Italy.
54. Icelandic Heart Association, Kopavogur, Iceland.
55. The Blavatnik School of Computer Science, Tel-Aviv University, Tel-Aviv, Israel.
56. Department of Molecular Microbiology and Biotechnology, Tel-Aviv University, Tel-Aviv, Israel.
57. International Computer Science Institute, Berkeley, California, USA.
58. Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, UK.
59. Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA.
60. Division of Research, Kaiser Permanente of Northern California, Oakland, California, USA.
61. Surgery Department, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand.
62. Department of Cardiology C5-P, Leiden University Medical Center, Leiden, The Netherlands.
63. Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands.

SUPPLEMENTARY DATA

64. Massachusetts General Hospital, Boston, Massachusetts, USA.
65. Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.
66. Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK.
67. 1st Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece.
68. Science Center, Tampere University Hospital, Tampere, Finland.
69. Montreal Heart Institute, Montréal, Québec, Canada.
70. Département de Médecine, Université de Montréal, succursale Centre-ville, Montréal, Québec, Canada.
71. Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
72. Clinical Neurosciences Division, School of Medicine, University of Southampton, Southampton, UK.
73. Southampton Eye Unit, Southampton General Hospital, Southampton, UK.
74. Scientific Direction, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Fondazione Cà Granda, Ospedale Maggiore Policlinico, Milano, Italy.
75. Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Belfast, Ireland, UK.
76. Institute of Human Genetics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Neuherberg, Germany.
77. Institute of Human Genetics, Technische Universität München, Klinikum rechts der Isar, Munich, Germany.
78. Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, Scania University Hospital, Lund University, Malmö, Sweden.
79. Division of Cardiology, Azienda Ospedaliera Niguarda Ca'Granda, Milan, Italy.
80. Genetics Division and Drug Discovery, GlaxoSmithKline, King of Prussia, Pennsylvania, USA.
81. Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
82. Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz, Johannes-Gutenberg Universität Mainz, Germany.
83. Emory University School of Medicine, Atlanta, Georgia, USA.
84. Cardiff University, Cardiff, Wales, UK.
85. A. Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Medicine and Medical Specialties, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano and Luigi Villa Foundation, Milan, Italy.
86. The Institute for Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
87. Second Department of Cardiology, Attikon Hospital, School of Medicine, University of Athens, Athens, Greece.
88. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.
89. Department of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands.
90. Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands.
91. Medizinische Klinik I, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany.

SUPPLEMENTARY DATA

92. Chronic Disease Epidemiology and Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland.
93. Department of Human Genetics and Cardiology, Leiden University Medical Center, Leiden, The Netherlands.
94. Genetic Epidemiology Group, Wellcome Trust Sanger Institute, Cambridge, UK.
95. Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK.
96. Pacific Biosciences, Menlo Park, California, USA.
97. Sage Bionetworks, Palo Alto, California, USA.
98. Institut für Klinische Molekularbiologie, Christian-Albrechts Universität, Kiel, Germany.
99. Institute of Physiology and Biochemistry of Nutrition, Max Rubner-Institute, Kiel, Germany.
100. Clinical Research Center Kiel, Kiel Innovation and Technology Center, Kiel, Germany.
101. Cardiology Division, Leeds Teaching Hospitals National Health Service Trust, Leeds, UK.
102. Laboratory of Epidemiology, Demography and Biometry, Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA.
103. Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri, USA.
104. Leibniz-Institute for Arteriosclerosis Research, University of Münster, Münster, Germany.
105. Leicester National Institute for Health Research Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, UK.
106. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.
107. Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
108. Medical Research Council Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK.
109. Institute of Medical Information Science, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, München, Germany.
110. Department of Cardiovascular Surgery, University of Leicester, Leicester, UK.
111. William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
112. INSERM UMRS 937, Pierre and Marie Curie University, Université Pierre et Marie Curie (UPMC)-Paris 6, Faculté de Médecine Pierre et Marie Curie, Paris, France.
113. Synlab Center of Laboratory Diagnostics Heidelberg, Heidelberg, Germany.
114. Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria.
115. Institute of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany.
116. Department of Haematology, University of Cambridge and NHS Blood and Transplant, Cambridge, UK.
117. Department of Health Sciences, University of Leicester, Leicester, UK.
118. Atherogenomics Laboratory, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.
119. These authors contributed equally to this work.

SUPPLEMENTARY DATA

C4D Consortium authors and affiliations

HPS

Jemma C. Hopewell, Sarah Parish, Alison Offer, Robert Clarke, Louise Bowman, Peter Sleight, Jane Armitage, Richard Peto, Rory Collins.

Affiliations: Clinical Trial Service Unit, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK

LOLIPOP

John C. Chambers, Goncalo Abecasis, Nabeel Ahmed, Mark Caulfield, Peter Donnelly, Paul Elliott, Philippe Froguel, Angad S Kooner, Mark McCarthy, Nilesh Samani, James Scott, Joban Sehmi, Weihua Zhang, Jaspal S. Kooner.

Affiliations

John Chambers: Epidemiology and Biostatistics, Imperial College London, Norfolk Place, London, W2 1PG, UK; Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Middlesex, UB1 3HW, UK

Gonzalo Abecasis: Department Biostatistics, University of Michigan, 1420 Washington Heights, Ann Arbor, MI 48109, USA

Nabeel Ahmed: Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Middlesex, UB1 3HW, UK

Mark Caulfield: William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK

Peter Donnelly: Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK; Department Statistics, Oxford University, 1 South Parks Road, Oxford, OX1 3TG, UK

Paul Elliott: Epidemiology and Biostatistics, Imperial College London, Norfolk Place, London, W2 1PG, UK; MRC-HPA Centre for Environment and Health, Imperial College London, UK

Philippe Froguel: Genomic Medicine, Imperial College London, Du Cane Road, London, W12 0NN, UK

Angad S Kooner: Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Middlesex, UB1 3HW, UK

Mark McCarthy: Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK; Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University, Old Road, Oxford, OX3 7LJ, UK; Oxford NIHR Biomedical Research Centre, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LJ UK

Nilesh Samani: Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK; Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK

James Scott: National Heart and Lung Institute, Imperial College London, Du Cane Road, London, W12 0NN, UK

Joban Sehmi: National Heart and Lung Institute, Imperial College London, Du Cane Road, London, W12 0NN, UK

Weihua Zhang: Epidemiology and Biostatistics, Imperial College London, Norfolk Place, London, W2 1PG, UK; Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Middlesex, UB1 3HW, UK

Jaspal S Kooner: National Heart and Lung Institute, Imperial College London, Du Cane Road, London, W12 0NN, UK; Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Middlesex, UB1 3HW, UK

PROCARDIS

SUPPLEMENTARY DATA

Sweden: Rona Strawbridge, Maria Sabater-Lleal, Anders Mälarstig, Bengt Sennblad, John Öhrvik, Angela Silveira, Mai-Lis Hellénus, Ferdinand van't Hooft, Per Eriksson, Gunnar Olsson, Anders Hamsten; Germany: Stephan Rust, Gerd Assmann, Udo Seedorf; Italy: Simona Barlera, Gianni Tognoni, Maria Grazia Franzosi. UK: Robert Clarke, Pamela Linksted, Jemma C. Hopewell, Rory Collins, John F. Peden, Anuj Goel, Halit Ongen, Theodosios Kyriakou, Fiona Green, Martin Farrall, Hugh Watkins.

Affiliations

Rona Strawbridge, Maria Sabater-Lleal, Anders Mälarstig, Bengt Sennblad, John Öhrvik, Angela Silveira, Ferdinand van't Hooft, Per Eriksson, Anders Hamsten: All at Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Building L8:03, Karolinska University Hospital Solna, S-171 76 Stockholm, Sweden

Mai-Lis Hellénus: Cardiology Unit, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, S-17176 Stockholm, Sweden

Gunnar Olsson: Cardiovascular Drug Research at the Department of Medicine, Solna, Sweden and Cardiovascular and Gastrointestinal Innovative Medicines, Global Research & Development, AstraZeneca, Sweden

Stephan Rust, Gerd Assmann, Udo Seedorf: Gesellschaft für Arterioskleroseforschung e.V., Leibniz-Institut für Arterioskleroseforschung an der Universität Münster (LIFA), Domagkstr. 3, 48149 Münster, Germany

Simona Barlera, Maria Grazia Franzosi: Department of Cardiovascular Research, Istituto Mario Negri, Via La Masa 19, Milano, 20156, Italy

Gianni Tognoni: Consorzio Mario Negri Sud, 8/A - 66030 Santa Maria Imbaro (Chieti) , Italy

Robert Clarke, Pamela Linksted, Jemma C. Hopewell, Rory Collins: Clinical Trial Service Unit, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK

John F. Peden, Anuj Goel, Halit Ongen, Theodosios Kyriakou, Fiona Green, Martin Farrall, Hugh Watkins: Department of Cardiovascular Medicine, The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK; Department of Cardiovascular Medicine, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK

PROMIS

Danish Saleheen, Asif Rasheed, Moazzam Zaidi, Nabi Shah, Maria Samuel, Nadeem Mallick, Muhammad Azhar, Khan Zaman, Adbus Samad, Muhammad Ishaq, Ali Gardezi, Fazal-ur-Rehman Memon, Nilesh Samani, Philippe Frossard, Panos Deloukas, John Danesh

Affiliations

Danish Saleheen: Center for Non-Communicable Diseases Pakistan , Center for Non-Communicable Diseases Pakistan, Karachi, 75300, Pakistan; Department of Public Health and Primary Care, University of Cambridge, worts causeway, Cambridge CB1 8RN, UK

Asif Rasheed, Moazzam Zaidi, Nabi Shah, Maria Samuel: Center for Non-Communicable Diseases Pakistan , Center for Non-Communicable Diseases Pakistan, Karachi, 75300, Pakistan

Nadeem Mallick, Muhammad Azhar: Department of Cardiology, Punjab Institute of Cardiology, Jail Road, Lahore, Pakistan

SUPPLEMENTARY DATA

Khan Shah Zaman: Department of Cardiology, National Institute of Cardiovascular Diseases Karachi, Pakistan

Adbus Samad, Muhammad Ishaq: Department of Cardiology, Karachi Institute of Heart Diseases, Federal B. Area, Karachi, 75950, Pakistan

Ali Gardezi: Department of Cardiology, Ch. Pervaiz Elahi Institute of Cardiology , Multan, Pakistan

Fazal-ur-Rehman Memon: Department of Cardiology, Red Crescent Institute of Cardiology, Latifabad, Hyderabad, Pakistan

Nilesh Samani: Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK; Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK

Philippe Frossard: Center for Non-Communicable Diseases Pakistan , Center for Non-Communicable Diseases Pakistan, Karachi, 75300, Pakistan

Panos Deloukas: Human Genetics, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton CB10 1SA UK

John Danesh: Department of Public Health and Primary Care, University of Cambridge, worts causeway, Cambridge CB1 8RN, UK

SUPPLEMENTARY DATA

SUPPLEMENTARY METHODS

Imputation and quality control

All genome-wide association studies (GWAS) filtered out samples and single nucleotide polymorphisms (SNPs) with poor performance using different criteria. SNPs were discarded if they presented: (i) minor allele frequency (MAF) <0.01 ; (ii) distortion from Hardy-Weinberg equilibrium ($P < 10^{-4}$ to 10^{-6}); or (iii) call rate $<95\%$. Samples were generally excluded by the following criteria: (i) call rate $<95\%$ or 97% ; (ii) individual heterozygosity out of the sample-specific bounds; or (iii) ethnic outliers as identified by genome-wide principal components analysis and multi-dimensional scaling. After these quality control filters were applied, we used the HapMap II CEU phased reference panel to carry out imputation (expected genotypes of SNPs not present on the array) of approximately 2.5M autosomal SNPs with MACH (1) or IMPUTE (2). Imputation settings and post-imputation filters are specified as described in the Supplementary Table 1, including: (i) post-imputation SNP quality measures $r^2_{\text{hat}} < 0.3$ (MACH) or $\text{proper_info} < 0.4$ (IMPUTE); and (ii) exclusion of SNPs with ambiguous strand or mapping annotation. From a total of $\sim 2.5\text{M}$ imputed SNPs, we included SNPs in the meta-analyses if they passed post-imputation quality control metrics and were available in at least 2,500 participants. Thus 2,499,255 SNPs were included in the meta-analysis.

Additional trait analyses

To characterize the manner by which elevations in proinsulin levels affect glycemia, we investigated associations between top hits identified in the proinsulin GWAS with other glucometabolic traits (fasting glucose [n ranging 44,601–46,186 depending on the SNP analyzed], two-hour glucose [n=15,088–15,252], fasting insulin [n=36,775–38,335], fasting C-peptide [n=1,537–2,956], two-hour insulin [n=6,923–7,083]), measures of beta-cell function (HOMA-B [n=35,046–36,606] and the insulinogenic index [n=10,902–14,956]), measures of insulin resistance/sensitivity (HOMA-IR [n=35,512–37,072] and the Matsuda index [n=7,055–9,561]), glycated hemoglobin (A1C) (n=33,736–44,731), and 32-33 split-proinsulin levels (n=4,103–6,343) in non-diabetic individuals using fixed effects meta-analysis methods and adjusting for age and sex. We also constructed a genotype score composed of the nine proinsulin-raising alleles and tested it for association with coronary artery disease in summary case-control data provided by the CARDIoGRAM (3) and C4D (4) consortia.

Gene expression studies

Human tissue panel

Genes at each locus were chosen on the basis of proximity to the index SNP and biological credibility: the probe chosen for each gene was designed to cover the widest range of known transcripts. Expression assays were performed using adult human total RNA obtained from a commercial tissue panel (Clontech: adrenal gland, bone marrow, whole brain, cerebellum, colon, heart, human reference, kidney, liver, lung, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, uterus), fetal human total RNA obtained from spontaneous abortions available as part of a commercial tissue panel (Clontech: liver and brain), or extracted from existing collections at the University of Oxford with full ethical consent (pancreas n=3, omental adipose n=5, subcutaneous adipose n=5, islets n=3).

SUPPLEMENTARY DATA

Fluorescence-activated cell-sorted beta cells

Beta cells were obtained from three adult lean, normoglycemic organ donors in accordance with French regulations and with the local institutional ethical committee, as previously described (5). Briefly, pancreatic islets were isolated after ductal distension of the pancreata and digestion of the tissue with Liberase (Roche Diagnostics). Human beta cells were sorted by fluorescence-activated cell (FAC) sorting analysis of semi-purified preparations of islet cells using Newport Green, a specific zinc-fluorescent probe (5).

Total RNA was extracted from all tissues using Nucleospin RNA II kit (Macherey Nagel) according to the manufacturer's instructions. Samples were treated with DNase 1 (Ambion) to ensure residual genomic contamination was removed. For each tissue, 1 µg RNA was used to generate cDNA by random primed first strand synthesis according to manufacturer's protocols (Qiagen), including a DNase1 treatment to eliminate residual genomic DNA contamination. Reverse transcriptase-negative reactions were also performed to generate negative control samples. Each reaction used 4 µl of cDNA diluted at 1:50, 5 µl gene expression mastermix (Applied Biosystems), 0.5 µl VIC-labelled endogenous control assay and 0.5 µl FAM-labelled test assay (Applied Biosystems). TaqMan assay IDs available upon request. Reactions were performed in triplicate. A standard curve was generated by serially diluting pooled cDNA from all samples. Real-time PCR was performed on an AB7900 thermal cycler (Applied Biosystems) and fluorescence quantified using SDSv2.3 software (Applied Biosystems). Expression levels were determined with respect to the geometric mean of three endogenous control assays (*HPRT*, *B2M*, *PPIA*) and, for gene-specific plots only, normalized to expression level of that gene in the cDNA pool.

Islets from donors with and without type 2 diabetes

Islets from cadaveric donors were provided by the Nordic network for clinical islets transplantation by the courtesy of Prof. Olle Korsgren, Uppsala University. Islets were obtained from 41 non-diabetic donors (14 women and 17 men), with a mean (\pm SD) age of 57 ± 12 years, A1C $5.0 \pm 0.5\%$, body mass index (BMI) 26 ± 3 kg/m², purity $75 \pm 12\%$, and 6 diabetic donors (2 women, 4 men), age 57 ± 14 years, A1C $6.9 \pm 1.4\%$, BMI 28 ± 4 kg/m², purity $64 \pm 13\%$. The islets were cultured in CMRL 1066 (ICN Biomedicals, Costa Mesa, CA, USA), supplemented with 10 mmol/L HEPES, 2 mmol/L L-glutamine, 50 µg/ml gentamicin, 0.25 µg/ml Fungizone (GIBCO, BRL, Gaithersburg, MD, USA), 20 µg/ml ciprofloxacin (Bayer Healthcare, Leverkusen, Germany), and 10 mmol/L nicotinamide at 37 °C (5% CO₂) for 2-6 days prior to RNA preparation. All islet donors had given consent to donate organs for medical research. All procedures were approved by the ethical committees at Uppsala and Lund Universities.

eQTL analyses

For analyses in lymphoblastoid cell lines (LCL), skin and adipose tissue, mRNA transcript levels were measured using Illumina's whole-genome expression array HumanHT-12 version 3. Samples (156 LCL, 160 skin, 166 adipose) were derived simultaneously from a subset of well-phenotyped healthy female twins of the MuTHER resource (6). Genotyping of DNA from the same individuals was performed in parallel using Illumina's 1M-Duo and 1.2M-Duo custom chips. Log₂ transformed expression signals were normalized separately per tissue as follows: quantile normalization was performed across three replicates of each individual followed by quantile normalization across all individuals, and the eQTL analysis was performed separately for each tissue. Within each tissue, twins from the same pair were separated by ID in two samples analyzed independently of each other. For each gene we tested for association between SNP genotype and normalized expression values using Spearman rank correlation, testing all SNPs mapping within a 2 MB window centered on the gene's

SUPPLEMENTARY DATA

transcription site. Statistical significance was evaluated through permutations of expression phenotypes relative to genotypes (7), defining significance thresholds of 0.001 and 0.01.

For analyses in liver, sample selection for gene expression biobanks has been described previously (8). In brief, liver biopsies were collected from patients undergoing cardiac valve surgery. After hybridization of extracted RNA to Affymetrix ST 1.0 Exon arrays, data was RMA normalized and log₂ transformed. DNA was extracted from whole blood and genotyping was carried out using the Illumina 610w-Quad beadarray platform. An additive genetic model was used to test for association between SNPs and gene expression.

SUPPLEMENTARY METHODS REFERENCES

1. Li Y, Abecasis GR: Mach 1.0: Rapid haplotype reconstruction and missing genotype inference. *Am J Hum Genet* 79:2290, 2006
2. Marchini J, Howie B, Myers S, McVean G, Donnelly P: A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* 39:906-913, 2007
3. Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AFR, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buyschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NEE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJP, Khaw K-T, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoop JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WHW, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JCM, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J: Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 43:333-338, 2011
4. Peden JF, Hopewell JC, Saleheen D, Chambers JC, Hager J, Soranzo N, Collins R, Danesh J, Elliott P, Farrall M, Stirrups K, Zhang W, Hamsten A, Parish S, Lathrop M, Watkins HC, Clarke R, Deloukas P, Kooner JS, Goel A, Ongen H, Strawbridge RJ, Heath S, Malarstig A, Helgadottir A, Ohrvik J, Murtaza M, Potter S, Hunt SE, Delepine M, Jalilzadeh S, Axelsson T, Syvanen AC, Gwilliam R, Bumpstead S, Gray E, Edkins S, Folkersen L, Kyriakou T, Franco-Cereceda A, Gabrielsen A, Seedorf U, Eriksson P, Offer A, Bowman L, Sleight P, Armitage J, Peto R, Abecasis G, Ahmed N, Caulfield M, Donnelly P, Froguel P, Kooner AS, McCarthy MI, Samani NJ, Scott J, Sehmi J, Silveira A, Hellenius ML, van 't Hooft FM, Olsson G, Rust S, Assmann G, Barlera S, Tognoni G, Franzosi MG, Linksted P, Green FR, Rasheed A, Zaidi M,

SUPPLEMENTARY DATA

Shah N, Samuel M, Mallick NH, Azhar M, Zaman KS, Samad A, Ishaq M, Gardezi AR, Memon FU, Frossard PM, Spector T, Peltonen L, Nieminen MS, Sinisalo J, Salomaa V, Ripatti S, Bennett D, Leander K, Gigante B, de Faire U, Pietri S, Gori F, Marchioli R, Sivapalaratnam S, Kastelein JJ, Trip MD, Theodoraki EV, Dedoussis GV, Engert JC, Yusuf S, Anand SS: A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. *Nat Genet* 43:339-344, 2011

5. Lukowiak B, Vandewalle B, Riachy R, Kerr-Conte J, Gmyr V, Belaich S, Lefebvre J, Pattou F: Identification and purification of functional human beta-cells by a new specific zinc-fluorescent probe. *J Histochem Cytochem* 49:519-528, 2001

6. Nica AC, Parts L, Glass D, Nisbet J, Barrett A, Sekowska M, Travers M, Potter S, Grundberg E, Small K, Hedman AK, Bataille V, Tzenova Bell J, Surdulescu G, Dimas AS, Ingle C, Nestle FO, di Meglio P, Min JL, Wilk A, Hammond CJ, Hassanali N, Yang TP, Montgomery SB, O'Rahilly S, Lindgren CM, Zondervan KT, Soranzo N, Barroso I, Durbin R, Ahmadi K, Deloukas P, McCarthy MI, Dermitzakis ET, Spector TD: The architecture of gene regulatory variation across multiple human tissues: the MuTHER study. *PLoS Genet* 7:e1002003, 2011

7. Stranger BE, Nica AC, Forrest MS, Dimas A, Bird CP, Beazley C, Ingle CE, Dunning M, Flicek P, Koller D, Montgomery S, Tavaré S, Deloukas P, Dermitzakis ET: Population genomics of human gene expression. *Nat Genet* 39:1217-1224, 2007

8. Folkersen L, van't Hooft F, Chernogubova E, Agardh HE, Hansson GK, Hedin U, Liska J, Syvanen AC, Paulsson-Berne G, Franco-Cereceda A, Hamsten A, Gabrielsen A, Eriksson P: Association of genetic risk variants with expression of proximal genes identifies novel susceptibility genes for cardiovascular disease. *Circ Cardiovasc Genet* 3:365-373, 2010

SUPPLEMENTARY DATA

Supplementary Table 2: SNPs with suggestive evidence of association that did not reach genome-wide significance on follow-up

SNP	Nearest gene	CHR	Position	Alleles (effect/other)	Freq	Discovery <i>P</i> value (n=10530-10701)	Beta (SE)	Replication <i>P</i> value (n=8902-15757)	Combined <i>P</i> value (n=19432-26451)	Heterogeneity <i>I</i> ² in % (Q-test <i>P</i> -value)
rs12805658*	<i>FCHSD2</i>	11	72232948	A/C	0.25	1.0 x 10 ⁻⁶	0.0038 (0.0109)	0.743	1.0x10 ⁻⁴	52.8 (0.031)
rs11897268	<i>CYS1</i>	2	10157626	A/G	0.18	1.3 x 10 ⁻⁶	-0.0029 (0.0062)	0.639	0.002	42.2 (0.043)
rs3765542	<i>RAPGEF1</i>	9	133448199	T/C	0.44	1.3 x 10 ⁻⁶	-0.0072 (0.0046)	0.116	6.9 x 10 ⁻⁵	37.1 (0.086)
rs306549	<i>DDX31</i>	9	134459997	C/G	0.24	1.4 x 10 ⁻⁶	0.0085 (0.005)	0.088	7.9 x 10 ⁻⁵	63.5 (4.5 x 10 ⁻⁴)
rs179456	<i>TRPS1</i>	8	116764286	A/G	0.22	1.5 x 10 ⁻⁶	0.0084 (0.0053)	0.116	9.3 x 10 ⁻⁵	43.4 (0.048)
rs1874361	<i>SLC26A9</i>	1	204174809	A/C	0.49	2.8 x 10 ⁻⁶	-0.0022 (0.0046)	0.632	0.003	56.9 (5.9 x 10 ⁻³)
rs16893121	<i>C5orf17</i>	5	24137801	T/C	0.05	3.0 x 10 ⁻⁶	-0.0072 (0.0092)	0.439	0.091	56.0 (5.5 x 10 ⁻³)
rs283062	<i>SLC35F1</i>	6	118728149	A/G	0.58	5.2 x 10 ⁻⁶	0.0028 (0.0046)	0.384	0.002	55.9 (7.2 x 10 ⁻³)
rs1877915	<i>ENSG00000201744</i>	4	97156018	T/G	0.09	5.5 x 10 ⁻⁶	-0.0012 (0.0046)	0.796	0.226	65.0 (6.0 x 10 ⁻⁴)
rs7818040	<i>Q6ZRX2_HUMAN</i>	8	31998998	A/G	0.03	7.0 x 10 ⁻⁶	0.0164 (0.0308)	0.404	0.004	50.9 (0.026)
rs11887728	<i>FN1</i>	2	216117604	A/G	0.22	9.8 x 10 ⁻⁶	0.0015 (0.0054)	0.785	0.059	50.2 (0.020)
rs871906**	gene desert	1	216185134	A/C	0.68	1.3 x 10 ⁻⁵	-0.0035 (0.0047)	0.451	0.093	48.2 (0.026)
rs7605582**	<i>ASAP2</i>	2	9333541	A/G	0.65	2.5 x 10 ⁻⁵	0.0046 (0.0047)	0.328	0.002	55.2 (8.2 x 10 ⁻³)

SUPPLEMENTARY DATA

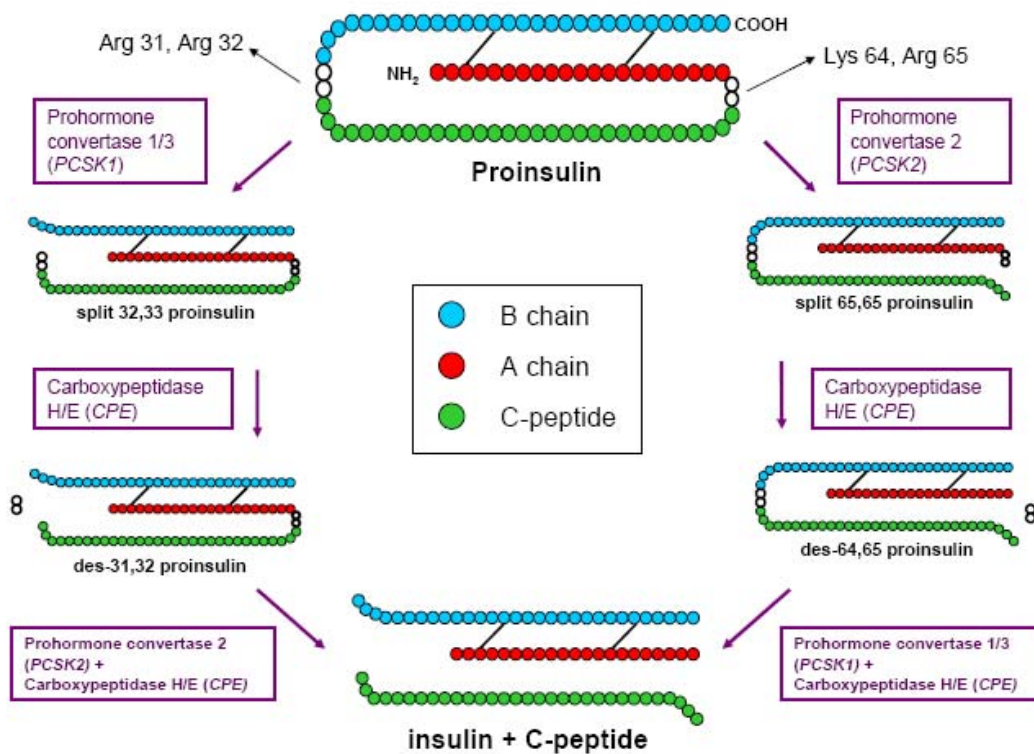
Beta coefficients for the effect allele are shown after adjustments for sex, age, geographic covariates (if applicable) and age squared (Framingham only).

* This SNP near *ARAP1* was selected for further testing based on a suggestive *P* value (1.0×10^{-6}) when analyses for chromosome 11 were conditioned for the top two signals (*ARAP1* rs11603334 and *MADD* rs10501320). The conditional analysis results are shown.

** The last two SNPs (those with $P > 10^{-5}$ at discovery) were selected for follow-up based on the presumed biological role of nearby genes.

SUPPLEMENTARY DATA

Supplementary Figure 1: The proinsulin processing pathway. Insulin biosynthesis via proinsulin processing occurs in secretory granules of the pancreatic beta cell. Proinsulin is composed of two chains, A and B, joined by a connecting peptide (C-peptide). Protein (*encoding gene*) shown. Prohormone convertase 1/3 (*PCSK1*) cleaves the carboxyl sites Arginine 31, Arginine 32 at the B/C chain junction and prohormone convertase 2 (*PCSK2*) cleaves the carboxyl sites Lysine 64, Arginine 65 at the A/C chain junction to produce split proinsulins. The prohormone convertase 1/3 pathway is predominant in the physiological state. Split fragments are further modified by carboxypeptidases to remove exposed basic residues, producing des-proinsulins. Finally, proinsulin is cleaved at the remaining carboxyl site to separate mature insulin and C-peptide molecules, which are secreted in equimolar amounts (modified from Assmann, A., Hinault, C. & Kulkarni, R.N. Growth factor control of pancreatic islet regeneration and function. *Pediatr Diabetes* 10, 14-32 (2009)).

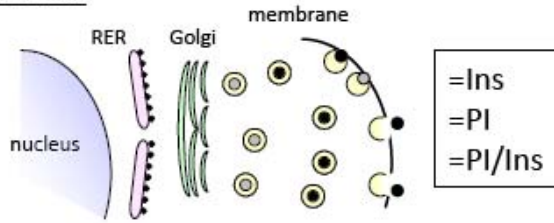


SUPPLEMENTARY DATA

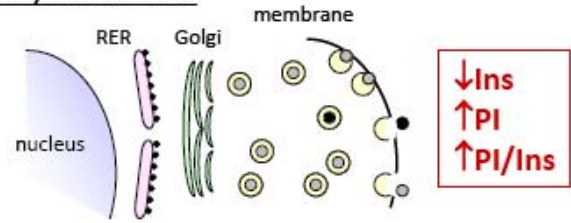
Supplementary Figure 2: Conditions in which circulating proinsulin levels may be altered out of proportion to changes in fasting insulin. *a.* The *INS* gene is transcribed in the nucleus and its mRNA is translated into preproinsulin by ribosomes in the rough endoplasmic reticulum (RER). The pre-peptide signal directs the peptide to the Golgi apparatus, and further proteolytic processing occurs as outlined in Supplementary Figure 1. Granules containing proinsulin (shown in gray) gradually progress into those containing mature insulin (shown in black), which is secreted in a glucose-dependent manner. Some proinsulin (PI) is also secreted, and a proinsulin/insulin ratio (PI/Ins) can thereby be derived. *b.* Under the increased demand of insulin resistance, more insulin is synthesized and secreted; if the beta cell is compensated, the PI/Ins ratio should not be altered substantially. If, however, the beta cell cannot keep up with insulin demand (*c.*), a greater number of immature vesicles reach exocytosis, resulting in an increase in the PI/Ins ratio. Similarly, enzyme defects in the proinsulin processing pathway (*d.*) or structural problems with vesicular trafficking (*e.*) could also result in a raised PI/Ins ratio. *f.* Conversely, a decrease in *effective* beta-cell mass (whether caused by deranged pancreatic beta-cell development, or early defects in the vesicular or proinsulin processing pathways that occur proximally to the proinsulin cleavage step) could result in beta cells that are capable of processing a reduced amount of insulin effectively but in insufficient amounts, leading to an insulin-deficient state which nonetheless is characterized by a decrease in the PI/Ins ratio. The latter four situations (highlighted in red) are relevant for diabetes pathophysiology. Not shown in this beta-cell centered diagram are situations in which the clearance of proinsulin or insulin are differentially affected.

SUPPLEMENTARY DATA

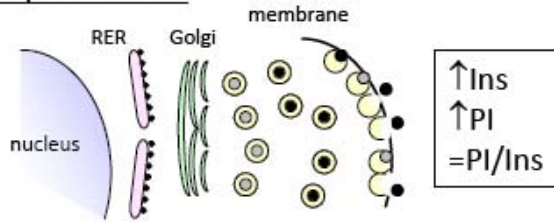
a. normal



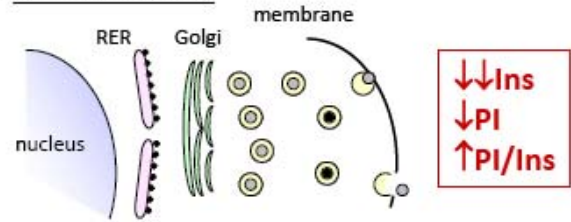
d. enzyme defects



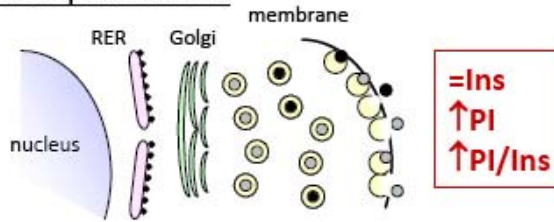
b. compensated IR



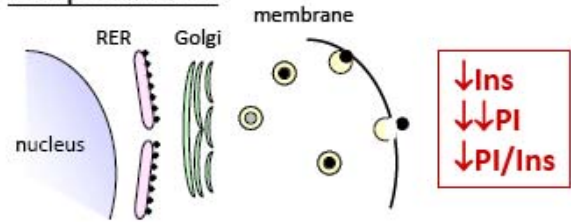
e. vesicle defects



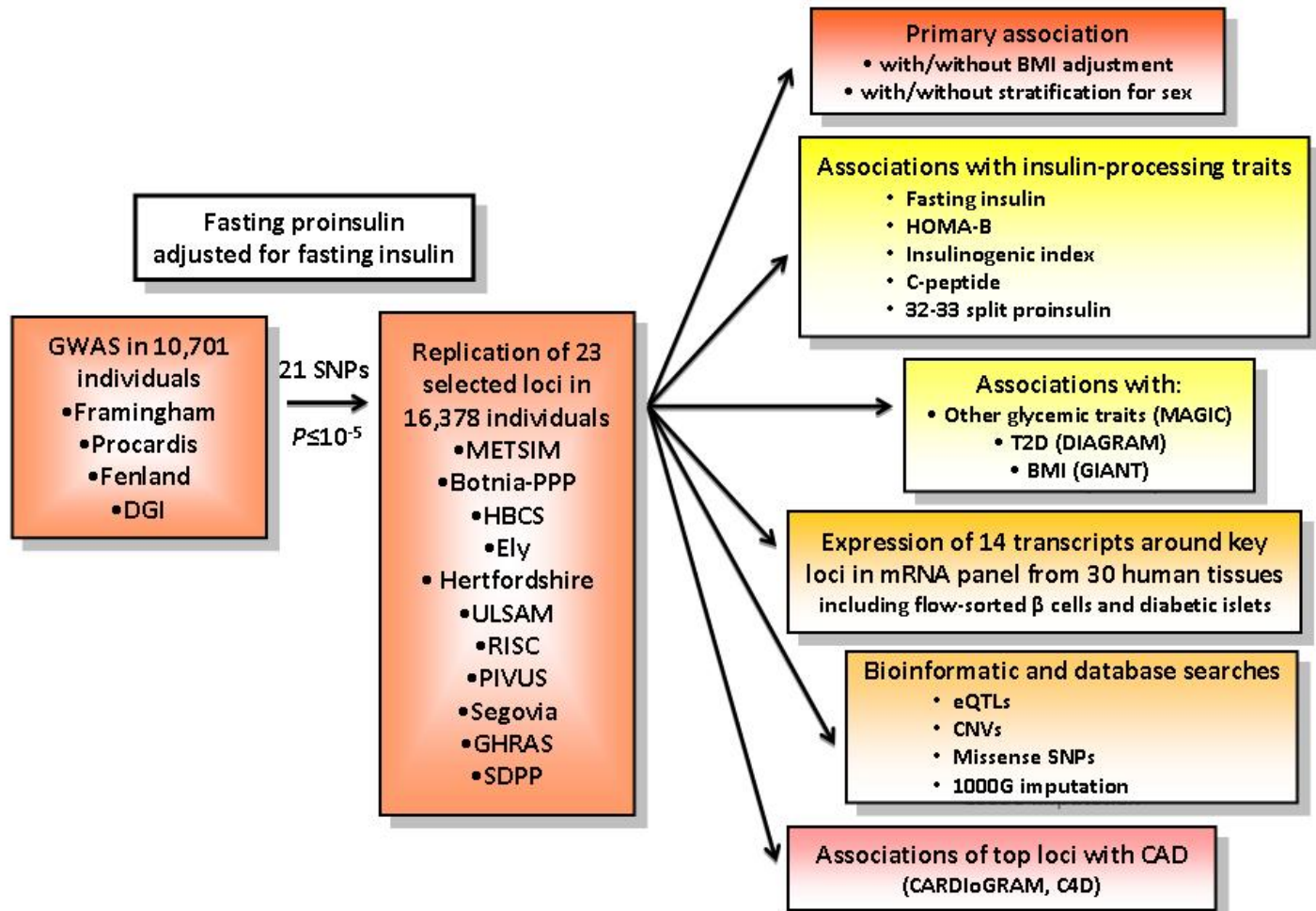
c. uncompensated IR



f. low β-cell mass

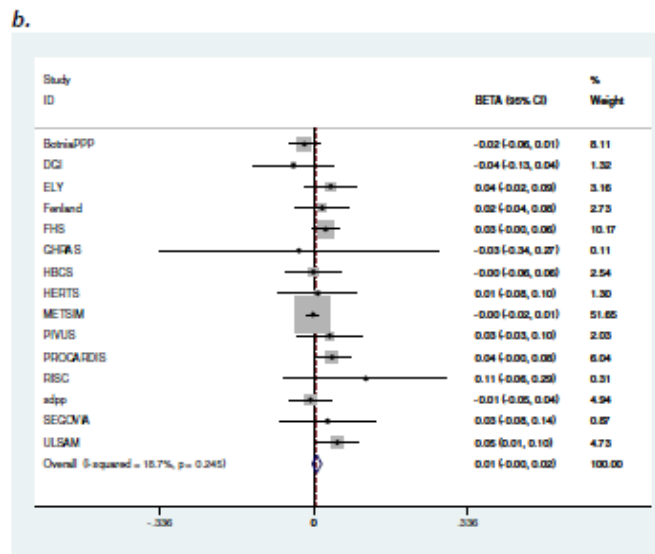
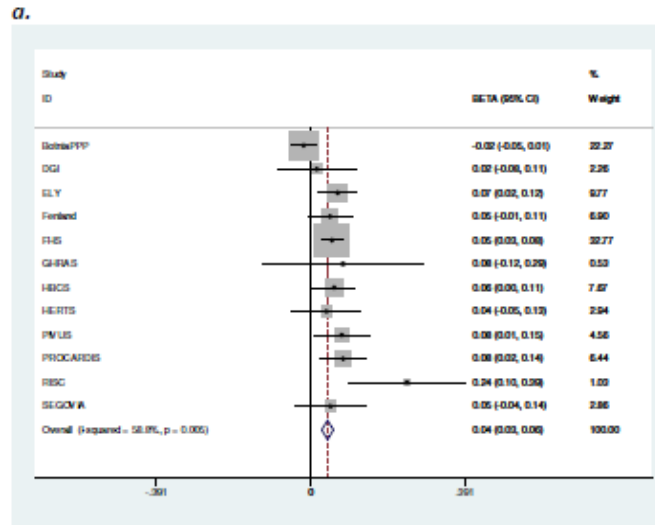


Supplementary Figure 3: Flow chart detailing the study design.



SUPPLEMENTARY DATA

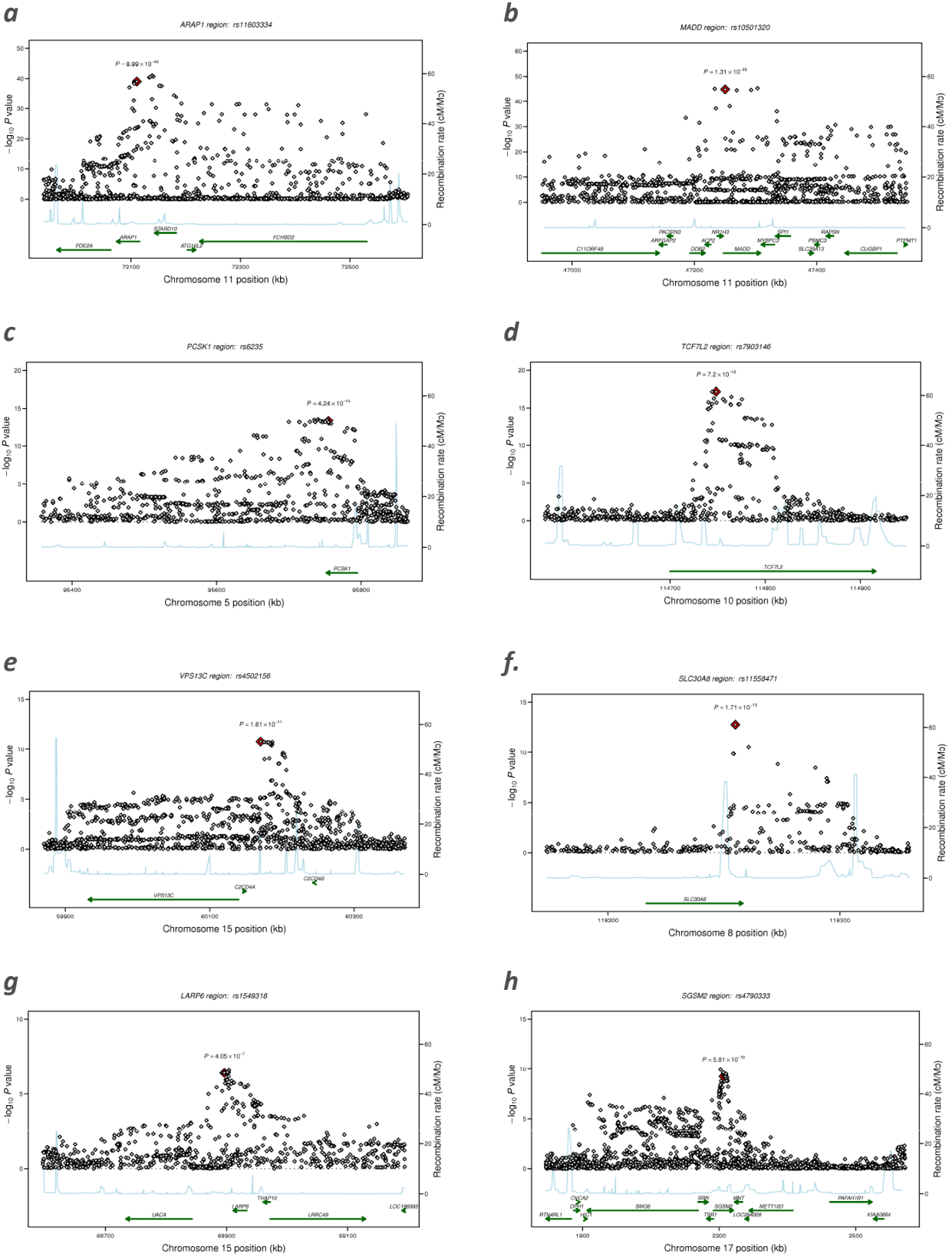
Supplementary Figure 4: Meta-analyses demonstrating the sex-specific association at *DDX31*. The association of SNP rs306549 with proinsulin was seen in women ($P=2.1 \times 10^{-8}$, panel *a.*) but not men ($P=0.17$, panel *b.*). The P -value for sex interaction was 8.9×10^{-5} .



SUPPLEMENTARY DATA

Supplementary Figure 5: Regional plots of top proinsulin-associated loci after imputation using the 1000 Genomes CEU reference panel (August 2009), in the four discovery cohorts with GWAS data. None of the rare variants exert a much larger effect than that observed for the index variant at each locus (red diamond). Annotation is comparable to that provided for Figure 2 (see Fig. 2 legend for details). *a.* *ARAP1* region, *b.* *MADD* region, *c.* *PCSK1* region, *d.* *TCF7L2* region, *e.* *VPS13C/C2CD4A/B* region, *f.* *SLC30A8* region, *g.* *LARP6* region, *h.* *SGSM2* region.

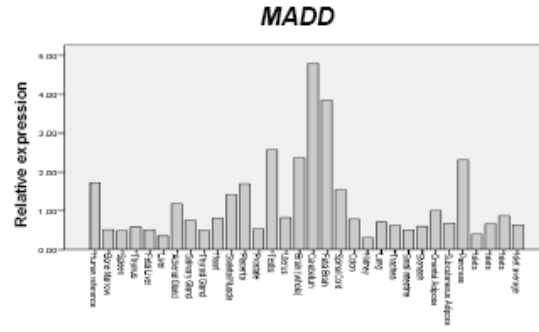
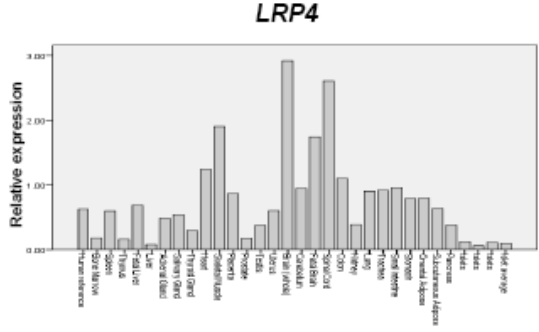
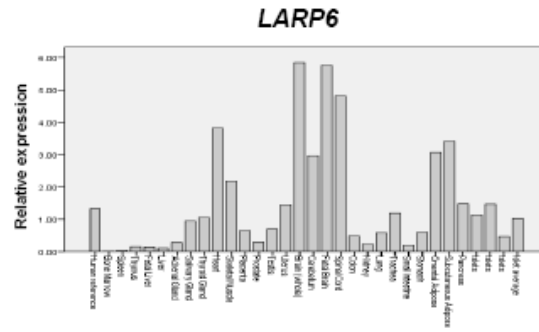
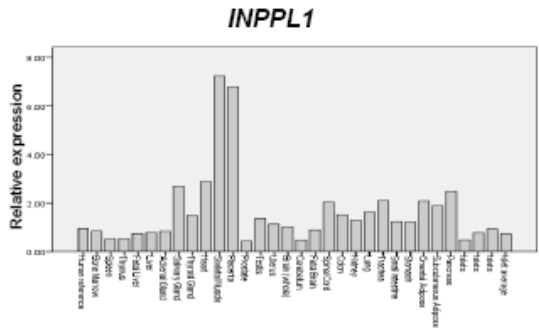
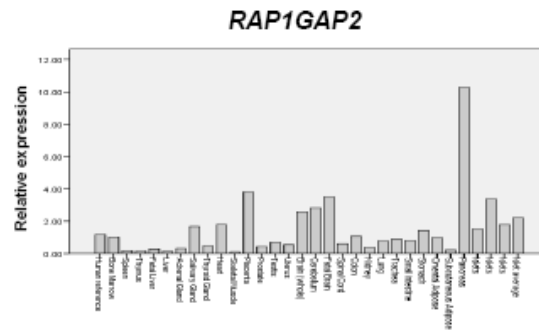
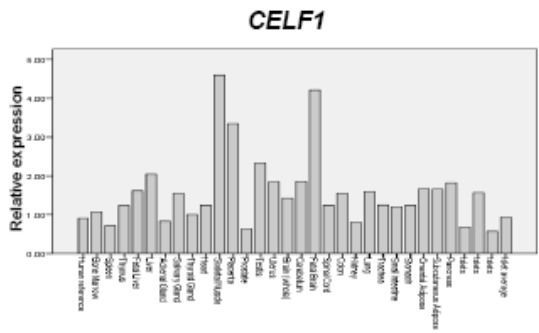
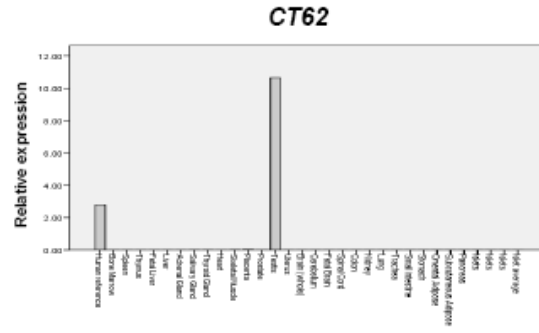
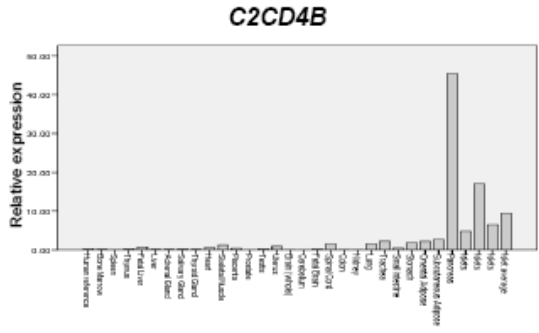
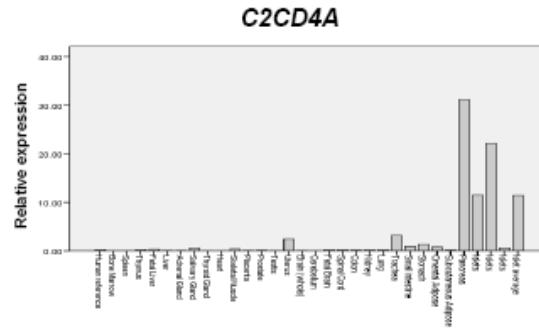
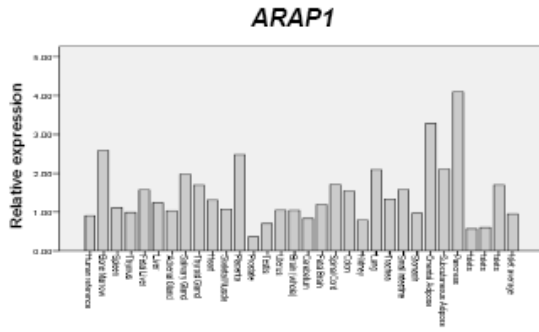
SUPPLEMENTARY DATA



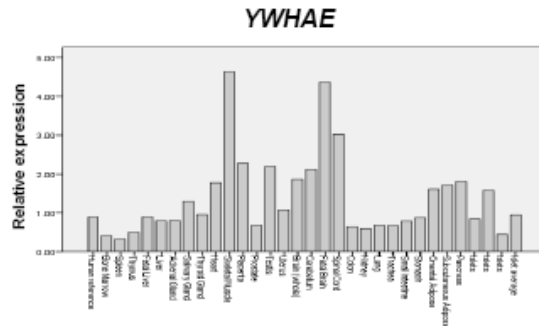
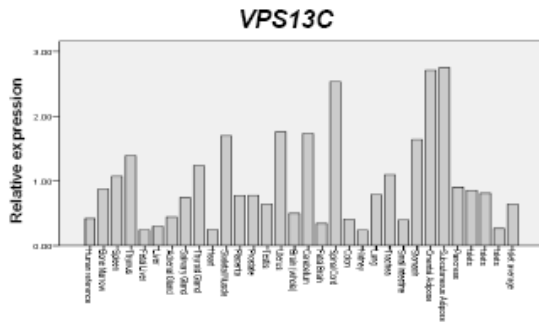
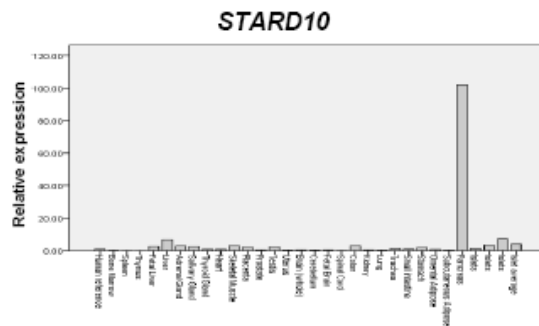
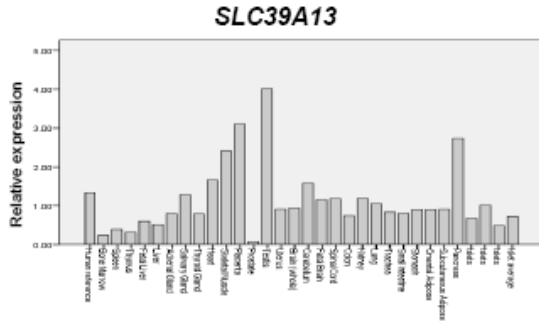
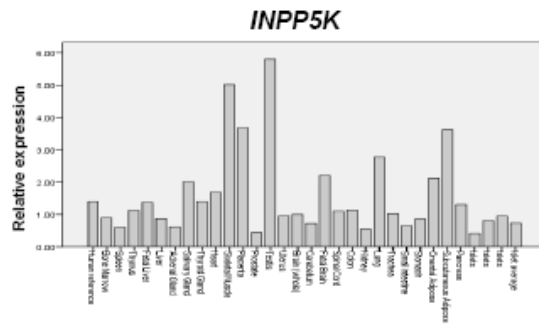
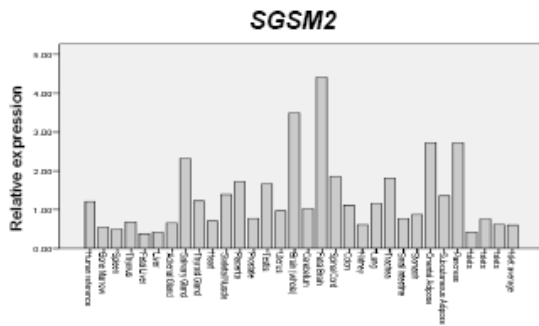
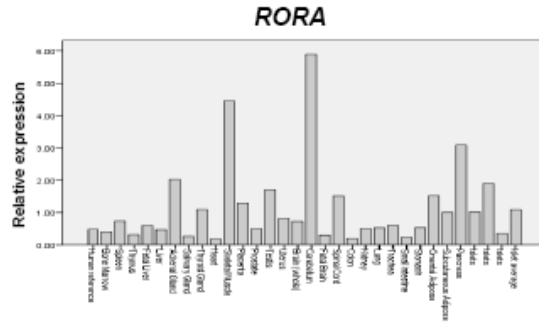
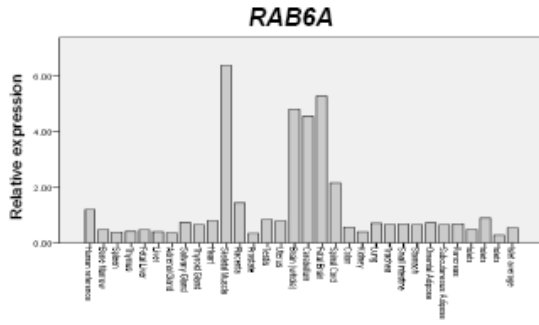
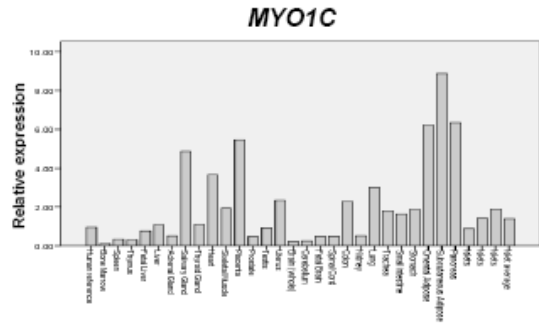
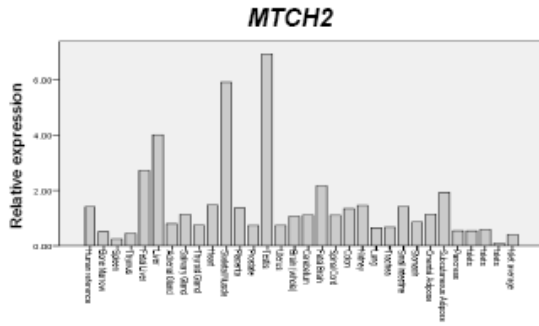
SUPPLEMENTARY DATA

Supplementary Figure 6: Expression profiles of biologically plausible genes within significant association signals across a range of human tissue types, including islet preparations from three donors. Expression levels determined with respect to the geometric mean of three endogenous control assays, and displayed relative to expression level in a sample cDNA pool.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA



BOX: CANDIDATE GENES NEAREST TO LOCI ASSOCIATED WITH PROINSULIN LEVELS

ARAP1 encodes a protein that contains SAM, ARF-GAP, RHO-GAP, ankyrin repeat, RAS-associating, and pleckstrin homology (PH) domains. *In vitro*, this protein displays RHO-GAP and phosphatidylinositol (3,4,5) trisphosphate (PIP3)-dependent ARF-GAP activity. The encoded protein associates with the Golgi apparatus, and the ARF-GAP activity mediates changes in the Golgi and the formation of filopodia. It is thought to regulate the cell-specific trafficking of receptor proteins involved in apoptosis. Multiple transcript variants encoding different isoforms have been found; there is moderate expression in pancreatic exocrine glands, and we have demonstrated expression in FAC-sorted beta cells, where it may influence the maturation of the secretory granule. Also at this locus, **STARD10** encodes a lipid transfer protein for phosphatidylethanolamine and phosphatidylcholine. Ser284 phosphorylation regulates level of lipid transfer activity by preventing membrane association (1). We show strong expression in pancreas, where it could play a role in vesicle fusion or lipid sensitivity. **PDE2A** encodes a cyclic nucleotide phosphodiesterase that regulates the cellular concentrations of the cyclic nucleotides cAMP and cGMP, both of which function as essential second messengers and modulate a large number of cellular pathways, including insulin secretion (2); it is weakly expressed in islets. **RAB6A** is abundantly expressed in exocytotic vesicles targeted to the plasma membrane (3); we have shown it is expressed in FAC-sorted beta cells, where it may influence insulin secretion. **INPPL1** encodes an SH2-containing 5'-inositol phosphatase involved in insulin signalling; we have demonstrated expression in FAC-sorted beta cells. Finally, **ATG16L2** is an autophagy-related gene localized to the cytoplasm and involved in protein transport (4), and **FCHSD2** contains FCH, FBH, two SH3 and C-terminal Proline-rich domains, and is distantly related to formin-binding proteins (5).

MADD encodes mitogen-activated protein kinase (MAPK) activating death domain, an adaptor protein that interacts with the tumor necrosis factor α receptor to activate MAPK and propagate apoptotic signals. MADD was first identified as insulinoma-glucagonoma clone 20 (IG20) through cDNA analysis of insulinoma cells (6). Both PKC and MAPK have been implicated in the proliferation of beta cells induced by GLP-1 (7), suggesting that **MADD** may contribute to beta-cell mass and insulin secretion in this manner as well. Also in this region, **SLC39A13** encodes a putative zinc transporter required for connective tissue development and BMP/TGF- β signaling (8); it is expressed in FAC-sorted beta cells (9), where the zinc transport and T2D-associated gene **SLC30A8** is also thought to exert its effects. Finally, **MTCH2** is ~312 kb upstream of **MADD** and encodes a putative mitochondrial carrier protein potentially involved in cellular apoptosis. This locus has been associated with BMI (10), although the BMI-associated SNP (rs10838738) is in low LD with the proinsulin-associated SNP ($r^2=0.21$ in HapMap CEU).

PCSK1 encodes proprotein convertase subtilisin/kexin type 1 (more commonly known as prohormone convertase 1/3; PC1/3), an enzyme expressed in neuroendocrine cells that mediates the processing of

SUPPLEMENTARY DATA

prohormones into their mature forms. PCSK1 processes hormones influencing glucose/insulin homeostasis such as insulin, glucagon and glucagon-like-peptide 1 (GLP-1), as well as hormones involved in appetite control (11-13). Previous studies have shown associations between SNPs in *PCSK1* and obesity (14; 15), resting energy expenditure (16) and fat oxidation rate (17). Both *PCSK1* SNPs rs6234 and rs6235 encode missense mutations, although neither polymorphism results in a change in enzyme activity, protein maturation or protein secretion. Both SNPs are located in the C-terminus, important for correct targeting and specificity of the enzyme (18).

TCF7L2 encodes the transcription factor 7-like 2, whose intronic SNP rs7903146 harbors the strongest association signal for T2D reported to date (19). It contributes to T2D susceptibility by reducing insulin secretion, perhaps by impairing the beta cell response to incretins (20). The same SNP has been shown to alter an enhancer element which affects transcriptional activity (21).

At the ***VPS13C/C2CD4A/B*** locus, the SNP most significantly associated with proinsulin levels lies in an intergenic region between two genes. ***VPS13C*** encodes vacuolar protein sorting-associated protein, a member of a family of proteins involved in trafficking of membrane proteins between the trans-Golgi network and the pre-vacuolar compartment (22). Expression profiles of *VPS13C* show the presence of transcripts in brain, adipose tissue, liver, pancreas, and most strongly, in sorted beta cells (23). ***C2CD4A*** (also known as *NLF1* or *FAM148A*) belongs to a gene family encoding nuclear factors which are up-regulated in response to inflammatory signals and may regulate other genes which control cellular architecture (24). Expression of *C2CD4A* and ***C2CD4B*** is much higher in pancreas than in other human tissues, and we have demonstrated the presence of both transcripts in FAC-sorted beta cells. A correlated SNP in *C2CD4A/B* has been recently associated with T2D in Japanese (25). Finally, ***RORA*** encodes a retinoic acid receptor-related orphan receptor which is a member of the NR1 subfamily of nuclear hormone receptors. Its target genes include the core mammalian circadian clock component NPAS2 (*BMAL1/clock*) (26); it also regulates the expression and secretion of fibroblast growth factor 21, a hepatic hormone that regulates peripheral glucose tolerance and hepatic lipid metabolism (27).

SLC30A8 encodes ZnT-8, a zinc transporter localized in insulin vesicle membranes that transports zinc from the cytoplasm into insulin secretory granules (28). Insulin is stored as a hexamer bound to two zinc ions, and ZnT-8 provides zinc to allow for insulin storage and secretion (29). It is expressed almost exclusively in pancreatic islets with low levels in the cortex and thyroid (30). Overexpression of *SLC30A8* in insulinoma cells increases glucose-stimulated insulin secretion (31). The *SLC30A8* non-synonymous SNP rs13266634 (in near-perfect LD with the SNP reported here, $r^2 = 0.957$ in HapMap CEU) results in a non-synonymous R325W substitution. It was identified as a T2D association signal by the first GWAS in this disease (32) and has been replicated by subsequent studies (33-35); it has been shown to impair insulin secretion (36; 37).

LARP6 encodes La ribonucleoprotein domain family, member 6, a protein first described to be involved in programmed cell death of intersegmental muscles of the moth *Manduca sexta* (38). More recently LARP6 has been shown to bind to the conserved 5' stem-loop of collagen mRNAs thereby regulating translation of mRNAs encoding type I collagen (39). Also in this region, ***UACA*** encodes autoantigen with

SUPPLEMENTARY DATA

coiled-coil domains and ankyrin repeats, a protein which appears to be involved in stress-induced apoptosis (40). Mice rendered null for this protein develop hepatitis, hepatocellular carcinoma and hypercholesterolemia (41). **THAP10** (THAP domain containing 10) and **LRRC49** (leucine rich repeat containing 49) are two genes that encode proteins of little known function that are downregulated and hypermethylated in breast cancer (42). Here we have shown that **CT62** is only expressed in human testis, and is therefore an unlikely biological candidate. Finally, **THSD4** encodes thrombospondin, type I, domain containing 4, a protein with homology with members of the thrombospondin family of extracellular calcium-binding proteins that modulate cellular attachment, proliferation and migration. Proteins in this family have been implicated in wound healing, inflammation and angiogenesis. SNPs at this locus (~536 kb away from our index SNP) have been associated with lung function (43).

SGSM2 encodes the small G protein signaling modulator 2, which interacts with RAB4 and RAB11 in sorting and recycling of vacuoles between early endosome and the plasma membrane (44). GLUT4 and the glucagon receptor illustrate proteins that are recycled through RAB4 and RAB11 positive vesicles (45-48). Also in this region, **YWHAE** encodes the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide. This protein belongs to the 14-3-3 family of proteins, which mediate signal transduction by binding to phosphoserine-containing proteins. It interacts with CDC25 phosphatases, RAF1 and IRS1, suggesting a role in diverse biochemical activities related to signal transduction, such as cell division and regulation of insulin sensitivity (49; 50). **INPP5K** (skeletal muscle- and kidney-enriched inositol phosphatase) hydrolyzes the D5 position of inositol phosphates and corresponding phospholipids. It thus negatively regulates insulin signaling by inhibiting phosphorylation of downstream targets such as Akt and p70 S6 kinase. Knockdown of endogenous **SKIP** expression increases insulin-induced GLUT4 translocation, membrane ruffle formation and glycogen synthesis in rat myocytes (51). **MYO1C** (myosin 1 C) belongs to the unconventional myosins. Myosins are molecular motors that utilize energy from ATP hydrolysis to generate mechanical force. **MYO1C** is highly expressed in adipocytes where it functions in an insulin signaling pathway that controls the movement of GLUT4-containing vesicles to the plasma membrane (52). Finally, **RAP1GAP2** (RAP1 GTPase activating protein 2) encodes a GTPase-activating protein that activates the small guanine-nucleotide-binding protein Rap1 in platelets (53). The protein also interacts with synaptotagmin-like protein 1 and Rab27 and regulates secretion of dense granules from platelets at sites of endothelial damage (54). In the pancreas Rap1 is essential in regulation of insulin granule dynamics by cAMP (55).

SUPPLEMENTARY DATA

Box references:

1. Olayioye MA, Buchholz M, Schmid S, Schoffler P, Hoffmann P, Pomorski T: Phosphorylation of StarD10 on serine 284 by casein kinase II modulates its lipid transfer activity. *J Biol Chem* 282:22492-22498, 2007
2. Heikaus CC, Pandit J, Kleivit RE: Cyclic nucleotide binding GAF domains from phosphodiesterases: structural and mechanistic insights. *Structure* 17:1551-1557, 2009
3. Grigoriev I, Splinter D, Keijzer N, Wulf PS, Demmers J, Ohtsuka T, Modesti M, Maly IV, Grosveld F, Hoogenraad CC, Akhmanova A: Rab6 regulates transport and targeting of exocytotic carriers. *Dev Cell* 13:305-314, 2007
4. Dunwell T, Hesson L, Rauch TA, Wang L, Clark RE, Dallol A, Gentle D, Catchpoole D, Maher ER, Pfeifer GP, Latif F: A genome-wide screen identifies frequently methylated genes in haematological and epithelial cancers. *Mol Cancer* 9:44, 2010
5. Katoh M: Identification and characterization of human FCHSD1 and FCHSD2 genes in silico. *Int J Mol Med* 13:749-754, 2004
6. Goto Y, De Silva MG, Toscani A, Prabhakar BS, Notkins AL, Lan MS: A novel human insulinoma-associated cDNA, IA-1, encodes a protein with "zinc-finger" DNA-binding motifs. *J Biol Chem* 267:15252-15257, 1992
7. Drucker DJ: The role of gut hormones in glucose homeostasis. *J Clin Invest* 117:24-32, 2007
8. Fukada T, Civic N, Furuichi T, Shimoda S, Mishima K, Higashiyama H, Idaira Y, Asada Y, Kitamura H, Yamasaki S, Hojyo S, Nakayama M, Ohara O, Koseki H, Dos Santos HG, Bonafe L, Ha-Vinh R, Zankl A, Unger S, Kraenzlin ME, Beckmann JS, Saito I, Rivolta C, Ikegawa S, Superti-Furga A, Hirano T: The zinc transporter SLC39A13/ZIP13 is required for connective tissue development; its involvement in BMP/TGF-beta signaling pathways. *PLoS ONE* 3:e3642, 2008
9. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccascaccia RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllenstein U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR,

SUPPLEMENTARY DATA

Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, LeCoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurdsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tanaka T, Thorand B, Tichet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP, Wichmann HE, Illig T, Rudan I, Wright AF, Stumvoll M, Campbell H, Wilson JF, Bergman RN, Buchanan TA, Collins FS, Mohlke KL, Tuomilehto J, Valle TT, Altshuler D, Rotter JI, Siscovick DS, Penninx BW, Boomsma DI, Deloukas P, Spector TD, Frayling TM, Ferrucci L, Kong A, Thorsteinsdottir U, Stefansson K, van Duijn CM, Aulchenko YS, Cao A, Scuteri A, Schlessinger D, Uda M, Ruukonen A, Jarvelin MR, Waterworth DM, Vollenweider P, Peltonen L, Mooser V, Abecasis GR, Wareham NJ, Sladek R, Froguel P, Watanabe RM, Meigs JB, Groop L, Boehnke M, McCarthy MI, Florez JC, Barroso I: New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 42:105-116, 2010

10. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccascella RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P, Kuokkanen M, Kuusisto J, Laitinen J, Lakatta EG, Luan J, Luben RN, Mangino M, McArdle WL, Meitinger T, Mulas A, Munroe PB, Narisu N, Ness AR, Northstone K, O'Rahilly S, Purmann C, Rees MG, Ridderstrale M, Ring SM, Rivadeneira F, Ruukonen A, Sandhu MS, Saramies J, Scott LJ, Scuteri A, Silander K, Sims MA, Song K, Stephens J, Stevens S, Stringham HM, Tung YC, Valle TT, Van Duijn CM, Vimalaswaran KS, Vollenweider P, Waeber G, Wallace C, Watanabe RM, Waterworth DM, Watkins N, Witteman JC, Zeggini E, Zhai G, Zillikens MC, Altshuler D, Caulfield MJ, Chanock SJ, Farooqi IS, Ferrucci L, Guralnik JM, Hattersley AT, Hu FB, Jarvelin MR, Laakso M, Mooser V, Ong KK, Ouwehand WH, Salomaa V, Samani NJ, Spector TD, Tuomi T, Tuomilehto J, Uda M, Uitterlinden AG, Wareham NJ,

SUPPLEMENTARY DATA

- Deloukas P, Frayling TM, Groop LC, Hayes RB, Hunter DJ, Mohlke KL, Peltonen L, Schlessinger D, Strachan DP, Wichmann HE, McCarthy MI, Boehnke M, Barroso I, Abecasis GR, Hirschhorn JN: Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 41:25-34, 2009
11. Seidah NG, Benjannet S, Hamelin J, Mamarbachi AM, Basak A, Marcinkiewicz J, Mbikay M, Chretien M, Marcinkiewicz M: The subtilisin/kexin family of precursor convertases. Emphasis on PC1, PC2/7B2, POMC and the novel enzyme SKI-1. *Ann N Y Acad Sci* 885:57-74, 1999
12. Goodge KA, Hutton JC: Translational regulation of proinsulin biosynthesis and proinsulin conversion in the pancreatic beta-cell. *Semin Cell Dev Biol* 11:235-242, 2000
13. Pritchard LE, Turnbull AV, White A: Pro-opiomelanocortin processing in the hypothalamus: impact on melanocortin signalling and obesity. *J Endocrinol* 172:411-421, 2002
14. Benzinou M, Creemers JW, Choquet H, Lobbens S, Dina C, Durand E, Guerardel A, Boutin P, Jouret B, Heude B, Balkau B, Tichet J, Marre M, Potoczna N, Horber F, Le Stunff C, Czernichow S, Sandbaek A, Lauritzen T, Borch-Johnsen K, Andersen G, Kiess W, Korner A, Kovacs P, Jacobson P, Carlsson LM, Walley AJ, Jorgensen T, Hansen T, Pedersen O, Meyre D, Froguel P: Common nonsynonymous variants in *PCSK1* confer risk of obesity. *Nat Genet* 40:943-945, 2008
15. Chang YC, Chiu YF, Shih KC, Lin MW, Sheu WH, Donlon T, Curb JD, Jou YS, Chang TJ, Li HY, Chuang LM: Common *PCSK1* haplotypes are associated with obesity in the Chinese population. *Obesity (Silver Spring)* 18:1404-1409, 2010
16. Goossens GH, Petersen L, Blaak EE, Hul G, Arner P, Astrup A, Froguel P, Patel K, Pedersen O, Polak J, Oppert JM, Martinez JA, Sorensen TI, Saris WH: Several obesity- and nutrient-related gene polymorphisms but not *FTO* and *UCP* variants modulate postabsorptive resting energy expenditure and fat-induced thermogenesis in obese individuals: the NUGENOB study. *Int J Obes (Lond)* 33:669-679, 2009
17. Corpeleijn E, Petersen L, Holst C, Saris WH, Astrup A, Langin D, MacDonald I, Martinez JA, Oppert JM, Polak J, Pedersen O, Froguel P, Arner P, Sorensen TI, Blaak EE: Obesity-related polymorphisms and their associations with the ability to regulate fat oxidation in obese Europeans: the NUGENOB study. *Obesity (Silver Spring)* 18:1369-1377, 2010
18. Bernard N, Kitabgi P, Rovere-Jovene C: The Arg617-Arg618 cleavage site in the C-terminal domain of PC1 plays a major role in the processing and targeting of the enzyme within the regulated secretory pathway. *J Neurochem* 85:1592-1603, 2003
19. Florez JC: The new type 2 diabetes gene *TCF7L2*. *Curr Opin Clin Nutr Metab Care* 10:391-396, 2007
20. Pearson ER: Translating *TCF7L2*: from gene to function. *Diabetologia* 52:1227-1230, 2009
21. Gaulton KJ, Nammo T, Pasquali L, Simon JM, Giresi PG, Fogarty MP, Panhuis TM, Mieczkowski P, Secchi A, Bosco D, Berney T, Montanya E, Mohlke KL, Lieb JD, Ferrer J: A map of open chromatin in human pancreatic islets. *Nat Genet* 42:255-259, 2010

SUPPLEMENTARY DATA

22. Velayos-Baeza A, Vettori A, Copley RR, Dobson-Stone C, Monaco AP: Analysis of the human VPS13 gene family. *Genomics* 84:536-549, 2004
23. Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P, Lyssenko V, Bouatia-Naji N, Dupuis J, Jackson AU, Kao WH, Li M, Glazer NL, Manning AK, Luan J, Stringham HM, Prokopenko I, Johnson T, Grarup N, Boesgaard TW, Lecoeur C, Shneider P, O'Connell J, Ingelsson E, Couper DJ, Rice K, Song K, Andreasen CH, Dina C, Kottgen A, Le Bacquer O, Pattou F, Taneera J, Steinthorsdottir V, Rybin D, Ardlie K, Sampson M, Qi L, van Hoek M, Weedon MN, Aulchenko YS, Voight BF, Grallert H, Balkau B, Bergman RN, Bielinski SJ, Bonnetfond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E, Buchanan TA, Bumpstead SJ, Cavalcanti-Proenca C, Charpentier G, Chen YD, Chines PS, Collins FS, Cornelis M, G JC, Delplanque J, Doney A, Egan JM, Erdos MR, Firmann M, Forouhi NG, Fox CS, Goodarzi MO, Graessler J, Hingorani A, Isomaa B, Jorgensen T, Kivimaki M, Kovacs P, Krohn K, Kumari M, Lauritzen T, Levy-Marchal C, Mayor V, McAteer JB, Meyre D, Mitchell BD, Mohlke KL, Morken MA, Narisu N, Palmer CN, Pakyz R, Pascoe L, Payne F, Pearson D, Rathmann W, Sandbaek A, Sayer AA, Scott LJ, Sharp SJ, Sijbrands E, Singleton A, Siscovick DS, Smith NL, Sparso T, Swift AJ, Syddall H, Thorleifsson G, Tonjes A, Tuomi T, Tuomilehto J, Valle TT, Waeber G, Walley A, Waterworth DM, Zeggini E, Zhao JH, Illig T, Wichmann HE, Wilson JF, van Duijn C, Hu FB, Morris AD, Frayling TM, Hattersley AT, Thorsteinsdottir U, Stefansson K, Nilsson P, Syvanen AC, Shuldiner AR, Walker M, Bornstein SR, Schwarz P, Williams GH, Nathan DM, Kuusisto J, Laakso M, Cooper C, Marmot M, Ferrucci L, Mooser V, Stumvoll M, Loos RJ, Altshuler D, Psaty BM, Rotter JI, Boerwinkle E, Hansen T, Pedersen O, Florez JC, McCarthy MI, Boehnke M, Barroso I, Sladek R, Froguel P, Meigs JB, Groop L, Wareham NJ, Watanabe RM: Genetic variation in *GIPR* influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet* 42:142-148, 2010
24. Warton K, Foster NC, Gold WA, Stanley KK: A novel gene family induced by acute inflammation in endothelial cells. *Gene* 342:85-95, 2004
25. Yamauchi T, Hara K, Maeda S, Yasuda K, Takahashi A, Horikoshi M, Nakamura M, Fujita H, Grarup N, Cauchi S, Ng DP, Ma RC, Tsunoda T, Kubo M, Watada H, Maegawa H, Okada-Iwabu M, Iwabu M, Shojima N, Shin HD, Andersen G, Witte DR, Jorgensen T, Lauritzen T, Sandbaek A, Hansen T, Ohshige T, Omori S, Saito I, Kaku K, Hirose H, So WY, Beury D, Chan JC, Park KS, Tai ES, Ito C, Tanaka Y, Kashiwagi A, Kawamori R, Kasuga M, Froguel P, Pedersen O, Kamatani N, Nakamura Y, Kadowaki T: A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at *UBE2E2* and *C2CD4A-C2CD4B*. *Nat Genet* 42:864-868, 2010
26. Crumbley C, Wang Y, Kojetin DJ, Burriss TP: Characterization of the core mammalian clock component, NPAS2, as a REV-ERBalpha/RORalpha target gene. *J Biol Chem* 285:35386-35392, 2010
27. Wang Y, Solt LA, Burriss TP: Regulation of FGF21 expression and secretion by retinoic acid receptor-related orphan receptor alpha. *J Biol Chem* 285:15668-15673, 2010
28. Chimienti F, Devergnas S, Favier A, Seve M: Identification and cloning of a b-cell-specific Zinc transporter, ZnT-8, localized into insulin secretory granules. *Diabetes* 53:2330-2337, 2004

SUPPLEMENTARY DATA

29. Chimienti F, Favier A, Seve M: ZnT-8, a pancreatic beta-cell-specific zinc transporter. *Biometals* 18:313-317, 2005
30. Murgia C, Devirgiliis C, Mancini E, Donadel G, Zalewski P, Perozzi G: Diabetes-linked zinc transporter ZnT8 is a homodimeric protein expressed by distinct rodent endocrine cell types in the pancreas and other glands. *Nutr Metab Cardiovasc Dis* 19:431-439, 2009
31. Chimienti F, Devergnas S, Pattou F, Schuit F, Garcia-Cuenca R, Vandewalle B, Kerr-Conte J, Van Lommel L, Grunwald D, Favier A, Seve M: In vivo expression and functional characterization of the zinc transporter ZnT8 in glucose-induced insulin secretion. *J Cell Sci* 119:4199-4206, 2006
32. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P: A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445:828-830, 2007
33. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University and Novartis Institutes for BioMedical Research: Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 316:1331-1336, 2007
34. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding C-J, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li X-Y, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M: A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316:1341-1345, 2007
35. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JRB, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney ASF, The Wellcome Trust Case Control C, McCarthy MI, Hattersley AT: Replication of genome-wide association signals in U.K. samples reveals risk loci for type 2 diabetes. *Science* 316:1336-1341, 2007
36. Boesgaard T, Žilinskaitė J, Vanttinen M, Laakso M, Jansson PA, Hammarstedt A, Smith U, Stefan N, Fritsche A, Häring H, Hribal M, Sesti G, Zobel D, Pedersen O, Hansen T, for the EC: The common *SLC30A8* Arg325Trp variant is associated with reduced first-phase insulin release in 846 non-diabetic offspring of type 2 diabetes patients—the EUGENE2 study. *Diabetologia* 51:816-820, 2008
37. Ingelsson E, Langenberg C, Hivert MF, Prokopenko I, Lyssenko V, Dupuis J, Magi R, Sharp S, Jackson AU, Assimes TL, Shrader P, Knowles JW, Zethelius B, Abbasi FA, Bergman RN, Bergmann A, Berne C, Boehnke M, Bonnycastle LL, Bornstein SR, Buchanan TA, Bumpstead SJ, Bottcher Y, Chines P, Collins FS, Cooper CC, Dennison EM, Erdos MR, Ferrannini E, Fox CS, Graessler J, Hao K, Isomaa B, Jameson KA, Kovacs P, Kuusisto J, Laakso M, Ladenvall C, Mohlke KL, Morcken MA, Narisu N, Nathan DM, Pascoe L, Payne F, Petrie JR, Sayer AA, Schwarz PE, Scott LJ, Stringham HM, Stumvoll M, Swift AJ, Syvanen AC, Tuomi T, Tuomilehto J, Tonjes A, Valle TT, Williams GH, Lind L, Barroso I, Quertermous T, Walker M,

SUPPLEMENTARY DATA

Wareham NJ, Meigs JB, McCarthy MI, Groop L, Watanabe RM, Florez JC: Detailed physiologic characterization reveals diverse mechanisms for novel genetic Loci regulating glucose and insulin metabolism in humans. *Diabetes* 59:1266-1275, 2010

38. Valavanis C, Wang Z, Sun D, Vaine M, Schwartz LM: Acheron, a novel member of the Lupus Antigen family, is induced during the programmed cell death of skeletal muscles in the moth *Manduca sexta*. *Gene* 393:101-109, 2007

39. Cai L, Fritz D, Stefanovic L, Stefanovic B: Binding of LARP6 to the conserved 5' stem-loop regulates translation of mRNAs encoding type I collagen. *J Mol Biol* 395:309-326, 2010

40. Sakai T, Liu L, Teng X, Mukai-Sakai R, Shimada H, Kaji R, Mitani T, Matsumoto M, Toida K, Ishimura K, Shishido Y, Mak TW, Fukui K: Nucling recruits Apaf-1/pro-caspase-9 complex for the induction of stress-induced apoptosis. *J Biol Chem* 279:41131-41140, 2004

41. Sakai T, Liu L, Teng X, Ishimaru N, Mukai-Sakai R, Tran NH, Kim SM, Sano N, Hayashi Y, Kaji R, Fukui K: Inflammatory disease and cancer with a decrease in Kupffer cell numbers in Nucling-knockout mice. *Int J Cancer* 126:1079-1094, 2010

42. De Souza Santos E, De Bessa SA, Netto MM, Nagai MA: Silencing of *LRRC49* and *THAP10* genes by bidirectional promoter hypermethylation is a frequent event in breast cancer. *Int J Oncol* 33:25-31, 2008

43. Repapi E, Sayers I, Wain LV, Burton PR, Johnson T, Obeidat M, Zhao JH, Ramasamy A, Zhai G, Vitart V, Huffman JE, Igl W, Albrecht E, Deloukas P, Henderson J, Granell R, McArdle WL, Rudnicka AR, Barroso I, Loos RJ, Wareham NJ, Mustelin L, Rantanen T, Surakka I, Imboden M, Wichmann HE, Grkovic I, Jankovic S, Zgaga L, Hartikainen AL, Peltonen L, Gyllensten U, Johansson A, Zaboli G, Campbell H, Wild SH, Wilson JF, Glaser S, Homuth G, Volzke H, Mangino M, Soranzo N, Spector TD, Polasek O, Rudan I, Wright AF, Heliövaara M, Ripatti S, Pouta A, Naluai AT, Olin AC, Toren K, Cooper MN, James AL, Palmer LJ, Hingorani AD, Wannamethee SG, Whincup PH, Smith GD, Ebrahim S, McKeever TM, Pavord ID, MacLeod AK, Morris AD, Porteous DJ, Cooper C, Dennison E, Shaheen S, Karrasch S, Schnabel E, Schulz H, Grallert H, Bouatia-Naji N, Delplanque J, Froguel P, Blakey JD, Britton JR, Morris RW, Holloway JW, Lawlor DA, Hui J, Nyberg F, Jarvelin MR, Jackson C, Kahonen M, Kaprio J, Probst-Hensch NM, Koch B, Hayward C, Evans DM, Elliott P, Strachan DP, Hall IP, Tobin MD: Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 42:36-44, 2010

44. Yang H, Sasaki T, Minoshima S, Shimizu N: Identification of three novel proteins (SGSM1, 2, 3) which modulate small G protein (RAP and RAB)-mediated signaling pathway. *Genomics* 90:249-260, 2007

45. Cormont M, Bortoluzzi MN, Gautier N, Mari M, van Obberghen E, Le Marchand-Brustel Y: Potential role of Rab4 in the regulation of subcellular localization of Glut4 in adipocytes. *Mol Cell Biol* 16:6879-6886, 1996

SUPPLEMENTARY DATA

46. Vollenweider P, Martin SS, Haruta T, Morris AJ, Nelson JG, Cormont M, Le Marchand-Brustel Y, Rose DW, Olefsky JM: The small guanosine triphosphate-binding protein Rab4 is involved in insulin-induced GLUT4 translocation and actin filament rearrangement in 3T3-L1 cells. *Endocrinology* 138:4941-4949, 1997
47. Kessler A, Tomas E, Immler D, Meyer HE, Zorzano A, Eckel J: Rab11 is associated with GLUT4-containing vesicles and redistributes in response to insulin. *Diabetologia* 43:1518-1527, 2000
48. Krilov L, Nguyen A, Miyazaki T, Unson CG, Bouscarel B: Glucagon receptor recycling: role of carboxyl terminus, beta-arrestins, and cytoskeleton. *Am J Physiol Cell Physiol* 295:C1230-1237, 2008
49. Ogihara T, Isobe T, Ichimura T, Taoka M, Funaki M, Sakoda H, Onishi Y, Inukai K, Anai M, Fukushima Y, Kikuchi M, Yazaki Y, Oka Y, Asano T: 14-3-3 protein binds to insulin receptor substrate-1, one of the binding sites of which is in the phosphotyrosine binding domain. *J Biol Chem* 272:25267-25274, 1997
50. Conklin DS, Galaktionov K, Beach D: 14-3-3 proteins associate with cdc25 phosphatases. *Proc Natl Acad Sci U S A* 92:7892-7896, 1995
51. Ijuin T, Takenawa T: SKIP negatively regulates insulin-induced GLUT4 translocation and membrane ruffle formation. *Mol Cell Biol* 23:1209-1220, 2003
52. Bose A, Guilherme A, Robida SI, Nicoloso SM, Zhou QL, Jiang ZY, Pomerleau DP, Czech MP: Glucose transporter recycling in response to insulin is facilitated by myosin Myo1c. *Nature* 420:821-824, 2002
53. Schultess J, Danielewski O, Smolenski AP: Rap1GAP2 is a new GTPase-activating protein of Rap1 expressed in human platelets. *Blood* 105:3185-3192, 2005
54. Neumuller O, Hoffmeister M, Babica J, Prella C, Gegenbauer K, Smolenski AP: Synaptotagmin-like protein 1 interacts with the GTPase-activating protein Rap1GAP2 and regulates dense granule secretion in platelets. *Blood* 114:1396-1404, 2009
55. Shibasaki T, Takahashi H, Miki T, Sunaga Y, Matsumura K, Yamanaka M, Zhang C, Tamamoto A, Satoh T, Miyazaki J, Seino S: Essential role of Epac2/Rap1 signaling in regulation of insulin granule dynamics by cAMP. *Proc Natl Acad Sci U S A* 104:19333-19338, 2007