

Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes

Supplementary Note

Andrew P Morris, Benjamin F Voight, Tanya M Teslovich, Teresa Ferreira, Ayellet V Segrè, Valgerdur Steinthorsdottir, Rona J Strawbridge, Hassan Khan, Harald Grallert, Anubha Mahajan, Inga Prokopenko, Hyun Min Kang, Christian Dina, Tonu Esko, Ross M Fraser, Stavroula Kanoni, Ashish Kumar, Vasiliki Lagou, Claudia Langenberg, Jian'an Luan, Cecilia M Lindgren, Martina Müller-Nurasyid, Sonali Pechlivanis, N William Rayner, Laura J Scott, Steven Wiltshire, Loic Yengo, Leena Kinnunen, Elizabeth J Rossin, Soumya Raychaudhuri, Andrew D Johnson, Antigone S Dimas, Ruth JF Loos, Sailaja Vedantam, Han Chen, Jose C Florez, Caroline Fox, Ching-Ti Liu, Denis Rybin, David J Couper, Wen Hong L Kao, Man Li, Marilyn C Cornelis, Peter Kraft, Qi Sun, Rob M van Dam, Heather M Stringham, Peter S Chines, Krista Fischer, Pierre Fontanillas, Oddgeir L Holmen, Sarah E Hunt, Anne U Jackson, Augustine Kong, Robert Lawrence, Julia Meyer, John RB Perry, Carl GP Platou, Simon Potter, Emil Rehnberg, Neil Robertson, Suthesh Sivapalaratnam, Alena Stančáková, Kathleen Stirrups, Gudmar Thorleifsson, Emmi Tikkanen, Andrew R Wood, Peter Almgren, Mustafa Atalay, Rafn Benediktsson, Lori L Bonnycastle, Noël Burtt, Jason Carey, Guillaume Charpentier, Andrew T Crenshaw, Alex SF Doney, Mozghan Dorkhan, Sarah Edkins, Valur Emilsson, Elodie Eury, Tom Forsen, Karl Gertow, Bruna Gigante, George B Grant, Christopher J Groves, Candace Guiducci, Christian Herder, Astradur B Hreidarsson, Jennie Hui, Alan James, Anna Jonsson, Wolfgang Rathmann, Norman Klopp, Jasmina Kravic, Karel Krjutškov, Cordelia Langford, Karin Leander, Eero Lindholm, Stéphane Lobbens, Satu Männistö, Ghazala Mirza, Thomas W Mühleisen, Bill Musk, Melissa Parkin, Loukianos Rallidis, Jouko Saramies, Bengt Sennblad, Sonia Shah, Gunnar Sigurðsson, Angela Silveira, Gerald Steinbach, Barbara Thorand, Joseph Trakalo, Fabrizio Veglia, Roman Wennauer, Wendy Winckler, Delilah Zabaneh, Harry Campbell, Cornelia van Duijn, Andre G Uitterlinden, Albert Hofman, Eric Sijbrands, Goncalo R Abecasis, Katharine R Owen, Eleftheria Zeggini, Mieke D Trip, Nita G Forouhi, Ann-Christine Syvänen, Johan G Eriksson, Leena Peltonen, Markus M Nöthen, Beverley Balkau, Colin NA Palmer, Valeriya Lyssenko, Tiinamaija Tuomi, Bo Isomaa, David J Hunter, Lu Qi, Wellcome Trust Case Control Consortium, MAGIC Investigators, GIANT Consortium, AGEN-T2D Consortium, SAT2D Consortium, Alan R Shuldiner, Michael Roden, Ines Barroso, Tom Wilsgaard, John Beilby, Kees Hovingh, Jackie F Price, James F Wilson, Rainer Rauramaa, Timo A Lakka, Lars Lind, George Dedoussis, Inger Njølstad, Nancy L Pedersen, Kay-Tee Khaw, Nicholas J Wareham, Sirkka M Keinänen-Kiukaanniemi, Timo E Saaristo, Eeva Korpi-Hyövähti, Juha Saltevo, Markku Laakso, Johanna Kuusisto, Andres Metspalu, Francis S Collins, Karen L Mohlke, Richard N Bergman, Jaakko Tuomilehto, Bernhard O Boehm, Christian Gieger, Kristian Hveem, Stephane Cauchi, Philippe Froguel, Damiano Baldassarre, Elena Tremoli, Steve E Humphries, Danish Saleheen, John Danesh, Erik Ingelsson, Samuli Ripatti, Veikko Salomaa, Raimund Erbel, Karl-Heinz Jöckel, Susanne Moebus, Annette Peters, Thomas Illig, Ulf de Faire, Anders Hamsten, Andrew D Morris, Peter J Donnelly, Timothy M Frayling, Andrew T Hattersley, Eric Boerwinkle, Olle Melander, Sekar Kathiresan, Peter M Nilsson, Panos Deloukas, Unnur Thorsteinsdottir, Leif C Groop, Kari Stefansson, Frank Hu, James S Pankow, Josée Dupuis, James B Meigs, David Altshuler, Michael Boehnke, and Mark I McCarthy for the DIAGRAM Consortium.

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Resources interrogated for expression analyses

We identified proxies ($CEU r^2 > 0.8$) for each lead T2D SNP in novel susceptibility loci (also including *GRB14* and *HMG20A*). We interrogated public databases and unpublished resources for *cis*-eQTL expression with these SNPs in multiple tissues: fresh lymphocytes¹; fresh leukocytes²; leukocytes from individuals with Celiac disease³; lymphoblastoid cell lines (LCL) derived from asthmatic children⁴; LCL from HapMap^{5,6}; peripheral blood monocytes^{7,8}; omental and subcutaneous fat^{9,10}; endometrial carcinomas¹¹; brain cortex^{7,12}; three studies of brain regions including prefrontal cortex, visual cortex and cerebellum (Emilsson, personal communication); liver¹³⁻¹⁵; osteoblasts¹⁶; skin¹⁷; and additional fibroblast, T cell and LCL samples¹⁸.

Biological hypotheses related to disease pathogenesis tested with GSEA

Adipocytokine signalling. Adipocytokines have been implicated in the development of insulin resistance. Leptin and adiponectin are potential insulin sensitizers and TNF-alpha is a potential insulin antagonist¹⁹.

Amyloid metabolism. The islet amyloid polypeptide inhibits insulin and glucagon secretion from pancreatic beta-islet cells. Islet amyloid deposits have been associated with T2D and pancreatic beta-cell loss^{20,21}.

Branched-chain amino acid metabolism. Elevated branched-chain amino acid plasma levels are associated with high insulin resistance and/or low circulating levels of insulin in T2D cases. The branched-chain amino acids, isoleucine, leucine and valine, are strong predictors of future diabetes. Leucine acutely stimulates insulin secretion in pancreatic beta cells²²⁻²⁴.

Cell cycle. Several cell cycle regulators lie in previously established T2D loci, including *CDKN2B/A*, *CDKN1C*, and *CCNE2*. The majority of these genes regulate CDK4 or CDK6, shown to play a role in beta-islet pancreatic cell proliferation, which in turn may affect insulin secretion. These regulators may also have an effect on peripheral tissues relevant to T2D²⁵⁻²⁷.

Circadian rhythm. Several studies showed that people with an altered circadian rhythm have an increased risk of developing T2D. *MTNR1B* regulates circadian rhythm and contains common variants associated with T2D, fasting glucose, and pancreatic beta-cell function, suggesting a causal role for circadian rhythm in T2D. The melatonin system was shown to regulate glucose homeostasis²⁸⁻³².

Endoplasmic reticulum (ER) stress response (unfolded protein response). *WFS1*, a component of the unfolded protein response, lies near common variants associated with T2D and harbours rare mutations associated with Wolfram syndrome, a rare syndrome that causes diabetes mellitus, amongst other disorders. *WFS1* is up-regulated during insulin secretion. Inactivation of *WFS1* in beta-cells causes ER stress and dysfunction. Furthermore, *EIF2AK3*, a key component of the ER stress response pathway, contains rare mutations that cause neonatal diabetes³³⁻³⁵.

Fatty acid metabolism. Elevated plasma free fatty acid (FFA) concentrations are linked with the onset of skeletal muscle and hepatic insulin resistance and are associated with T2D. Elevated blood fatty-acid concentrations reduce muscle glucose uptake, and increase liver glucose production, contributing to elevated blood glucose levels. FFA also affects insulin secretion from the pancreas. However, in pre-diabetic patients, FFA stimulation of insulin secretion is not sufficient to fully compensate for the FFA-induced insulin resistance, leading to hyperglycaemia^{36,37}.

Glycolysis and gluconeogenesis. Glucokinase, *GCK*, the first glycolytic enzyme, and *GCKR*, a regulator of *GCK*, contain or lie near common SNPs associated with T2D. Studies have shown that hepatic gluconeogenesis is increased in people with T2D compared with controls following overnight fasting^{38,39}.

Inflammation. Elevated levels of the inflammatory cytokines, TNF-alpha and IL-6, and the C-reactive protein that rises in response to inflammation, predict the development of T2D. However, whether inflammation is a primary cause of T2D or secondary to hyperglycaemia (or other T2D features) is not yet clear. A potential mechanism of causality is through macrophages that release cytokines, causing neighbouring liver, muscle or fat cells to become insulin resistant. Inflammation in pancreatic islets could also lead to a decrease in beta-cell mass affecting insulin secretion levels⁴⁰⁻⁴³.

Insulin signalling. Alterations in insulin signalling may lead to insulin resistance in peripheral tissues such as fat, liver and muscle, a major risk factor for T2D^{27,44}.

Insulin synthesis and secretion. Insufficient insulin secretion is one of the major causes of T2D. Many of the established T2D common SNP associations lie near genes implicated in beta-cell function, such as *KCNJ11* and *ABCC8*. These ATP sensitive potassium channel subunits, proximal to each other on the chromosome, are targets of anti-diabetes drugs (sulfonylurea and/or meglitinides) that lead to an increase in insulin secretion. Mutations in these genes are also associated with different forms of neonatal diabetes^{27,44}.

Mitochondrial dysfunction. Mitochondrial dysfunction has been implicated in both rare and common forms of diabetes. T2D cases have less mitochondria in their skeletal muscle, and oxidative phosphorylation genes are collectively down-regulated in muscle, compared with healthy individuals. However, pronounced genetic evidence for a causal effect of decreased mitochondrial activity on T2D has not yet been shown⁴⁵⁻⁴⁷.

NOTCH signalling. *NOTCH2* contains a common variant associated with T2D. NOTCH signalling plays a role in pancreas development^{35,48}.

PPARG signalling. *PPARG* contains a common variant associated with T2D, and is the target of thiazolidinedione (TZD) drugs, used clinically to reduce insulin resistance in T2D patients. *PPARG* plays a role in fat, liver and muscle^{49,50}.

Vitamin D metabolism. Vitamin D deficiency has been suggested to be associated with T2D and insulin resistance. Vitamin D may also play a role in insulin secretion by promoting calcium absorption in the pancreas⁵¹⁻⁵³.

WNT signalling. A strong common variant association signal lies in an intron of *TCF7L2*, a transcription factor that regulates WNT targets. The WNT signalling pathway may play a role in both the insulin secretion and insulin sensitivity features of T2D. For example, WNT signalling activation in the pancreas leads to pancreatic beta cell proliferation, and improved insulin sensitivity in skeletal muscle⁵⁴⁻⁵⁷.

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Membership of MAGIC

Robert A Scott¹, Vasiliki Lagou^{2,3}, Ryan P Welch⁴⁻⁶, Eleanor Wheeler⁷, May E Montasser⁸, Jian'an Luan¹, Reedik Mägi^{2,9}, Rona J Strawbridge^{10,11}, Emil Rehnberg¹², Stefan Gustafsson¹², Stavroula Kanoni⁷, Laura J Rasmussen-Torvik¹³, Loïc Yengo^{14,15}, Cecile Lecoeur^{14,15}, Dmitry Shungin¹⁶⁻¹⁸, Serena Sanna¹⁹, Carlo Sidore^{5,6,19,20}, Paul C D Johnson²¹, J Wouter Jukema^{22,23}, Toby Johnson^{24,25}, Anubha Mahajan², Niek Verweij²⁶, Gudmar Thorleifsson²⁷, Jouke-Jan Hottenga²⁸, Sonia Shah²⁹, Albert V Smith^{30,31}, Bengt Sennblad¹⁰, Christian Gieger³², Perttu Salo³³, Markus Perola^{9,33,34}, Nicholas J Timpson³⁵, David M Evans³⁵, Beate St. Pourcain³⁶, Ying Wu³⁷, Jeanette S Andrews³⁸, Jennie Hui³⁹⁻⁴², Lawrence F Bielak⁴³, Wei Zhao⁴³, Momoko Horikoshi^{2,3}, Pau Navarro⁴⁴, Aaron Isaacs^{45,46}, Jeffrey R O'Connell⁸, Kathleen Stirrups⁷, Veronique Vitart⁴⁴, Caroline Hayward⁴⁴, Tõnu Esko^{9,47}, Evelin Mihailov⁴⁷, Ross M Fraser⁴⁸, Tove Fall¹², Benjamin F Voight^{49,50}, Soumya Raychaudhuri⁵¹, Han Chen⁵², Cecilia M Lindgren², Andrew P Morris², Nigel W Rayner^{2,3}, Neil Robertson^{2,3}, Denis Rybin⁵³, Ching-Ti Liu⁵², Jacques S Beckmann^{54,55}, Sara M Willems⁴⁶, Peter S Chines⁵⁶, Anne U Jackson^{5,6}, Hyun Min Kang^{5,6}, Heather M Stringham^{5,6}, Kijoung Song⁵⁷, Toshiko Tanaka⁵⁸, John F Peden^{2,59}, Anuj Goel^{2,60}, Andrew A Hicks⁶¹, Ping An⁶², Martina Müller-Nurasyid^{32,63,64}, Anders Franco-Cereceda⁶⁵, Lasse Folkersen^{10,11}, Letizia Marullo^{2,66}, Hanneke Jansen⁶⁷, Albertine J Oldehinkel⁶⁸, Marcel Bruinenberg⁶⁹, James S Pankow⁷⁰, Kari E North^{71,72}, Nita G Forouhi¹, Ruth J F Loos¹, Sarah Edkins⁷, Tibor V Varga¹⁶, Göran Hallmans⁷³, Heikki Oksa⁷⁴, Mulas Antonella¹⁹, Ramaiah Nagaraja⁷⁵, Stella Trompet^{22,23}, Ian Ford²¹, Stephan J L Bakker⁷⁶, Augustine Kong²⁷, Meena Kumari⁷⁷, Bruna Gigante⁷⁸, Christian Herder⁷⁹, Patricia B Munroe^{24,25}, Mark Caulfield^{24,25}, Jula Antti³³, Massimo Mangino⁸⁰, Kerrin Small⁸⁰, Iva Miljkovic⁸¹, Yongmei Liu⁸², Mustafa Atalay⁸³, Wieland Kiess^{84,85}, Alan L James^{39,86,87}, Fernando Rivadeneira^{45,88-90}, Andre G Uitterlinden^{45,88-90}, Colin N A Palmer⁹¹, Alex S F Doney⁹¹, Gonneke Willemsen²⁸, Johannes H Smit⁹², Susan Campbell⁴⁴, Ozren Polasek⁹³, Lori L Bonnycastle⁵⁶, Serge Hercberg⁹⁴, Maria Dimitriou⁹⁵, Jennifer L Bolton⁹⁶, Gerard R Fowkes⁹⁶, Peter Kovacs⁹⁷, Jaana Lindström⁹⁸, Tatijana Zemunik⁹³, Stefania Bandinelli⁹⁹, Sarah H Wild⁴⁸, Hanneke V Basart¹⁰⁰, Wolfgang Rathmann¹⁰¹, Harald Grallert¹⁰², Winfried Maerz^{104,105}, Marcus E Kleber^{105,106}, Bernhard O Boehm¹⁰⁷, Annette Peters¹⁰⁸, Peter P Pramstaller^{61,109,110}, Michael A Province⁶², Ingrid B Borecki⁶², Nicholas D Hastie⁴⁴, Igor Rudan⁴⁸, Harry Campbell⁴⁸, Hugh Watkins^{2,60}, Martin Farrall^{2,60}, Michael Stumvoll^{84,111}, Luigi Ferrucci⁵⁸, Dawn M Waterworth⁵⁷, Richard N Bergman¹¹², Francis S Collins⁵⁶, Jaakko Tuomilehto¹¹³⁻¹¹⁶, Richard M Watanabe^{117,118}, Eco J C de Geus²⁸, Brenda W Penninx⁹², Albert Hofman⁹⁰, Ben A Oostra^{45,46,89}, Bruce M Psaty¹¹⁹⁻¹²², Peter Vollenweider¹²³, James F Wilson⁴⁸, Alan F Wright⁴⁴, G Kees Hovingh¹⁰⁰, Andres Metspalu^{9,47}, Matti Uusitupa^{124,125}, Patrik K E Magnusson¹², Kirsten O Kyvik^{126,127}, Jaakko Kaprio^{34,128,129}, Jackie F Price⁹⁶, George V Dedoussis⁹⁵, Panos Deloukas⁷, Pierre Meneton¹³⁰, Lars Lind¹³¹, Michael Boehnke^{5,6}, Alan R Shuldiner^{8,132}, Cornelia M van Duijn^{45,46,89,90}, Andrew D Morris⁹¹, Anke Toenjes^{84,111}, Patricia A Peyser⁴³, John P Beilby^{39,41,42}, Antje Körner^{84,85}, Johanna Kuusisto¹³³, Markku Laakso¹³³, Stefan R Bornstein¹³⁴, Peter E H Schwarz¹³⁴, Timo A Lakka^{83,135}, Rainer Rauramaa^{135,136}, Linda S Adair¹³⁷, George Davey Smith³⁵, Tim D Spector⁸⁰, Thomas Illig^{102,138}, Ulf de Faire⁷⁸, Anders Hamsten^{10,11,139}, Vilmundur Gudnason^{30,31}, Mika Kivimaki⁷⁷, Aroon Hingorani⁷⁷, Sirkka M Keinänen-Kiukaanniemi^{140,141}, Timo E Saaristo^{74,142}, Dorret I Boomsma²⁸, Kari Stefansson^{27,31}, Pim van der Harst²⁶, Josée Dupuis^{52,143}, Nancy L Pedersen¹², Naveed Sattar¹⁴⁴, Tamara B Harris¹⁴⁵, Francesco Cucca^{19,20}, Samuli Ripatti¹⁴⁶⁻¹⁴⁸, Veikko Salomaa¹⁴⁹, Karen L Mohlke³⁷, Beverley Balkau^{150,151}, Philippe Froguel^{14,15,152}, Anneli Pouta^{153,154}, Marjo-Riitta Jarvelin¹⁵⁴⁻¹⁵⁷, Nicholas J Wareham¹, Nabila Bouatia-Naji^{14,15,158},

Mark I McCarthy^{2,3,159}, Paul W Franks^{16,17,160}, James B Meigs^{161,162}, Tanya M Teslovich^{5,6}, Jose C Florez¹⁶²⁻¹⁶⁵, Claudia Langenberg^{1,77}, Erik Ingelsson¹², Inga Prokopenko^{2,3}, Inês Barroso^{7,166,167}

¹Medical Research Council (MRC) Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom. ²Wellcome Trust Center for Human Genetics, University of Oxford, Oxford, UK. ³Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK. ⁴Bioinformatics Graduate Program, University of Michigan Medical School, Ann Arbor, MI 48109, USA. ⁵Center for Statistical Genetics, University of Michigan, Ann Arbor, MI 48109, USA. ⁶Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA. ⁷Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, CB10 1SA, Hinxton, UK. ⁸Division of Endocrinology, Diabetes and Nutrition, University of Maryland, School of Medicine, Baltimore, MD. ⁹Estonian Genome Center, University of Tartu, Tartu, Estonia. ¹⁰Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden. ¹¹Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. ¹²Dept of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden. ¹³Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ¹⁴Univ Lille Nord de France, Lille, F-59000, France. ¹⁵Le Centre national de la recherche scientifique (CNRS) UMR8199, Institut Pasteur de Lille, F-59019, France. ¹⁶Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Skåne University Hospital Malmö, SE-205 02 Malmö, Sweden. ¹⁷Department of Public Health & Clinical Medicine, Umeå University, Sweden. ¹⁸Department of Odontology, Umeå University, Sweden. ¹⁹Istituto di Ricerca Genetica e Biomedica, CNR, Monserrato, 09042, Italy. ²⁰Dipartimento di Scienze Biomediche, Università di Sassari, Sassari, Italy. ²¹Robertson Centre for Biostatistics, University of Glasgow, UK. ²²Interuniversity Cardiology Institute of the Netherlands (ICIN), Durrer Center for Cardiogenetic Research, Utrecht, the Netherlands. ²³Dept of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. ²⁴Department of Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ. ²⁵The Genome Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ. ²⁶Department of Cardiology, University of Groningen, University Medical Center Groningen, The Netherlands. ²⁷deCODE genetics, 101 Reykjavik, Iceland. ²⁸Department of Biological Psychology, VU University & EMGO+ institute, Amsterdam, The Netherlands. ²⁹University College London Genetics Institute (UGI), University College London, Gower Street, London WC1E 6BT, UK. ³⁰Icelandic Heart Association, Kopavogur, Iceland. ³¹Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland. ³²Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. ³³Dept of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland. ³⁴University of Helsinki, Institute of Molecular Medicine, Finland (FIMM). ³⁵MRC Council Centre for Causal Analyses in Translational Epidemiology (CAiTE) Centre, School of Social and Community Medicine, University of Bristol, UK. ³⁶School of Social and Community Medicine, University of Bristol, UK. ³⁷Department of Genetics, University of North Carolina, Chapel Hill, NC 27599 USA. ³⁸Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest School of Medicine. ³⁹Busselton Population Medical Research Institute, Sir Charles Gairdner Hospital, NEDLANDS, WA 6009, Australia. ⁴⁰School of Population Health, The University of Western Australia, NEDLANDS, WA 6009. ⁴¹School of Pathology and Laboratory Medicine, The University of Western Australia, NEDLANDS, WA 6009. ⁴²PathWest Laboratory Medicine WA, NEDLANDS WA 6009. ⁴³Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, 48109, USA. ⁴⁴MRC Human Genetics Unit at the Medical Research Council Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, EH4 2XU. ⁴⁵Centre for Medical Systems Biology (CMSB), Leiden, The Netherlands. ⁴⁶Genetic Epidemiology Unit, Dept. of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands. ⁴⁷Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia. ⁴⁸Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG. ⁴⁹The Broad Institute of Harvard and MIT, Boston MA, 02142, USA. ⁵⁰Department of Pharmacology, University of Pennsylvania Perelman School of Medicine, Philadelphia PA, 19104, USA. ⁵¹Divisions of Genetics & Rheumatology, Brigham and Women's Hospital, Boston, MA 02115 USA. ⁵²Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA. ⁵³Boston University Data Coordinating Center, Boston, Massachusetts, USA. ⁵⁴Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland. ⁵⁵The Service of Medical Genetics, CHUV, University Hospital, 1011 Lausanne Switzerland. ⁵⁶Genome Technology Branch, National Human Genome Research Institute, National Institutes of Health (NIH), Bethesda,

MD 20892, USA. ⁵⁷Genetics, GlaxoSmithKline, Upper Merion, PA. ⁵⁸Clinical Research Branch, National Institute on Aging, Baltimore MD. ⁵⁹Illumina Inc., Chesterford Research Park, Essex, CB10 1XL, United Kingdom. ⁶⁰Dept of Cardiovascular Medicine, University of Oxford. ⁶¹Centre for Biomedicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy - Affiliated Institute of the University of Lübeck, Lübeck, Germany. ⁶²Division of Statistical Genomics, Washington University School of Medicine, St. Louis, Missouri, USA. ⁶³Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany. ⁶⁴Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians-Universität, Munich, Germany. ⁶⁵Cardiothoracic Surgery Unit, Department of Molecular Medicine and Surgery, Karolinska Institutet. ⁶⁶Department of Evolutionary Biology, Genetic Section, University of Ferrara, Ferrara, 44121, Italy. ⁶⁷Dept of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. ⁶⁸Interdisciplinary Center for Pathology of Emotions, University of Groningen, University Medical Center Groningen, The Netherlands. ⁶⁹University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. ⁷⁰Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA. ⁷¹Carolina Center for Genome Sciences, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA. ⁷²Department of Epidemiology, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA. ⁷³Department of Public Health and Clinical Medicine, Section for Nutritional Research, Umeå University Hospital, Umeå, Sweden. ⁷⁴Pirkanmaa Hospital District, Tampere, Finland. ⁷⁵Laboratory of Genetics, National Institute on Aging, NIH, Baltimore, MD 21224. ⁷⁶Department of Internal Medicine, University of Groningen, University Medical Center Groningen, The Netherlands. ⁷⁷Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK. ⁷⁸Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. ⁷⁹Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany. ⁸⁰Department of Twin Research and Genetic Epidemiology, King's College London, Lambeth Palace Rd, London, SE1 7EH, UK. ⁸¹Department of Epidemiology, Center for Aging and Population Health, University of Pittsburgh, Pittsburgh, PA. ⁸²Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest School of Medicine. ⁸³Institute of Biomedicine, Physiology, University of Eastern Finland, Kuopio Campus, Kuopio, Finland. ⁸⁴University of Leipzig, IFB AdiposityDiseases, Leipzig, Germany. ⁸⁵Pediatric Research Center, Dept. of Women's & Child Health, University of Leipzig, Leipzig, Germany. ⁸⁶School of Medicine and Pharmacology, The University of Western Australia, NEDLANDS, WA 6009. ⁸⁷Pulmonary Physiology, Sir Charles Gairdner Hospital, NEDLANDS WA 6009. ⁸⁸Dept. of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands. ⁸⁹Netherlands Consortium for Healthy Ageing of the Netherlands (NCHAH) of the Genomics Initiative (NGI), Leiden, The Netherlands. ⁹⁰Dept. of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. ⁹¹Medical Research Institute, University of Dundee, Scotland DD19SY. ⁹²Department of Psychiatry, VU University Medical Centre, Amsterdam, The Netherlands. ⁹³Faculty of Medicine, University of Split, Soltanska 2, 21000 Split, Croatia. ⁹⁴U557 Institut National de la Santé et de la Recherche Médicale, U1125 Institut National de la Recherche Agronomique, Université Paris 13, Bobigny, France. ⁹⁵Department of Dietetics-Nutrition, Harokopio University, 70 El. Venizelou Str, Athens, Greece. ⁹⁶Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland. ⁹⁷University of Leipzig, Interdisciplinary Center for Clinical Research, Germany. ⁹⁸National Institute for Health and Welfare, Diabetes Prevention Unit, Helsinki, Finland. ⁹⁹Geriatric Department Azienda Sanitaria Firenze, Florence Italy. ¹⁰⁰Dept Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands. ¹⁰¹Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany. ¹⁰²Research Unit of Molecular Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. ¹⁰⁴Synlab Academy, Mannheim, Germany. ¹⁰⁵Mannheim Institute of Public Health, Social and Preventive Medicine, Medical Faculty of Mannheim, University of Heidelberg, Mannheim, Germany. ¹⁰⁶Ludwigshafen Risk and Cardiovascular Health (LURIC) Study nonprofit LLC, Freiburg, Germany. ¹⁰⁷Division of Endocrinology and Diabetes, Department of Medicine, University Hospital, Ulm, Germany. ¹⁰⁸Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. ¹⁰⁹Department of Neurology, General Central Hospital, Bolzano, Italy. ¹¹⁰Department of Neurology, University of Lübeck, Lübeck, Germany. ¹¹¹University of Leipzig, Department of Medicine, Leipzig, Germany. ¹¹²Diabetes and Obesity Research Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. ¹¹³Diabetes Prevention Unit, National Institute for Health and Welfare, 00271 Helsinki, Finland. ¹¹⁴South Ostrobothnia Central Hospital, 60220 Seinäjoki, Finland. ¹¹⁵Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, 28046 Madrid, Spain. ¹¹⁶Centre for Vascular Prevention, Danube-University Krems, 3500 Krems, Austria. ¹¹⁷Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA 90089, USA. ¹¹⁸Department of

Physiology & Biophysics, Keck School of Medicine of USC, Los Angeles, CA 90089, USA. ¹¹⁹Cardiovascular Health Research Unit, Departments of Medicine, University of Washington, Seattle, WA. ¹²⁰Group Health Research Institute, Group Health Cooperative, Seattle, WA. ¹²¹Department of Epidemiology, University of Washington, Seattle, WA. ¹²²Department of Health Services, University of Washington, Seattle, WA. ¹²³Department of Internal Medicine, University Hospital and University of Lausanne, 1011 Lausanne, Switzerland. ¹²⁴Department of Public Health and Clinical Nutrition, University of Eastern Finland, Finland. ¹²⁵Research Unit, Kuopio University Hospital, Kuopio, Finland. ¹²⁶Odense Patient data Explorative Network (OPEN), Odense, Denmark. ¹²⁷Institute of Regional Health Services Research, Odense, Denmark. ¹²⁸Hjelt Institute, Dept of Public Health, University of Helsinki, Finland. ¹²⁹National Institute for Health and Welfare, Dept of Mental Health and Substance Abuse Services, P.O. Box 30 (Mannerheimintie 166), 00300 Helsinki, Finland. ¹³⁰U872 Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, 75006 Paris, France. ¹³¹Dept of Medical Sciences, Uppsala University, Akademiska sjukhuset, 751 85 Uppsala, SWEDEN. ¹³²Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, MD. ¹³³Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland. ¹³⁴Dept of Medicine III, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany. ¹³⁵Kuopio Research Institute of Exercise Medicine, Kuopio, Finland. ¹³⁶Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland. ¹³⁷Department of Nutrition, University of North Carolina, Chapel Hill, NC, USA. ¹³⁸Hannover Unified Biobank, Hannover Medical School, Hannover, Germany. ¹³⁹Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden. ¹⁴⁰Faculty of Medicine, Institute of Health Sciences, University of Oulu, Oulu, Finland. ¹⁴¹Unit of General Practice, Oulu University Hospital, Oulu, Finland. ¹⁴²Finnish Diabetes Association, Kirjoniementie 15, 33680, Tampere, Finland. ¹⁴³National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA. ¹⁴⁴British Heart Foundation (BHF) Building, Institute of Cardiovascular and Medical Sciences, University of Glasgow. ¹⁴⁵Laboratory of Epidemiology, Demography, and Biometry, National Institute on Ageing, Bethesda, MD. ¹⁴⁶Institute for Molecular Medicine Finland, FIMM, University of Helsinki, Finland. ¹⁴⁷Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki, Finland. ¹⁴⁸Wellcome Trust Sanger Institute, UK. ¹⁴⁹Unit of Chronic Disease Epidemiology and Prevention, National Institute for Health and Welfare, Helsinki, Finland. ¹⁵⁰Inserm, Centre de recherche en Épidémiologie et Santé des Populations (CESP) Center for Research in Epidemiology and Public Health, U1018, Epidemiology of diabetes, obesity and chronic kidney disease over the lifecourse, Villejuif, France. ¹⁵¹University Paris Sud 11, UMRS 1018, Villejuif, France. ¹⁵²Department of Genomics of Common Disease, School of Public Health, Imperial College London, Hammersmith Hospital, W12 0NN, London, UK. ¹⁵³Department of Clinical Sciences/Obstetrics and Gynecology, University of Oulu, Oulu, Finland. ¹⁵⁴Department of Lifecourse and Services, National Institute for Health and Welfare, FI-90101 Oulu, Finland. ¹⁵⁵Biocenter Oulu, University of Oulu, Finland. ¹⁵⁶Department of Epidemiology and Biostatistics, School of Public Health, MRC-HPA Centre for Environment and Health, Faculty of Medicine, Imperial College London, UK. ¹⁵⁷Institute of Health Sciences, University of Oulu, Finland. ¹⁵⁸Inserm U970, Paris Cardiovascular Research Center PARCC, 56 rue Leblanc, F-75015 Paris. ¹⁵⁹Oxford National Institute for Health Research (NIHR) Biomedical Research Centre, Churchill Hospital, Oxford OX3 7LJ, UK. ¹⁶⁰Department of Nutrition, Harvard School of Public Health, Boston, MA. ¹⁶¹General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁶²Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. ¹⁶³Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁶⁴Diabetes Research Center, Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁶⁵Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA. ¹⁶⁶NIHR Cambridge Biomedical Research Centre, Level 4, Institute of Metabolic Science Box 289 Addenbrooke's Hospital Cambridge CB2 0QQ, UK. ¹⁶⁷University of Cambridge Metabolic Research Laboratories, Level 4, Institute of Metabolic Science Box 289 Addenbrooke's Hospital Cambridge CB2 0QQ, UK

Membership of the GIANT Consortium

Elizabeth K Speliotes^{1,2}, Cristen J Willer³, Sonja I Berndt⁴, Keri L Monda⁵, Gudmar Thorleifsson⁶, 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 Segre¹⁷⁻¹⁹, Karol Estrada²⁰⁻²², Liming Liang^{23,24}, James Nemesh¹⁸, Ju-Hyun Park⁴, Stefan Gustafsson²⁵, Tuomas O Kilpeläinen¹⁰, Jian Yang²⁶, Nabila Bouatia-Naji^{27,28}, Tõnu Esko²⁹⁻³¹, 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 Glazer^{44,45}, Michael E Goddard^{46,47}, Nancy L Heard-Costa⁴⁸, Volker Hoesel⁴⁹, Jouke-Jan Hottenga⁵⁰, Åsa Johansson^{51,52}, Toby Johnson^{33,34,53,54}, Shamika Ketkar³², Claudia Lamina^{15,55}, Shengxu Li¹⁰, Miriam F Moffatt⁵⁶, Richard H Myers⁵⁷, Narisu Narisu⁵⁸, John R B Perry⁷, Marjolein J Peters^{21,22}, Michael Preuss⁵⁹, Samuli Ripatti^{60,61}, Fernando Rivadeneira²⁰⁻²², Camilla Sandholt⁶², Laura J Scott³, Nicholas J Timpson⁶³, Jonathan P Tyrer⁶⁴, Sophie van Wingerden²⁰, Richard M Watanabe^{65,66}, Charles C White⁶⁷, Fredrik Wiklund²⁵, Christina Barlassina⁶⁸, Daniel I Chasman^{69,70}, Matthew N Cooper⁷¹, John-Olov Jansson⁷², Robert W Lawrence⁷¹, Niina Pellikka^{60,61}, Inga Prokopenko^{8,9}, Jianxin Shi⁴, Elisabeth Thiering¹⁵, Helene Alavere²⁹, Maria T S Alibrandi⁷³, Peter Almgren⁷⁴, Alice M Arnold^{75,76}, Thor Aspelund^{38,39}, Larry D Atwood⁴⁸, Beverley Balkau^{77,78}, Anthony J Balmforth⁷⁹, Amanda J Bennett⁹, Yoav Ben-Shlomo⁸⁰, Richard N Bergman⁶⁶, Sven Bergmann^{33,34}, Heike Biebermann⁸¹, Alexandra I F Blakemore⁸², Tanja Boes³⁷, Lori L Bonnycastle⁵⁸, Stefan R Bornstein⁸³, Morris J Brown⁸⁴, Thomas A Buchanan^{66,85}, Fabio Busonero⁸⁶, Harry Campbell⁸⁷, Francesco P Cappuccio⁸⁸, Christine Cavalcanti-Proença^{27,28}, Yii-Der Ida Chen⁸⁹, Chih-Mei Chen¹⁵, Peter S Chines⁵⁸, Robert Clarke⁹⁰, Lachlan Coin⁹¹, John Connell⁹², Ian N M Day⁶³, Martin den Heijer^{93,94}, Jubao Duan⁹⁵, Shah Ebrahim^{96,97}, Paul Elliott^{91,98}, Roberto Elosua⁹⁹, Gudny Eiriksdottir³⁸, Michael R Erdos⁵⁸, Johan G Eriksson¹⁰⁰⁻¹⁰⁴, Maurizio F Facheris^{105,106}, Stephan B Felix¹⁰⁷, Pamela Fischer-Posovszky¹⁰⁸, Aaron R Folsom¹⁰⁹, Nele Friedrich¹¹⁰, Nelson B Freimer¹¹¹, Mao Fu¹¹², Stefan Gaget^{27,28}, Pablo V Gejman⁹⁵, Eco J C Geus⁵⁰, Christian Gieger¹⁵, Anette P Gjessing⁶², Anuj Goel^{8,113}, Philippe Goyette¹¹⁴, Harald Grallert¹⁵, Jürgen Gräßler¹¹⁵, Danielle M Greenawalt¹¹⁶, Christopher J Groves⁹, Vilmondur Gudnason^{38,39}, Candace Guiducci¹, Anna-Liisa Hartikainen¹¹⁷, Neelam Hassanali⁹, Alistair S Hall⁷⁹, Aki S Havulinna¹¹⁸, Caroline Hayward¹¹⁹, Andrew C Heath¹²⁰, Christian Hengstenberg^{121,122}, Andrew A Hicks¹⁰⁵, Anke Hinney¹²³, Albert Hofman^{20,22}, Georg Homuth¹²⁴, Jennie Hui^{71,125,126}, Wilmar Igl⁵¹, Carlos Iribarren^{127,128}, Bo Isomaa^{103,129}, Kevin B Jacobs¹³⁰, Ivonne Jarick¹³¹, Elizabeth Jewell³, Ulrich John¹³², Torben Jørgensen^{133,134}, Pekka Jousilahti¹¹⁸, Antti Jula¹³⁵, Marika Kaakinen^{136,137}, Eero Kajantie^{101,138}, Lee M Kaplan^{2,70,139}, Sekar Kathiresan^{17,18,140-142}, Johannes Kettunen^{60,61}, Leena Kinnunen¹⁴³, Joshua W Knowles¹⁴⁴, Ivana Kolcic¹⁴⁵, Inke R König⁵⁹, Seppo Koskinen¹¹⁸, Peter Kovacs¹⁴⁶, Johanna Kuusisto¹⁴⁷, Peter Kraft^{23,24}, Kirsti Kvaløy¹⁴⁸, Jaana Laitinen¹⁴⁹, Olivier Lantieri¹⁵⁰, Chiara Lanzani⁷³, Lenore J Launer¹⁵¹, Cecile Lecoeur^{27,28}, Terho Lehtimäki¹⁵², Guillaume Lettre^{114,153}, Jianjun Liu¹⁵⁴, Marja-Liisa Lokki¹⁵⁵, Mattias Lorentzon¹⁵⁶, Robert N Luben¹⁵⁷, Barbara Ludwig⁸³, Paolo Manunta⁷³, Diana Marek^{33,34}, Michel Marre^{159,160}, Nicholas G Martin¹⁶¹, Wendy L McArdle¹⁶², Anne McCarthy¹⁶³, Barbara McKnight⁷⁵, Thomas Meitinger^{164,165}, Olle Melander¹⁶⁶, David Meyre^{27,28}, Kristian Midthjell¹⁴⁸, Grant W Montgomery¹⁶⁷, Mario A Morken⁵⁸, Andrew P Morris⁸, Rosanda

Mulic¹⁶⁸, Julius S Ngwa⁶⁷, Mari Nelis^{29–31}, Matt J Neville⁹, Dale R Nyholt¹⁶⁹, Christopher J O’Donnell^{141,170}, Stephen O’Rahilly¹⁷¹, Ken K Ong¹⁰, Ben Oostra¹⁷², Guillaume Paré¹⁷³, Alex N Parker¹⁷⁴, Markus Perola^{60,61}, Irene Pichler¹⁰⁵, Kirsi H Pietiläinen^{175,176}, Carl G P Platou^{148,177}, Ozren Polasek^{145,178}, Anneli Pouta^{117,179}, Suzanne Rafelt¹⁸⁰, Olli Raitakari^{181,182}, Nigel W Rayner^{8,9}, Martin Ridderstråle¹⁶⁶, Winfried Rief¹⁸³, Aimo Ruokonen¹⁸⁴, Neil R Robertson^{8,9}, Peter Rzehak^{15,185}, Veikko Salomaa¹¹⁸, Alan R Sanders⁹⁵, Manjinder S Sandhu^{10,16,157}, Serena Sanna⁸⁶, Jouko Saramies¹⁸⁶, Markku J Savolainen¹⁸⁷, Susann Scherag¹²³, Sabine Schipf^{110,188}, Stefan Schreiber¹⁸⁹, Heribert Schunkert¹⁹⁰, Kaisa Silander^{60,61}, Juha Sinisalo¹⁹¹, David S Siscovick^{45,192}, Jan H Smit¹⁹³, Nicole Soranzo^{16,35}, Ulla Sovio⁹¹, Jonathan Stephens^{194,195}, Ida Surakka^{60,61}, Amy J Swift⁵⁸, Mari-Liis Tammesoo²⁹, Jean-Claude Tardif^{114,153}, Maris Teder-Laving^{30,31}, Tanya M Teslovich³, John R Thompson^{196,197}, Brian Thomson¹, Anke Tönjes^{198,199}, Tiinamaija Tuomi^{103,200,201}, Joyce B J van Meurs^{20–22}, Gert-Jan van Ommen^{202,203}, Vincent Vatin^{27,28}, Jorma Viikari²⁰⁴, Sophie Visvikis-Siest²⁰⁵, Veronique Vitart¹¹⁹, Carla I G Vogel¹²³, Benjamin F Voight^{17–19}, Lindsay L Waite⁴¹, Henri Wallaschofski¹¹⁰, G Bragi Walters⁶, Elisabeth Widen⁶⁰, Susanna Wiegand⁸¹, Sarah H Wild⁸⁷, Gonneke Willemsen⁵⁰, Daniel R Witte²⁰⁶, Jacqueline C Witteman^{20,22}, Jianfeng Xu²⁰⁷, Qunyuan Zhang³², Lina Zgaga¹⁴⁵, Andreas Ziegler⁵⁹, Paavo Zitting²⁰⁸, John P Beilby^{125,126,209}, I Sadaf Farooqi¹⁷¹, Johannes Hebebrand¹²³, Heikki V Huikuri²¹⁰, Alan L James^{126,211}, Mika Kähönen²¹², Douglas F Levinson²¹³, Fabio Macciardi^{68,214}, Markku S Nieminen¹⁹¹, Claes Ohlsson¹⁵⁶, Lyle J Palmer^{71,126}, Paul M Ridker^{69,70}, Michael Stumvoll^{198,215}, Jacques S Beckmann^{33,216}, Heiner Boeing⁴³, Eric Boerwinkle²¹⁷, Dorret I Boomsma⁵⁰, Mark J Caulfield⁵⁴, Stephen J Chanock⁴, Francis S Collins⁵⁸, L Adrienne Cupples⁶⁷, George Davey Smith⁶³, Jeanette Erdmann¹⁹⁰, Philippe Froguel^{27,28,82}, Henrik Grönberg²⁵, Ulf Gyllensten⁵¹, Per Hall²⁵, Torben Hansen^{62,218}, Tamara B Harris¹⁵¹, Andrew T Hattersley⁷, Richard B Hayes²¹⁹, Joachim Heinrich¹⁵, Frank B Hu^{13,14,23}, Kristian Hveem¹⁴⁸, Thomas Illig¹⁵, Marjo-Riitta Jarvelin^{91,136,137,179}, Jaakko Kaprio^{60,175,220}, Fredrik Karpe^{9,221}, Kay-Tee Khaw¹⁵⁷, Lambertus A Kiemeny^{40,93,222}, Heiko Krude⁸¹, Markku Laakso¹⁴⁷, Debbie A Lawlor⁶³, Andres Metspalu^{29–31}, Patricia B Munroe⁵⁴, Willem H Ouwehand^{16,194,195}, Oluf Pedersen^{62,223,224}, Brenda W Penninx^{193,225,226}, Annette Peters¹⁵, Peter P Pramstaller^{105,106,227}, Thomas Quertermous¹⁴⁴, Thomas Reinehr²²⁸, Aila Rissanen¹⁷⁶, Igor Rudan^{87,168}, Nilesh J Samani^{180,196}, Peter E H Schwarz²²⁹, Alan R Shuldiner^{112,230}, Timothy D Spector³⁵, Jaakko Tuomilehto^{143,231,232}, Manuela Uda⁸⁶, André Uitterlinden^{20–22}, Timo T Valle¹⁴³, Martin Wabitsch¹⁰⁸, Gérard Waeber²³³, Nicholas J Wareham¹⁰, Hugh Watkins^{8,113} on behalf of Procardis Consortium, James F Wilson⁸⁷, Alan F Wright¹¹⁹, M Carola Zillikens^{21,22}, Nilanjana Chatterjee⁴, Steven A McCarroll^{17–19}, Shaun Purcell^{17,234,235}, Eric E Schadt^{236,237}, Peter M Visscher²⁶, Themistocles L Assimes¹⁴⁴, Ingrid B Borecki^{32,238}, Panos Deloukas¹⁶, Caroline S Fox²³⁹, Leif C Groop⁷⁴, Talin Haritunians⁸⁹, David J Hunter^{13,14,23}, Robert C Kaplan²⁴⁰, Karen L Mohlke²⁴¹, Jeffrey R O’Connell¹¹², Leena Peltonen^{16,60,61,234,242}, David Schlessinger²⁴³, David P Strachan²⁴⁴, Cornelia M van Duijn^{20,22}, H-Erich Wichmann^{15,185,245}, Timothy M Frayling⁷, Unnur Thorsteinsdottir^{6,246}, Gonçalo R Abecasis³, Inês Barroso^{16,247}, Michael Boehnke³, Kari Stefansson^{6,246}, Kari E North^{5,248}, Mark I McCarthy^{8,9,221}, Joel N Hirschhorn^{1,11,249}, Erik Ingelsson²⁵ & Ruth J F Loos¹⁰

¹Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA. ²Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts, USA. ³Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA. ⁴Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA. ⁵Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. ⁶deCODE Genetics,

Reykjavik, Iceland. ⁷Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK. ⁸Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. ⁹Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK. ¹⁰Medical Research Council (MRC) Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK. ¹¹Divisions of Genetics and Endocrinology and Program in Genomics, Children's Hospital, Boston, Massachusetts, USA. ¹²Regensburg University Medical Center, Department of Epidemiology and Preventive Medicine, Regensburg, Germany. ¹³Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA. ¹⁴Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA. ¹⁵Institute of Epidemiology, Helmholtz Zentrum München-German Research Center for Environmental Health, Neuherberg, Germany. ¹⁶Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK. ¹⁷Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁸Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. ¹⁹Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts, USA. ²⁰Department of Epidemiology, Erasmus Medical Center (MC), Rotterdam, The Netherlands. ²¹Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. ²²Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA), Rotterdam, The Netherlands. ²³Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA. ²⁴Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA. ²⁵Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ²⁶Queensland Statistical Genetics Laboratory, Queensland Institute of Medical Research, Queensland, Australia. ²⁷Centre National de la Recherche Scientifique (CNRS) UMR8199-IBL-Institut Pasteur de Lille, Lille, France. ²⁸University Lille Nord de France, Lille, France. ²⁹Estonian Genome Center, University of Tartu, Tartu, Estonia. ³⁰Estonian Biocenter, Tartu, Estonia. ³¹Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia. ³²Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, USA. ³³Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland. ³⁴Swiss Institute of Bioinformatics, Lausanne, Switzerland. ³⁵Department of Twin Research and Genetic Epidemiology, King's College London, London, UK. ³⁶Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. ³⁷Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany. ³⁸Icelandic Heart Association, Kopavogur, Iceland. ³⁹University of Iceland, Reykjavik, Iceland. ⁴⁰Comprehensive Cancer Center East, Nijmegen, The Netherlands. ⁴¹Hudson Alpha Institute for Biotechnology, Huntsville, Alabama, USA. ⁴²Department of Pharmacy and Pharmacology, University of Bath, Bath, UK. ⁴³Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. ⁴⁴Department of Medicine, University of Washington, Seattle, Washington, USA. ⁴⁵Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, USA. ⁴⁶University of Melbourne, Parkville, Australia. ⁴⁷Department of Primary Industries, Melbourne, Victoria, Australia. ⁴⁸Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA. ⁴⁹Technical University Munich, Chair of Biomathematics, Garching, Germany. ⁵⁰Department of Biological Psychology, Vrije Universiteit (VU) University Amsterdam, Amsterdam, The Netherlands. ⁵¹Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, Uppsala, Sweden. ⁵²Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. ⁵³Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK. ⁵⁴Clinical 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, UK. ⁵⁵Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria. ⁵⁶National Heart and Lung Institute, Imperial College London, London, UK. ⁵⁷Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA. ⁵⁸National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA. ⁵⁹Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany. ⁶⁰Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. ⁶¹National Institute for Health and Welfare, Department of Chronic Disease Prevention, Unit of Public Health Genomics, Helsinki, Finland. ⁶²Hagedorn Research Institute, Gentofte, Denmark. ⁶³MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, Oakfield House, Bristol, UK. ⁶⁴Department of Oncology, University of Cambridge, Cambridge, UK. ⁶⁵Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. ⁶⁶Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. ⁶⁷Department of Biostatistics, Boston

University School of Public Health, Boston, Massachusetts, USA. ⁶⁸University of Milan, Department of Medicine, Surgery and Dentistry, Milano, Italy. ⁶⁹Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA. ⁷⁰Harvard Medical School, Boston, Massachusetts, USA. ⁷¹Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia, Australia. ⁷²Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ⁷³University Vita-Salute San Raffaele, Division of Nephrology and Dialysis, Milan, Italy. ⁷⁴Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, Malmö, Sweden. ⁷⁵Department of Biostatistics, University of Washington, Seattle, Washington, USA. ⁷⁶Collaborative Health Studies Coordinating Center, Seattle, Washington, USA. ⁷⁷INSERM Centre de recherche en Epidémiologie et Santé des Populations (CESP) Centre for Research in Epidemiology and Public Health U1018, Villejuif, France. ⁷⁸University Paris Sud 11, Unité Mixte de Recherche en Santé (UMRS) 1018, Villejuif, France. ⁷⁹Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds, UK. ⁸⁰Department of Social Medicine, University of Bristol, Bristol, UK. ⁸¹Institute of Experimental Paediatric Endocrinology, Charité Universitätsmedizin Berlin, Berlin, Germany. ⁸²Department of Genomics of Common Disease, School of Public Health, Imperial College London, London, UK. ⁸³Department of Medicine III, University of Dresden, Dresden, Germany. ⁸⁴Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK. ⁸⁵Division of Endocrinology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. ⁸⁶Istituto di Neurogenetica e Neurofarmacologia del Consiglio Nazionale delle Ricerche (CNR), Monserrato, Cagliari, Italy. ⁸⁷Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, Scotland, UK. ⁸⁸University of Warwick, Warwick Medical School, Coventry, UK. ⁸⁹Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. ⁹⁰Clinical Trial Service Unit, Oxford, UK. ⁹¹Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London, UK. ⁹²University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. ⁹³Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. ⁹⁴Department of Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. ⁹⁵Northshore University Healthsystem, Evanston, Illinois, USA. ⁹⁶The London School of Hygiene and Tropical Medicine, London, UK. ⁹⁷South Asia Network for Chronic Disease, New Dehli, India. ⁹⁸MRC-Health Protection Agency (HPA) Centre for Environment and Health, London, UK. ⁹⁹Cardiovascular Epidemiology and Genetics, Institut Municipal D'investigacio Medica and Centro de Investigación Biomédica en Red CIBER Epidemiología y Salud Pública, Barcelona, Spain. ¹⁰⁰Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland. ¹⁰¹National Institute for Health and Welfare, Helsinki, Finland. ¹⁰²Helsinki University Central Hospital, Unit of General Practice, Helsinki, Finland. ¹⁰³Folkhalsan Research Centre, Helsinki, Finland. ¹⁰⁴Vasa Central Hospital, Vasa, Finland. ¹⁰⁵Institute of Genetic Medicine, European Academy Bozen-Bolzano (EURAC), Bolzano-Bozen, Italy, Affiliated Institute of the University of Lübeck, Lübeck, Germany. ¹⁰⁶Department of Neurology, General Central Hospital, Bolzano, Italy. ¹⁰⁷Department of Internal Medicine B, Ernst-Moritz-Arndt University, Greifswald, Germany. ¹⁰⁸Pediatric Endocrinology, Diabetes and Obesity Unit, Department of Pediatrics and Adolescent Medicine, Ulm, Germany. ¹⁰⁹Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA. ¹¹⁰Institut für Klinische Chemie und Laboratoriumsmedizin, Universität Greifswald, Greifswald, Germany. ¹¹¹Center for Neurobehavioral Genetics, University of California, Los Angeles, California, USA. ¹¹²Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA. ¹¹³Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, UK. ¹¹⁴Montreal Heart Institute, Montreal, Quebec, Canada. ¹¹⁵Department of Medicine III, Pathobiochemistry, University of Dresden, Dresden, Germany. ¹¹⁶Merck Research Laboratories, Merck and Co., Inc., Boston, Massachusetts, USA. ¹¹⁷Department of Clinical Sciences, Obstetrics and Gynecology, University of Oulu, Oulu, Finland. ¹¹⁸National Institute for Health and Welfare, Department of Chronic Disease Prevention, Chronic Disease Epidemiology and Prevention Unit, Helsinki, Finland. ¹¹⁹MRC Human Genetics Unit, Institute for Genetics and Molecular Medicine, Western General Hospital, Edinburgh, Scotland, UK. ¹²⁰Department of Psychiatry and Midwest Alcoholism Research Center, Washington University School of Medicine, St. Louis, Missouri, USA. ¹²¹Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Regensburg, Germany. ¹²²Regensburg University Medical Center, Innere Medizin II, Regensburg, Germany. ¹²³Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany. ¹²⁴Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany. ¹²⁵PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands, Western Australia, Australia. ¹²⁶Busselton Population Medical Research Foundation Inc., Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia. ¹²⁷Division of Research, Kaiser Permanente Northern California, Oakland, California, USA. ¹²⁸Department of Epidemiology

and Biostatistics, University of California, San Francisco, San Francisco, California, USA. ¹²⁹Department of Social Services and Health Care, Jakobstad, Finland. ¹³⁰Core Genotyping Facility, SAIC-Frederick, Inc., National Cancer Institute (NCI)-Frederick, Frederick, Maryland, USA. ¹³¹Institute of Medical Biometry and Epidemiology, University of Marburg, Marburg, Germany. ¹³²Institut für Epidemiologie und Sozialmedizin, Universität Greifswald, Greifswald, Germany. ¹³³Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark. ¹³⁴Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark. ¹³⁵National Institute for Health and Welfare, Department of Chronic Disease Prevention, Population Studies Unit, Turku, Finland. ¹³⁶Institute of Health Sciences, University of Oulu, Oulu, Finland. ¹³⁷Biocenter Oulu, University of Oulu, Oulu, Finland. ¹³⁸Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, Hospital District of Helsinki and Uusimaa (HUS), Helsinki, Finland. ¹³⁹Massachusetts General Hospital (MGH) Weight Center, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁴⁰Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts, USA. ¹⁴¹Framingham Heart Study of the National, Heart, Lung, and Blood Institute and Boston University, Framingham, Massachusetts, USA. ¹⁴²Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. ¹⁴³National Institute for Health and Welfare, Diabetes Prevention Unit, Helsinki, Finland. ¹⁴⁴Department of Medicine, Stanford University School of Medicine, Stanford, California, USA. ¹⁴⁵Andrija Stampar School of Public Health, Medical School, University of Zagreb, Zagreb, Croatia. ¹⁴⁶Interdisciplinary Centre for Clinical Research, University of Leipzig, Leipzig, Germany. ¹⁴⁷Department of Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, Finland. ¹⁴⁸Nord-Trøndelag Health Study (HUNT) Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway. ¹⁴⁹Finnish Institute of Occupational Health, Oulu, Finland. ¹⁵⁰Institut inter-régional pour la santé (IRSA), La Riche, France. ¹⁵¹Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA. ¹⁵²Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, Tampere, Finland. ¹⁵³Department of Medicine, Université de Montréal, Montréal, Quebec, Canada. ¹⁵⁴Human Genetics, Genome Institute of Singapore, Singapore, Singapore. ¹⁵⁵Transplantation Laboratory, Haartman Institute, University of Helsinki, Helsinki, Finland. ¹⁵⁶Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ¹⁵⁷Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, UK. ¹⁵⁹Department of Endocrinology, Diabetology and Nutrition, Bichat-Claude Bernard University Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France. ¹⁶⁰Cardiovascular Genetics Research Unit, Université Henri Poincaré-Nancy 1, Nancy, France. ¹⁶¹Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland, Australia. ¹⁶²Avon Longitudinal Study of Parents and Children (ALSPAC) Laboratory, Department of Social Medicine, University of Bristol, Bristol, UK. ¹⁶³Division of Health, Research Board, An Bord Taighde Sláinte, Dublin, Ireland. ¹⁶⁴Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany. ¹⁶⁵Institute of Human Genetics, Helmholtz Zentrum München-German Research Center for Environmental Health, Neuherberg, Germany. ¹⁶⁶Department of Clinical Sciences, Lund University, Malmö, Sweden. ¹⁶⁷Molecular Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland, Australia. ¹⁶⁸Croatian Centre for Global Health, School of Medicine, University of Split, Split, Croatia. ¹⁶⁹Neurogenetics Laboratory, Queensland Institute of Medical Research, Queensland, Australia. ¹⁷⁰National Heart, Lung, and Blood Institute, National Institutes of Health, Framingham, Massachusetts, USA. ¹⁷¹University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK. ¹⁷²Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands. ¹⁷³Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada. ¹⁷⁴Amgen, Cambridge, Massachusetts, USA. ¹⁷⁵Finnish Twin Cohort Study, Department of Public Health, University of Helsinki, Helsinki, Finland. ¹⁷⁶Obesity Research Unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland. ¹⁷⁷Department of Medicine, Levanger Hospital, The Nord-Trøndelag Health Trust, Levanger, Norway. ¹⁷⁸Gen-Info Ltd, Zagreb, Croatia. ¹⁷⁹National Institute for Health and Welfare, Oulu, Finland. ¹⁸⁰Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK. ¹⁸¹Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland. ¹⁸²The Department of Clinical Physiology, Turku University Hospital, Turku, Finland. ¹⁸³Clinical Psychology and Psychotherapy, University of Marburg, Marburg, Germany. ¹⁸⁴Department of Clinical Sciences and Clinical Chemistry, University of Oulu, Oulu, Finland. ¹⁸⁵Ludwig-Maximilians-Universität, Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Munich, Germany. ¹⁸⁶South Karelia Central Hospital, Lappeenranta, Finland. ¹⁸⁷Department of Clinical Sciences and Internal Medicine, University of Oulu, Oulu, Finland. ¹⁸⁸Institut für Community Medicine, Greifswald, Germany. ¹⁸⁹Christian-Albrechts-University, University Hospital Schleswig-Holstein, Institute for Clinical Molecular Biology and Department of Internal Medicine I, Kiel, Germany. ¹⁹⁰Universität zu Lübeck,

Medizinische Klinik II, Lübeck, Germany. ¹⁹¹Division of Cardiology, Cardiovascular Laboratory, Helsinki University Central Hospital, Helsinki, Finland. ¹⁹²Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington, USA. ¹⁹³Department of Psychiatry, Instituut voor Extramuraal Geneeskundig Onderzoek (EMGO) Institute, VU University Medical Center, Amsterdam, The Netherlands. ¹⁹⁴Department of Haematology, University of Cambridge, Cambridge, UK. ¹⁹⁵National Health Service (NHS) Blood and Transplant, Cambridge Centre, Cambridge, UK. ¹⁹⁶Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, UK. ¹⁹⁷Department of Health Sciences, University of Leicester, University Road, Leicester, UK. ¹⁹⁸Department of Medicine, University of Leipzig, Leipzig, Germany. ¹⁹⁹Coordination Centre for Clinical Trials, University of Leipzig, Leipzig, Germany. ²⁰⁰Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland. ²⁰¹Research Program of Molecular Medicine, University of Helsinki, Helsinki, Finland. ²⁰²Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. ²⁰³Center of Medical Systems Biology, Leiden University Medical Center, Leiden, The Netherlands. ²⁰⁴Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland. ²⁰⁵INSERM Cardiovascular Genetics team, Centre Investigation Clinique (CIC) 9501, Nancy, France. ²⁰⁶Steno Diabetes Center, Gentofte, Denmark. ²⁰⁷Center for Human Genomics, Wake Forest University, Winston-Salem, North Carolina, USA. ²⁰⁸Department of Physiatrics, Lapland Central Hospital, Rovaniemi, Finland. ²⁰⁹School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia, Australia. ²¹⁰Department of Internal Medicine, University of Oulu, Oulu, Finland. ²¹¹School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia. ²¹²Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, Finland. ²¹³Stanford University School of Medicine, Stanford, California, USA. ²¹⁴Department of Psychiatry and Human Behavior, University of California, Irvine (UCI), Irvine, California, USA. ²¹⁵Leipziger Interdisziplinärer Forschungs-komplex zu molekularen Ursachen umwelt- und lebensstilassoziierter Erkrankungen (LIFE) Study Centre, University of Leipzig, Leipzig, Germany. ²¹⁶Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, Lausanne, Switzerland. ²¹⁷Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA. ²¹⁸Faculty of Health Science, University of Southern Denmark, Odense, Denmark. ²¹⁹New York University Medical Center, New York, New York, USA. ²²⁰National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Unit for Child and Adolescent Mental Health, Helsinki, Finland. ²²¹NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK. ²²²Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. ²²³Institute of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark. ²²⁴Faculty of Health Science, University of Aarhus, Aarhus, Denmark. ²²⁵Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands. ²²⁶Department of Psychiatry, University Medical Centre Groningen, Groningen, The Netherlands. ²²⁷Department of Neurology, University of Lübeck, Lübeck, Germany. ²²⁸Institute for Paediatric Nutrition Medicine, Vestische Hospital for Children and Adolescents, University of Witten-Herdecke, Datteln, Germany. ²²⁹Department of Medicine III, Prevention and Care of Diabetes, University of Dresden, Dresden, Germany. ²³⁰Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, Maryland, USA. ²³¹Hjelt Institute, Department of Public Health, University of Helsinki, Helsinki, Finland. ²³²South Ostrobothnia Central Hospital, Seinajoki, Finland. ²³³Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, Lausanne, Switzerland. ²³⁴The Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, USA. ²³⁵Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA. ²³⁶Pacific Biosciences, Menlo Park, California, USA. ²³⁷Sage Bionetworks, Seattle, Washington, USA. ²³⁸Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA. ²³⁹Division of Intramural Research, National Heart, Lung, and Blood Institute, Framingham Heart Study, Framingham, Massachusetts, USA. ²⁴⁰Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, New York, USA. ²⁴¹Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. ²⁴²Department of Medical Genetics, University of Helsinki, Helsinki, Finland. ²⁴³Laboratory of Genetics, National Institute on Aging, Baltimore, Maryland, USA. ²⁴⁴Division of Community Health Sciences, St. George's, University of London, London, UK. ²⁴⁵Klinikum Grosshadern, Munich, Germany. ²⁴⁶Faculty of Medicine, University of Iceland, Reykjavík, Iceland. ²⁴⁷University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, Cambridge, UK. ²⁴⁸Carolina Center for Genome Sciences, School of Public Health, University of North Carolina Chapel Hill, Chapel Hill, North Carolina, USA. ²⁴⁹Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA.

Membership of the Wellcome Trust Case Control Consortium (WTCCC+)

Jan Aerts¹, Tariq Ahmad², Hazel Arbury¹, Anthony Attwood^{1,3,4}, Adam Auton⁵, Stephen G Ball⁶, Anthony J Balmforth⁶, Chris Barnes¹, Jeffrey C Barrett¹, Inês Barroso¹, Anne Barton⁷, Amanda J Bennett⁸, Sanjeev Bhaskar¹, Katarzyna Blaszczyk⁹, John Bowes⁷, Oliver J Brand^{8,10}, Peter S Braund¹¹, Francesca Bredin¹², Gerome Breen^{13,14}, Morris J Brown¹⁵, Ian N Bruce⁷, Jaswinder Bull¹⁶, Oliver S Burren¹⁷, John Burton¹, Jake Byrnes¹⁸, Sian Caesar¹⁹, Niall Cardin⁵, Chris M Clee¹, Alison J Coffey¹, John MC Connell²⁰, Donald F Conrad¹, Jason D Cooper¹⁷, Anna F Dominiczak²⁰, Kate Downes¹⁷, Hazel E Drummond²¹, Darshna Dudakia¹⁶, Andrew Dunham¹, Bernadette Ebbs¹⁶, Diana Eccles²², Sarah Edkins¹, Cathryn Edwards²³, Anna Elliot¹⁶, Paul Emery²⁴, David M Evans²⁵, Gareth Evans²⁶, Steve Eyre⁷, Anne Farmer¹⁴, I Nicol Ferrier²⁷, Edward Flynn⁷, Alistair Forbes²⁸, Liz Forty²⁹, Jayne A Franklyn^{10,30}, Timothy M Frayling², Rachel M Freathy², Eleni Giannoulidou⁵, Polly Gibbs¹⁶, Paul Gilbert⁷, Katherine Gordon-Smith^{19,29}, Emma Gray¹, Elaine Green²⁹, Chris J Groves⁸, Detelina Grozeva²⁹, Rhian Gwilliam¹, Anita Hall¹⁶, Naomi Hammond¹, Matt Hardy¹⁷, Pile Harrison³¹, Neelam Hassanali⁸, Husam Hebaishi¹, Sarah Hines¹⁶, Anne Hinks⁷, Graham A Hitman³², Lynne Hocking³³, Chris Holmes⁵, Eleanor Howard¹, Philip Howard³⁴, Joanna MM Howson¹⁷, Debbie Hughes¹⁶, Sarah Hunt¹, John D Isaacs³⁵, Mahim Jain¹⁸, Derek P Jewell³⁶, Toby Johnson³⁴, Jennifer D Jolley^{3,4}, Ian R Jones²⁹, Lisa A Jones¹⁹, George Kirov²⁹, Cordelia F Langford¹, Hana Lango-Allen², G Mark Lathrop³⁷, James Lee¹², Kate L Lee³⁴, Charlie Lees²¹, Kevin Lewis¹, Cecilia M Lindgren^{8,18}, Meeta Maisuria-Armer¹⁷, Julian Maller¹⁸, John Mansfield³⁸, Jonathan L Marchini⁵, Paul Martin⁷, Dunecan CO Massey¹², Wendy L McArdle³⁹, Peter McGuffin¹⁴, Kirsten E McLay¹, Gil McVean^{5,18}, Alex Mentzer⁴⁰, Michael L Mimmack¹, Ann E Morgan⁴¹, Andrew P Morris¹⁸, Craig Mowat⁴², Patricia B Munroe³⁴, Simon Myers¹⁸, William Newman²⁶, Elaine R Nimmo²¹, Michael C O'Donovan²⁹, Abiodun Onipinla³⁴, Nigel R Ovington¹⁷, Michael J Owen²⁹, Kimmo Palin¹, Aarno Palotie¹, Kirstie Parnell², Richard Pearson⁸, David Pernet¹⁶, John RB Perry^{2,18}, Anne Phillips⁴², Vincent Plagnol¹⁷, Natalie J Prescott⁹, Inga Prokopenko^{8,18}, Michael A Quail¹, Suzanne Rafelt¹¹, Nigel W Rayner^{8,18}, David M Reid³³, Anthony Renwick¹⁶, Susan M Ring³⁹, Neil Robertson^{8,18}, Samuel Robson¹, Ellie Russell²⁹, David St Clair¹³, Jennifer G Sambrook^{3,4}, Jeremy D Sanderson⁴⁰, Stephen J Sawcer⁴³, Helen Schuilenburg¹⁷, Carol E Scott¹, Richard Scott¹⁶, Sheila Seal¹⁶, Sue Shaw-Hawkins³⁴, Beverley M Shields², Matthew J Simmonds^{8,10}, Debbie J Smyth¹⁷, Elilan Somaskantharajah¹, Katarina Spanova¹⁶, Sophia Steer⁴⁴, Jonathan Stephens^{3,4}, Helen E Stevens¹⁷, Kathy Stirrups¹, Millicent A Stone^{45,46}, David P Strachan⁴⁷, Zhan Su⁵, Deborah PM Symmons⁷, John R Thompson⁴⁸, Wendy Thomson⁷, Martin D Tobin⁴⁸, Mary E Travers⁸, Clare Turnbull¹⁶, Damjan Vukcevic¹⁸, Louise V Wain⁴⁸, Mark Walker⁴⁹, Neil M Walker¹⁷, Chris Wallace¹⁷, Margaret Warren-Perry¹⁶, Nicholas A Watkins^{3,4}, John Webster⁵⁰, Michael N Weedon², Anthony G Wilson⁵¹, Matthew Woodburn¹⁷, B Paul Wordsworth⁵², Chris Yau⁵, Allan H Young^{27,53}, Eleftheria Zeggini¹, Matthew A Brown^{52,54}, Paul R Burton⁴⁸, Mark J Caulfield³⁴, Alastair Compston⁴³, Martin Farrall⁵⁵, Stephen CL Gough^{8,10,30}, Alistair S Hall⁶, Andrew T Hattersley^{2,56}, Adrian VS Hill¹⁸, Christopher G Mathew⁹, Marcus Pembrey⁵⁷, Jack Satsangi²¹, Michael R Stratton^{1,16}, Jane Worthington⁷, Matthew E Hurles¹, Audrey Duncanson⁵⁸, Willem H Ouwehand^{1,3,4}, Miles Parkes¹², Nazneen Rahman¹⁶, John A Todd¹⁷, Nilesh J Samani^{11,59}, Dominic P Kwiatkowski^{1,18}, Mark I McCarthy^{8,18,60}, Nick Craddock²⁹, Panos Deloukas¹, Peter Donnelly^{5,18}.

¹The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SA UK.

²Genetics of Complex Traits, Peninsula College of Medicine and Dentistry University of Exeter, EX1 2LU, UK.

³Department of Haematology, University of Cambridge, Long Road, Cambridge, CB2 0PT, UK. ⁴National Health

Service Blood and Transplant, Cambridge Centre, Long Road, Cambridge CB2 0PT, UK. ⁵Department of Statistics, University of Oxford, 1 South Parks Road, Oxford, OX1 3TG, UK. ⁶Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds, LS2 9JT, UK. ⁷arc Epidemiology Unit, Stopford Building, University of Manchester, Oxford Road, Manchester, M13 9PT, UK. ⁸Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK. ⁹Department of Medical and Molecular Genetics, King's College London School of Medicine, 8th Floor Guy's Tower, Guy's Hospital, London, SE1 9RT, UK. ¹⁰Centre for Endocrinology, Diabetes and Metabolism, Institute of Biomedical Research, University of Birmingham, Birmingham, B15 2TT, UK. ¹¹Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. ¹²IBD Genetics Research Group, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK. ¹³University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen AB25 2ZD, UK. ¹⁴SGDP, The Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK. ¹⁵Clinical Pharmacology Unit, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK. ¹⁶Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton SM2 5NG, UK. ¹⁷Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge CB2 0XY, UK. ¹⁸The Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK. ¹⁹Department of Psychiatry, University of Birmingham, National Centre for Mental Health, 25 Vincent Drive, Birmingham, B15 2FG, UK. ²⁰BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK. ²¹Gastrointestinal Unit, Division of Medical Sciences, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK. ²²Academic Unit of Genetic Medicine, University of Southampton, Southampton, UK. ²³Endoscopy Regional Training Unit, Torbay Hospital, Torbay TQ2 7AA, UK. ²⁴Academic Unit of Musculoskeletal Disease, University of Leeds, Chapel Allerton Hospital, Leeds, West Yorkshire LS7 4SA, UK. ²⁵MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, University of Bristol, Bristol, BS8 2BN, UK. ²⁶Department of Medical Genetics, Manchester Academic Health Science Centre (MAHSC), University of Manchester, Manchester M13 0JH, UK. ²⁷School of Neurology, Neurobiology and Psychiatry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK. ²⁸Institute for Digestive Diseases, University College London Hospitals Trust, London NW1 2BU, UK. ²⁹MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK. ³⁰University Hospital Birmingham NHS Foundation Trust, Birmingham, B15 2TT, UK. ³¹University of Oxford, Institute of Musculoskeletal Sciences, Botnar Research Centre, Oxford, OX3 7LD, UK. ³²Centre for Diabetes and Metabolic Medicine, Barts and The London, Royal London Hospital, Whitechapel, London, E1 1BB, UK. ³³Bone Research Group, Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, AB25 2ZD, UK. ³⁴Clinical 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. ³⁵Institute of Cellular Medicine, Musculoskeletal Research Group, 4th Floor, Catherine Cookson Building, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK. ³⁶Gastroenterology Unit, Radcliffe Infirmary, University of Oxford, Oxford, OX2 6HE, UK. ³⁷Centre National de Genotypage, 2, Rue Gaston Cremieux, Evry, Paris 91057, France. ³⁸Department of Gastroenterology & Hepatology, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK. ³⁹ALSPAC Laboratory, Department of Social Medicine, University of Bristol, BS8 2BN, UK. ⁴⁰Division of Nutritional Sciences, King's College London School of Biomedical and Health Sciences, London SE1 9NH, UK. ⁴¹NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Chapel Allerton Hospital, Leeds, West Yorkshire LS7 4SA, UK. ⁴²Department of General Internal Medicine, Ninewells Hospital and Medical School, Ninewells Avenue, Dundee DD1 9SY, UK. ⁴³Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK. ⁴⁴Clinical and Academic Rheumatology, Kings College Hospital National Health Service Foundation Trust, Denmark Hill, London SE5 9RS, UK. ⁴⁵University of Toronto, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada. ⁴⁶University of Bath, Claverdon, Norwood House, Room 5.11a Bath Somerset BA2 7AY, UK. ⁴⁷Division of Community Health Sciences, St George's, University of London, London SW17 0RE, UK. ⁴⁸Departments of Health Sciences and Genetics, University of Leicester, 217 Adrian Building, University Road, Leicester, LE1 7RH, UK. ⁴⁹Diabetes Research Group, School of Clinical Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK. ⁵⁰Medicine and Therapeutics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Grampian AB9 2ZB, UK. ⁵¹School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, S10 2JF, UK. ⁵²Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Nuffield Orthopaedic Centre, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LD, UK. ⁵³UBC Institute of Mental Health, 430-5950 University Boulevard

Vancouver, British Columbia, V6T 1Z3, Canada. ⁵⁴Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Ipswich Road, Woolloongabba, Brisbane, Queensland, 4102, Australia. ⁵⁵Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK. ⁵⁶Genetics of Diabetes, Peninsula College of Medicine and Dentistry, University of Exeter, Barrack Road, Exeter, EX2 5DW, UK. ⁵⁷Clinical and Molecular Genetics Unit, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK. ⁵⁸The Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK. ⁵⁹Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK. ⁶⁰Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LJ, UK.

Membership of the AGEN-T2D Consortium

Yoon Shin Cho^{1,2}, Chien-Hsiun Chen^{3,4}, Cheng Hu⁵, Jirong Long⁶, Rick Twee Hee Ong⁷, Xueling Sim⁸, Fumihiko Takeuchi⁹, Ying Wu¹⁰, Min Jin Go¹, Toshimasa Yamauchi¹¹, Yi-Cheng Chang¹², Soo Heon Kwak¹³, Ronald C W Ma¹⁴, Ken Yamamoto¹⁵, Linda S Adair¹⁶, Tin Aung^{17,18}, Qiuyin Cai⁶, Li-Ching Chang³, Yuan-Tsong Chen³, Yutang Gao¹⁹, Frank B Hu²⁰, Hyung-Lae Kim^{1,21}, Sangsoo Kim²², Young Jin Kim¹, Jeannette Jen-Mai Lee²³, Nanette R Lee²⁴, Yun Li^{10,25}, Jian Jun Liu²⁶, Wei Lu²⁷, Jiro Nakamura²⁸, Eitaro Nakashima^{28,29}, Daniel Peng-Keat Ng²³, Wan Ting Tay¹⁷, Fuu-Jen Tsai⁴, Tien Yin Wong^{17,18,30}, Mitsuhiro Yokota³¹, Wei Zheng⁶, Rong Zhang⁵, Congrong Wang⁵, Wing Yee So¹⁴, Keizo Ohnaka³², Hiroshi Ikegami³³, Kazuo Hara¹¹, Young Min Cho¹³, Nam H Cho³⁴, Tien-Jyun Chang¹², Yuqian Bao⁵, Ryoichi Takayanagi³², Kyong Soo Park^{13,35}, Weiping Jia⁵, Lee-Ming Chuang^{12,36}, Juliana C N Chan¹⁴, Shiro Maeda³⁷, Takashi Kadowaki¹¹, Jong-Young Lee¹, Jer-Yuarn Wu^{3,4}, Yik Ying Teo^{7,8,23,26,38}, E Shyong Tai^{23,39,40}, Xiao Ou Shu⁶, Karen L Mohlke¹⁰, Norihiro Kato⁹, Bok-Ghee Han¹, Mark Seielstad^{26,41,42}

¹Center for Genome Science, National Institute of Health, Osong Health Technology Administration Complex, Chungcheongbuk-do, Cheongwon-gun, Gangoe-myeon, Yeonje-ri, Republic of Korea. ²Department of Biomedical Science, Hallym University, 1 Hallymdaehak-gil, Chuncheon, Gangwon-do, 200-702, Republic of Korea. ³Institute of Biomedical Sciences, Academia Sinica, Nankang, Taipei, Taiwan. ⁴School of Chinese Medicine, China Medical University, Taichung, Taiwan. ⁵Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. ⁶Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, USA. ⁷Graduate School for Integrative Science and Engineering, National University of Singapore, Singapore, Singapore. ⁸Centre for Molecular Epidemiology, National University of Singapore, Singapore, Singapore. ⁹Research Institute, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo, Japan. ¹⁰Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. ¹¹Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. ¹²Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. ¹³Department of Internal Medicine, Seoul National University College of Medicine, Jongno-Gu, Seoul, Republic of Korea. ¹⁴Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China. ¹⁵Division of Genome Analysis, Research Center for Genetic Information, Medical Institute of Bioregulation, Kyushu University, Higashi-ku, Fukuoka, Japan. ¹⁶Department of Nutrition, University of North Carolina, Chapel Hill, North Carolina, USA. ¹⁷Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore. ¹⁸Department of Ophthalmology, National University of Singapore, Singapore, Singapore. ¹⁹Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China. ²⁰Department of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA. ²¹Department of Biochemistry, School of Medicine, Ewha Womans University, Seoul, Republic of Korea. ²²School of Systems Biomedical Science, Soongsil University, Dongjak-gu, Seoul, Republic of Korea. ²³Department of Epidemiology and Public Health, National University of Singapore, Singapore, Singapore. ²⁴Office of Population Studies Foundation Inc., University of San Carlos, Cebu City, Philippines. ²⁵Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, USA. ²⁶Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, Singapore. ²⁷Shanghai Institute of Preventive Medicine, Shanghai, China. ²⁸Division of Endocrinology and Diabetes, Department of Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan. ²⁹Department of Diabetes and Endocrinology, Chubu Rosai Hospital, Nagoya, Japan. ³⁰Centre for Eye Research Australia, University of Melbourne, East Melbourne, Victoria, Australia. ³¹Department of Genome Science, Aichi-Gakuin University, School of Dentistry, Nagoya, Japan. ³²Department of Geriatric Medicine, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan. ³³Department of Endocrinology, Metabolism and Diabetes, Kinki University School of Medicine, Osaka-sayama, Osaka, Japan. ³⁴Department of Preventive Medicine, Ajou University School of Medicine, Suwon, Republic of Korea. ³⁵World Class University Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine, Seoul National University, Jongno-Gu, Seoul, Republic of Korea. ³⁶Graduate Institute of Clinical Medicine, National Taiwan University School of Medicine, Taipei, Taiwan. ³⁷Laboratory for Endocrinology and Metabolism, RIKEN Center for

Genomic Medicine, Yokohama, Japan. ³⁸Department of Statistics and Applied Probability, National University of Singapore, Singapore, Singapore. ³⁹Department of Medicine, National University of Singapore, Singapore, Singapore. ⁴⁰Duke-National University of Singapore Graduate Medical School, Singapore, Singapore. ⁴¹Institute for Human Genetics, University of California, San Francisco, California, USA. ⁴²Blood Systems Research Institute, San Francisco, California, USA.

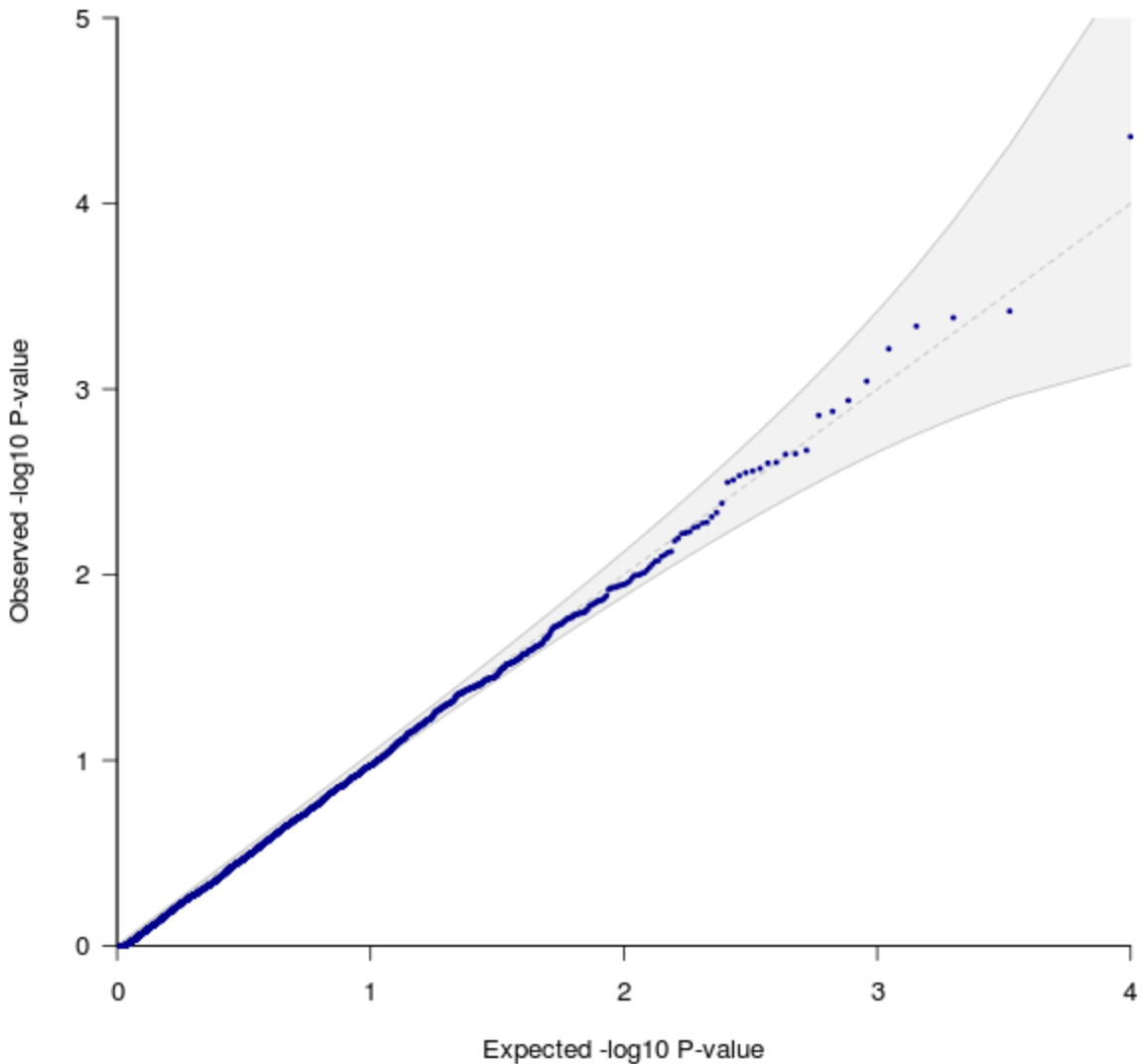
Membership of the SAT2D Consortium

Jaspal S Kooner^{1,2,3}, Danish Saleheen^{4,5}, Xueling Sim⁶, Joban Sehmi^{1,2}, Weihua Zhang⁷, Philippe Frossard⁴, Latonya F Been⁸, Kee-Seng Chia^{6,9}, Antigone S Dimas^{10,11}, Neelam Hassanali¹², Tazeen Jafar^{13,14}, Jeremy B M Jowett¹⁵, Xinzhong Li¹, Venkatesan Radha¹⁶, Simon D Rees^{17,18}, Fumihiko Takeuchi¹⁹, Robin Young⁵, Tin Aung^{20,21}, Abdul Basit²², Manickam Chidambaram¹⁶, Debashish Das², Elin Grundberg²³, Åsa K Hedman¹¹, Zafar I Hydrie²², Muhammed Islam¹³, Chiea-Chuen Khor^{6,21,24}, Sudhir Kowlessur²⁵, Malene M Kristensen¹⁵, Samuel Liju¹⁶, Wei-Yen Lim⁶, David R Matthews¹², Jianjun Liu²⁴, Andrew P Morris¹¹, Alexandra C Nica¹⁰, Janani M Pinidiyapathirage²⁶, Inga Prokopenko¹¹, Asif Rasheed⁴, Maria Samuel⁴, Nabi Shah⁴, A Samad Shera²⁷, Kerrin S Small^{23,28}, Chen Suo⁶, Ananda R Wickremasinghe²⁶, Tien Yin Wong^{20,21,29}, Mingyu Yang³⁰, Fan Zhang³⁰, Goncalo R Abecasis³², Anthony H Barnett^{17,18}, Mark Caulfield³³, Panos Deloukas³⁴, Timothy M Frayling³⁵, Philippe Froguel³⁶, Norihiro Kato¹⁹, Prasad Katulanda^{12,37}, M Ann Kelly^{17,18}, Junbin Liang³⁰, Viswanathan Mohan^{16,38}, Dharambir K Sanghera⁸, James Scott¹, Mark Seielstad³⁹, Paul Z Zimmet¹⁵, Paul Elliott^{7,40,46}, Yik Ying Teo^{6,9,24,41,42}, Mark I McCarthy^{11,12,43}, John Danesh⁵, E Shyong Tai^{9,44,45} & John C Chambers^{2,3,7}

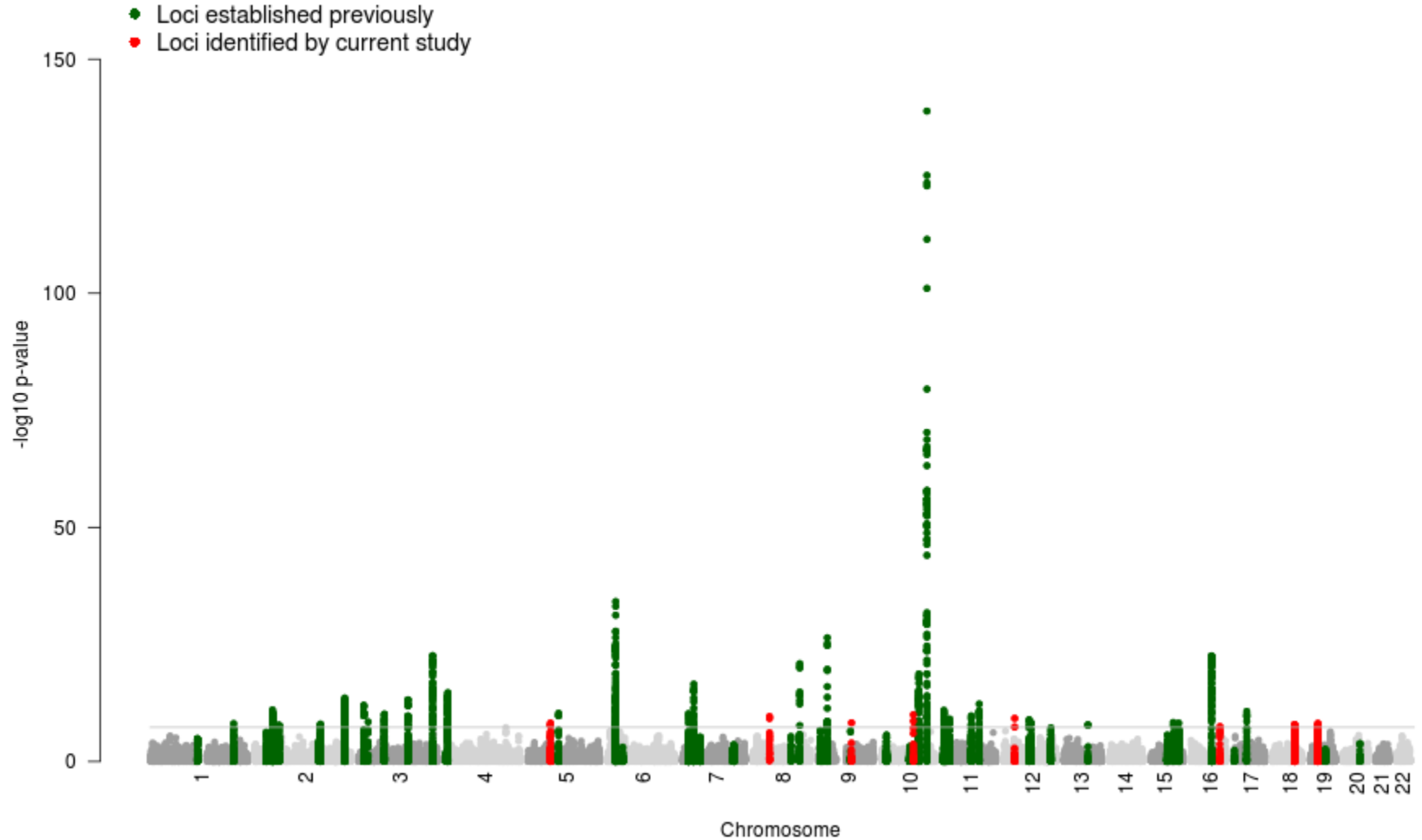
¹National Heart and Lung Institute (NHLI), Imperial College London, Hammersmith Hospital, London, UK. ²Ealing Hospital National Health Service (NHS) Trust, Middlesex, UK. ³Imperial College Healthcare NHS Trust, London, UK. ⁴Center for Non-Communicable Diseases Pakistan, Karachi, Pakistan. ⁵Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ⁶Centre for Molecular Epidemiology, National University of Singapore, Singapore. ⁷Epidemiology and Biostatistics, Imperial College London, London, UK. ⁸Department of Pediatrics, Section of Genetics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA. ⁹Department of Epidemiology and Public Health, National University of Singapore, Singapore. ¹⁰Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva, Switzerland. ¹¹Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. ¹²Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Churchill Hospital, Oxford, UK. ¹³Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan. ¹⁴Department of Medicine, Aga Khan University, Karachi, Pakistan. ¹⁵Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia. ¹⁶Department of Molecular Genetics, Madras Diabetes Research Foundation–Indian Council of Medical Research (ICMR) Advanced Centre for Genomics of Diabetes, Chennai, India. ¹⁷College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK. ¹⁸BioMedical Research Centre, Heart of England NHS Foundation Trust, Birmingham, UK. ¹⁹Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan. ²⁰Department of Ophthalmology, National University of Singapore, Singapore. ²¹Singapore Eye Research Institute, Singapore National Eye Centre, Singapore. ²²Baqai Institute of Diabetology and Endocrinology, Karachi, Pakistan. ²³Department of Twin Research and Genetic Epidemiology, King’s College London, London, UK. ²⁴Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore. ²⁵Ministry of Health, Port Louis, Mauritius. ²⁶Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka. ²⁷Diabetic Association Pakistan, Karachi, Pakistan. ²⁸Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, UK. ²⁹Center for Eye Research Australia, University of Melbourne, Melbourne, Victoria, Australia. ³⁰Beijing Genomics Institute, Shenzhen, China. ³²Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA. ³³Clinical Pharmacology and Barts and the London Genome Centre, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK. ³⁴Human Genetics, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, UK. ³⁵Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, Exeter, UK. ³⁶Genomics of Common Diseases, School of Public Health, Imperial College London, Hammersmith Hospital, London, UK. ³⁷Diabetes Research Unit, Department of Clinical Medicine, University of Colombo, Colombo, Sri Lanka. ³⁸Dr Mohan’s Diabetes Specialties Centre, Chennai, India. ³⁹Institute of Human Genetics, University of California, San Francisco, California, USA. ⁴⁰Medical Research Council (MRC)-Health Protection Agency (HPA) Centre for Environment and Health, Imperial College London, London, UK. ⁴¹Department of Statistics and

Applied Probability, National University of Singapore, Singapore. ⁴²National University of Singapore Graduate School for Integrative Science and Engineering, National University of Singapore, Singapore. ⁴³Oxford National Institute for Health Research (NIHR) Biomedical Research Centre, Churchill Hospital, Oxford, UK. ⁴⁴Department of Medicine, National University of Singapore, Singapore. ⁴⁵Duke-National University of Singapore Graduate Medical School, Singapore.

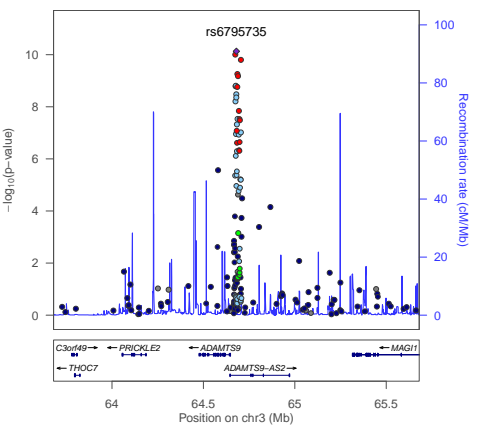
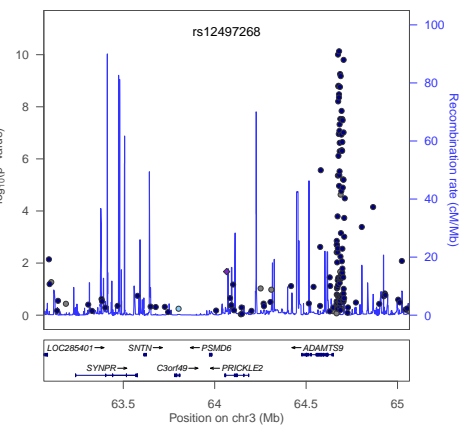
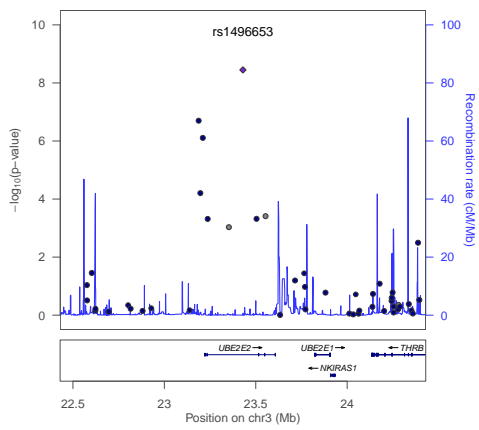
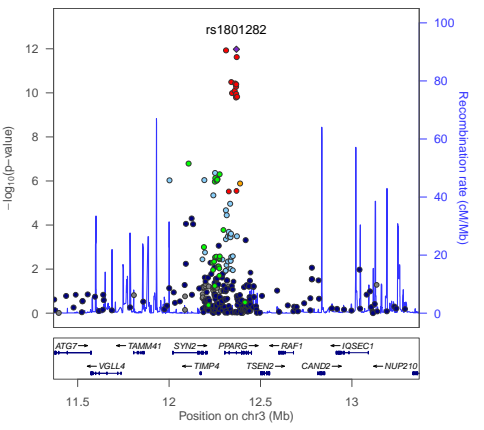
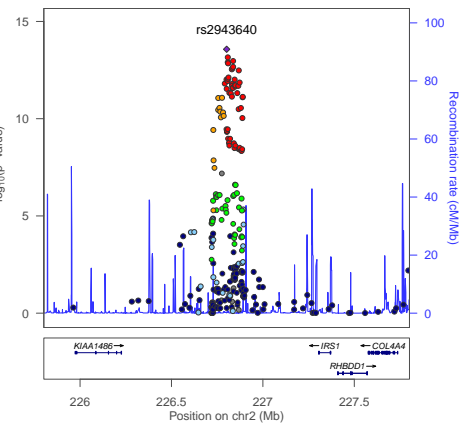
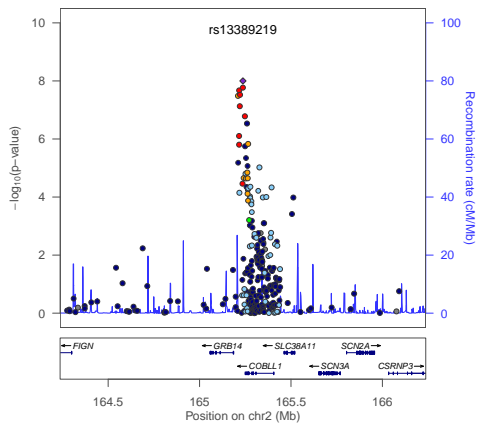
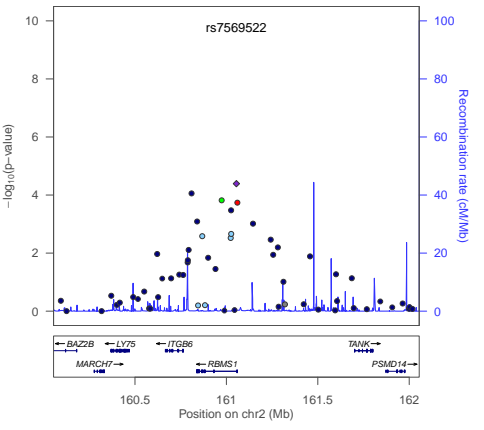
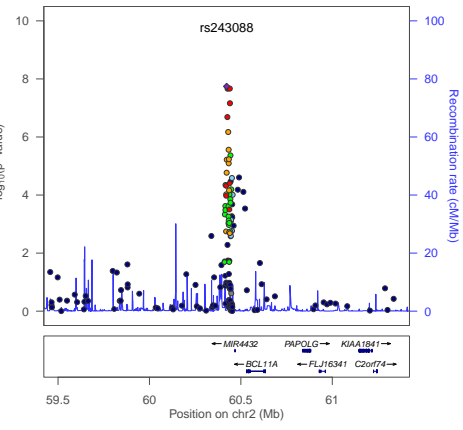
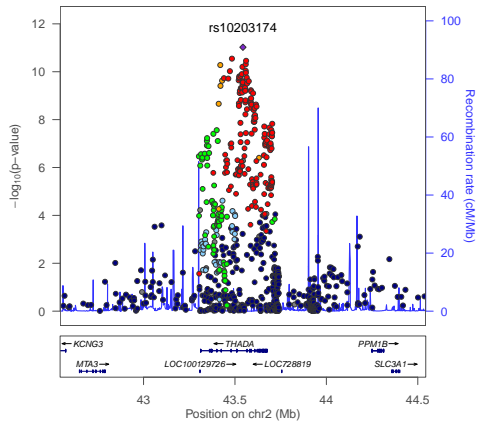
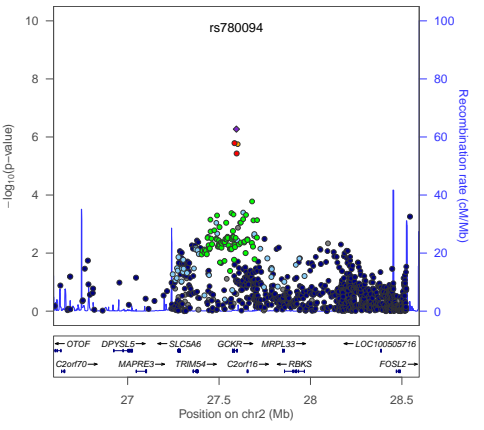
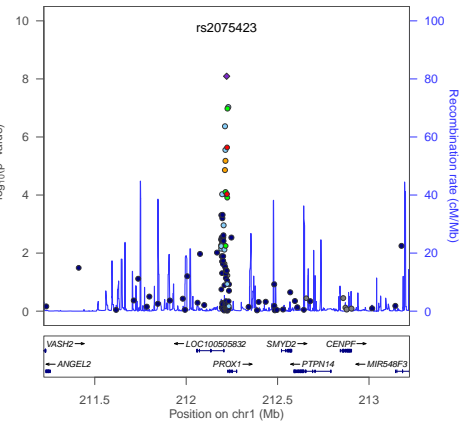
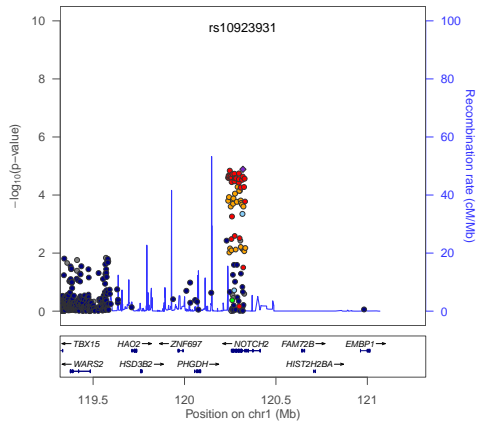
Supplementary Figure 1. QQ-plot for heterogeneity in allelic odds ratios between Stage 2 European descent meta-analysis and PROMIS. Each point represents a MetaboChip SNP passing quality control in the Stage 2 meta-analysis. The y-axis corresponds to the observed \log_{10} p-value from Cochran's Q-statistic of heterogeneity. The x-axis corresponds to the corresponding expected \log_{10} p-value under the null hypothesis of no heterogeneity in allelic odds ratios between the Stage 2 European meta-analysis and PROMIS. The grey funnel represents 95% confidence limits for the expected p-values.

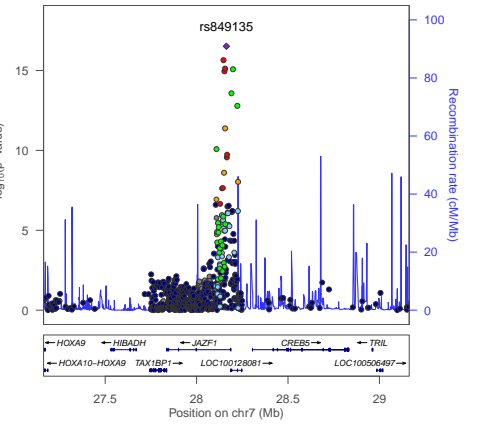
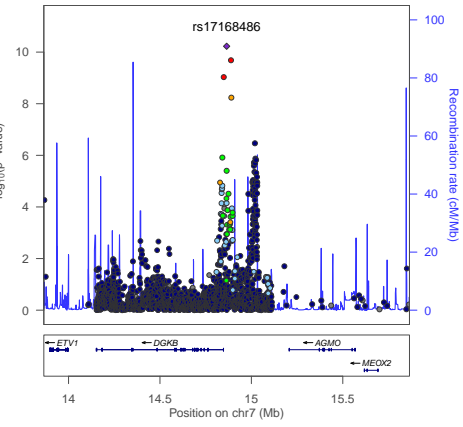
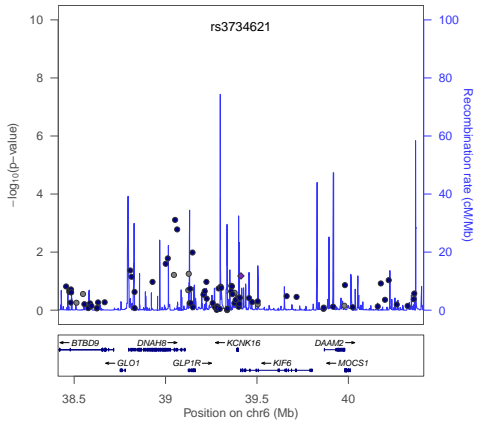
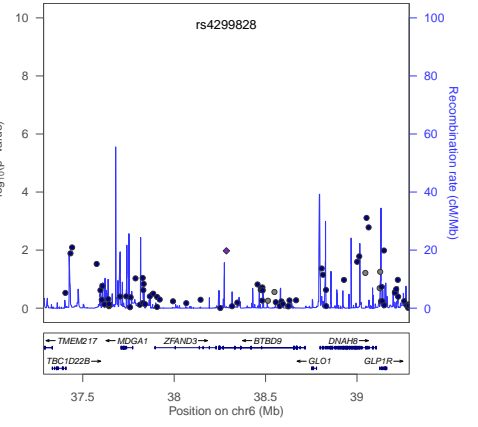
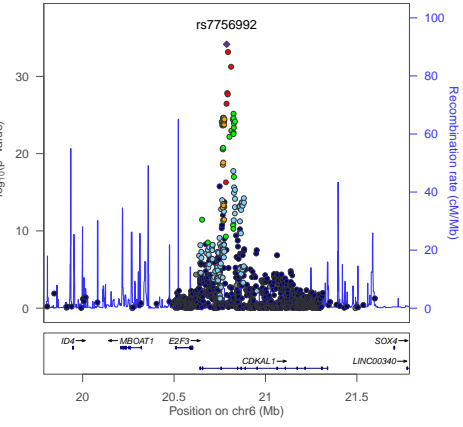
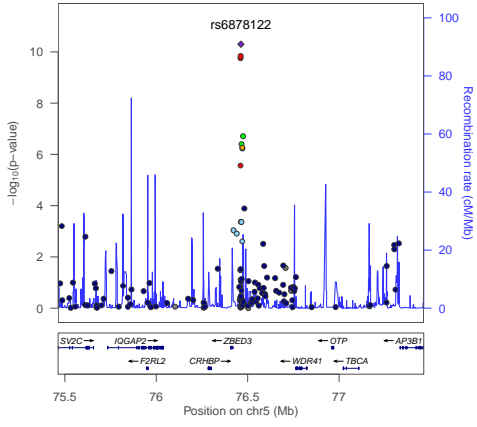
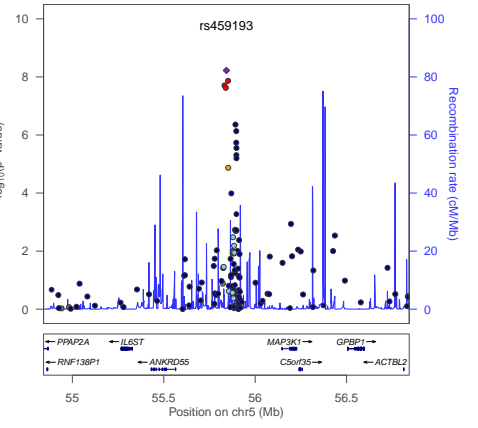
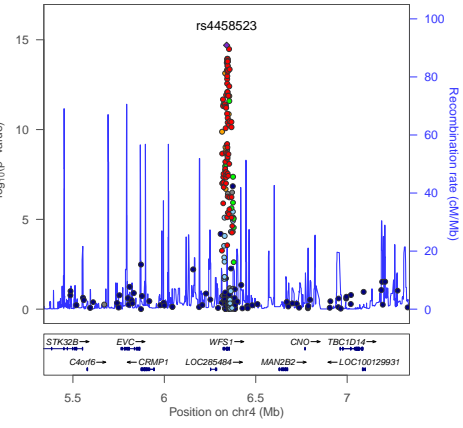
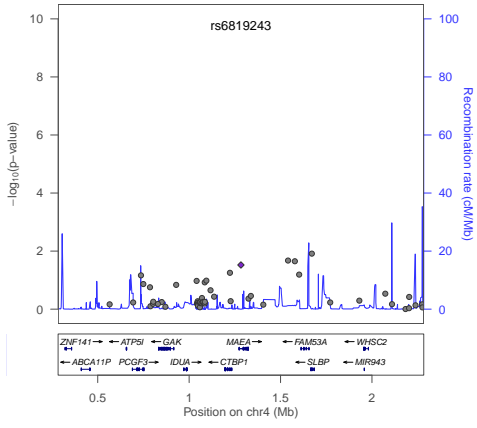
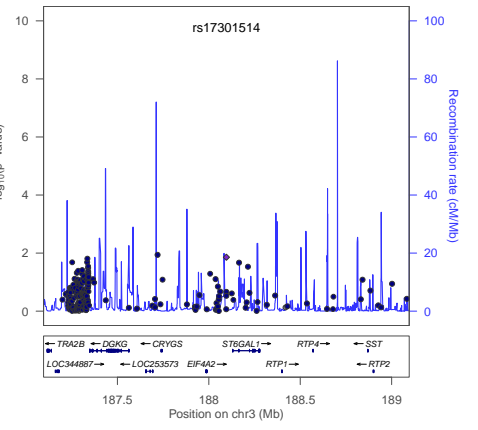
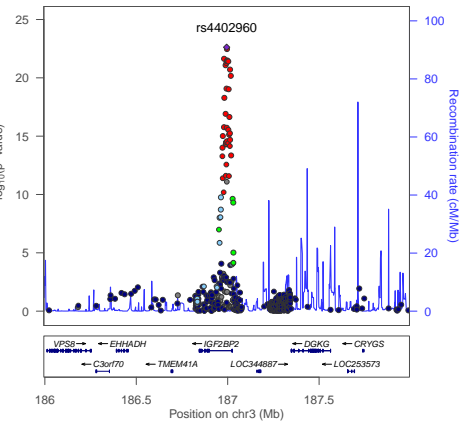
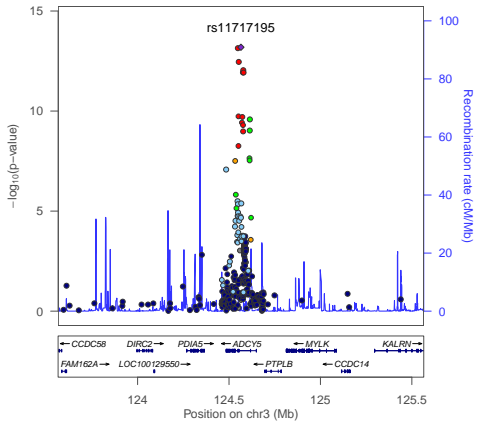


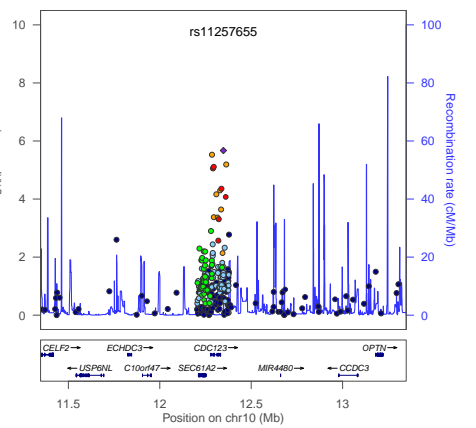
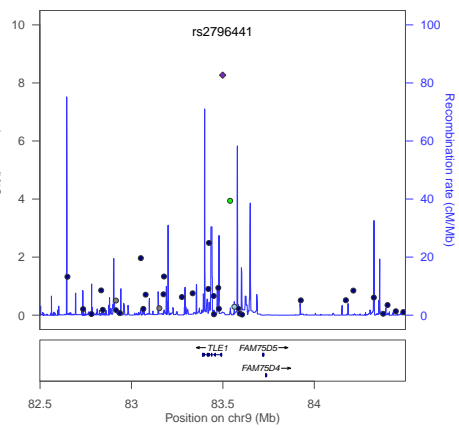
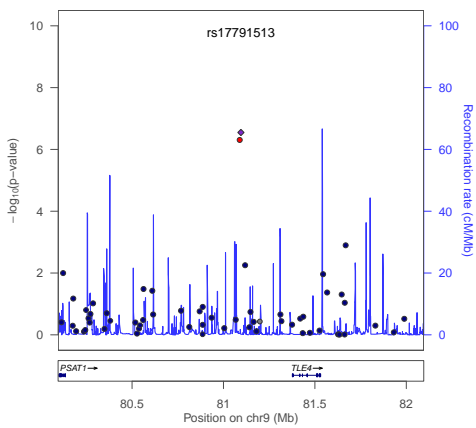
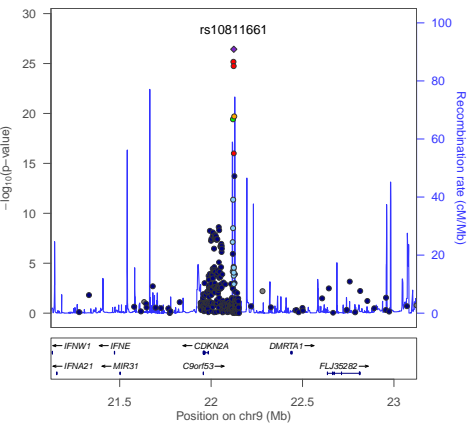
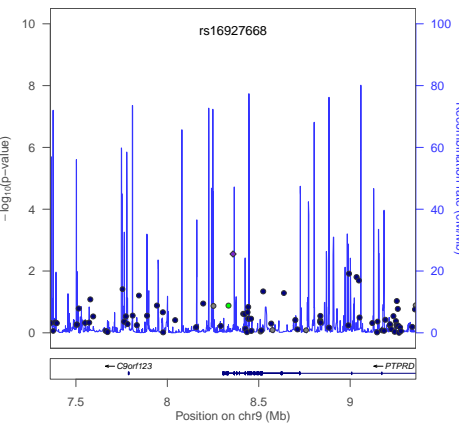
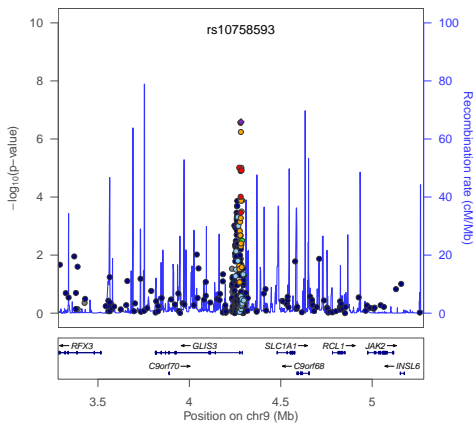
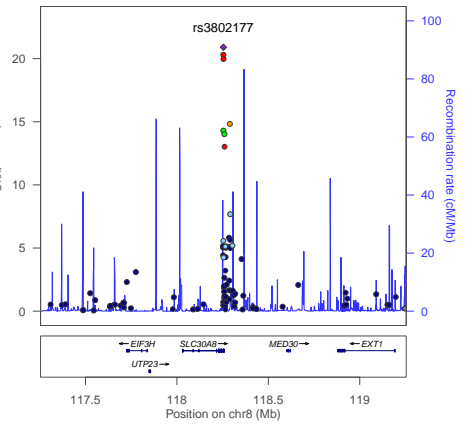
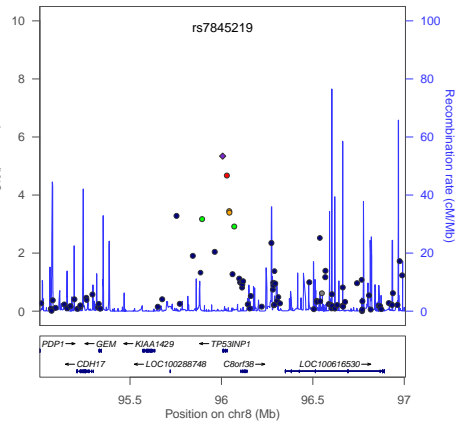
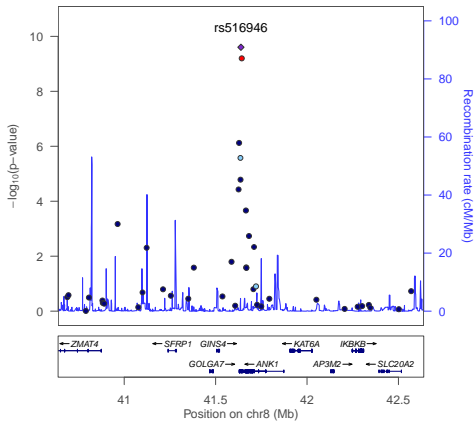
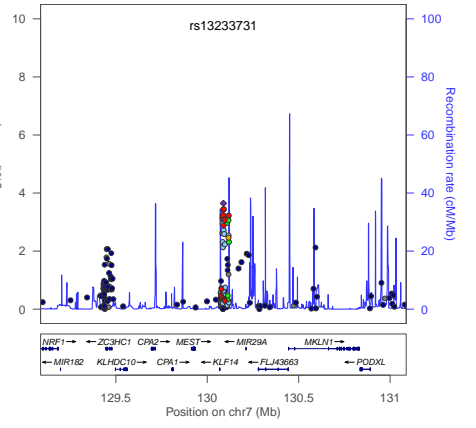
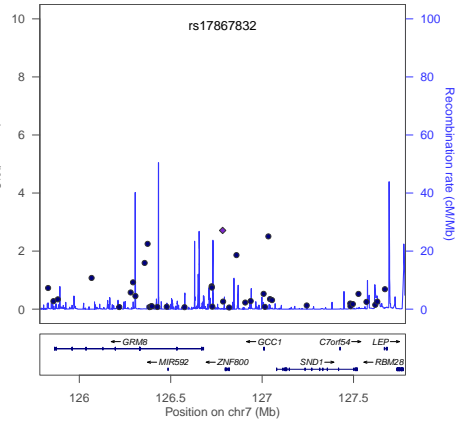
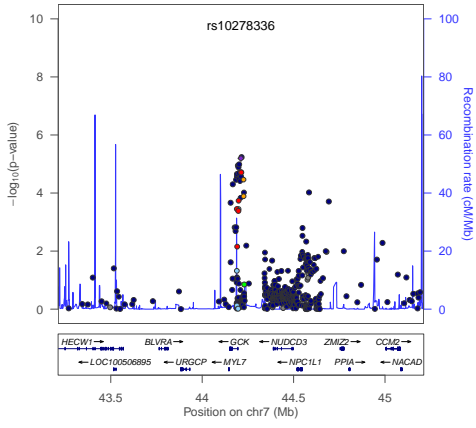
Supplementary Figure 2. Manhattan plot for the combined meta-analysis. Previously established loci are highlighted in green. Novel loci achieving genome-wide significance in the present study are highlighted in red.

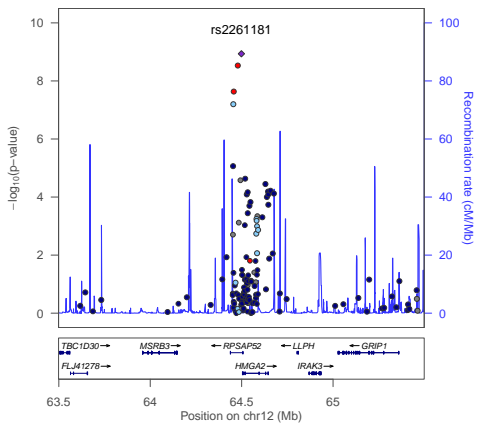
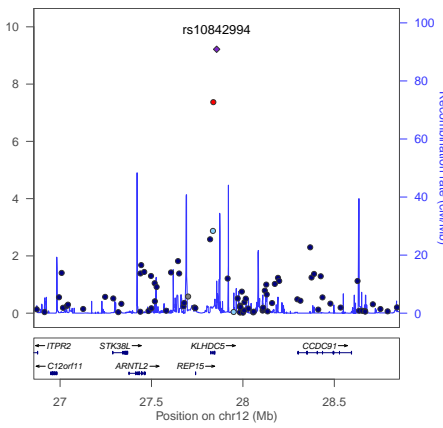
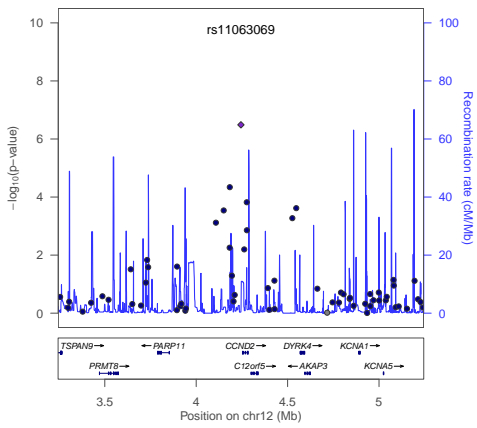
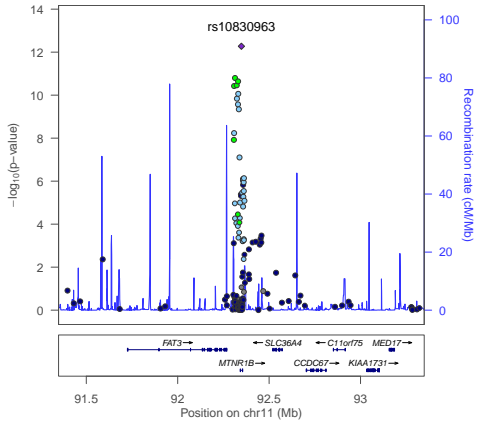
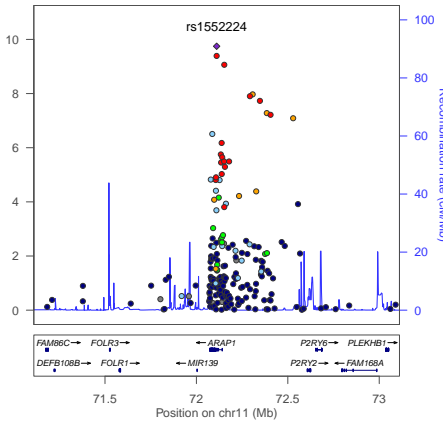
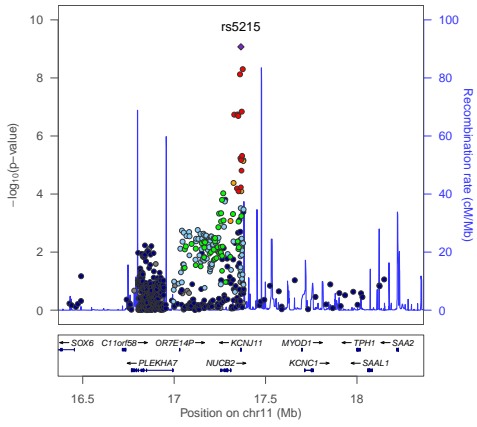
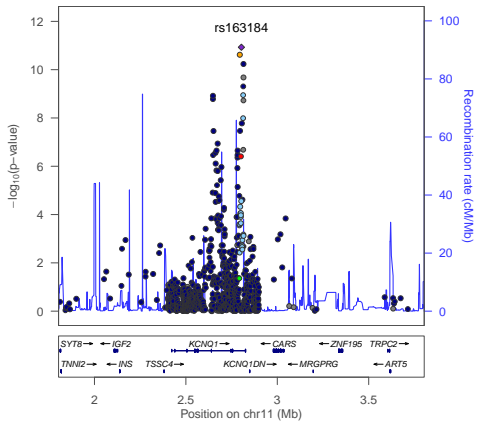
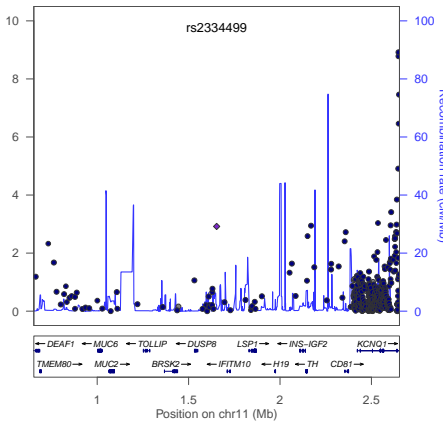
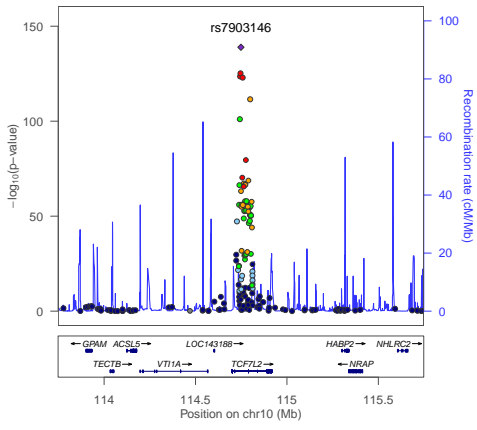
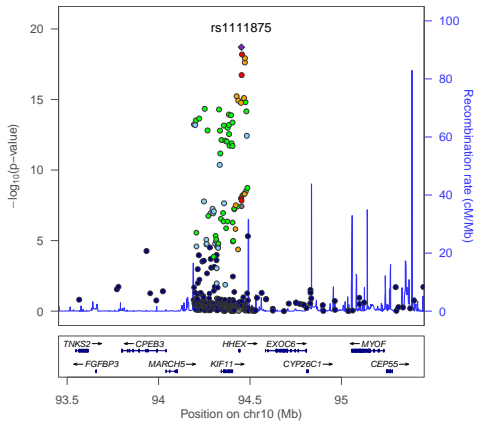
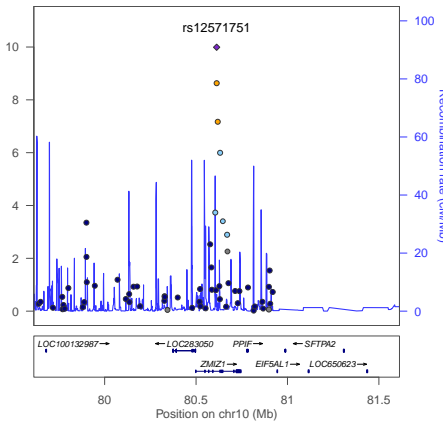
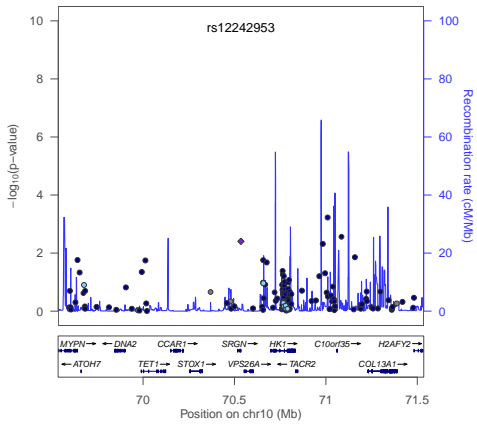


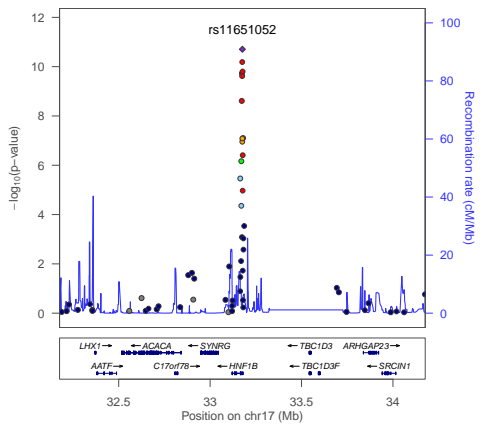
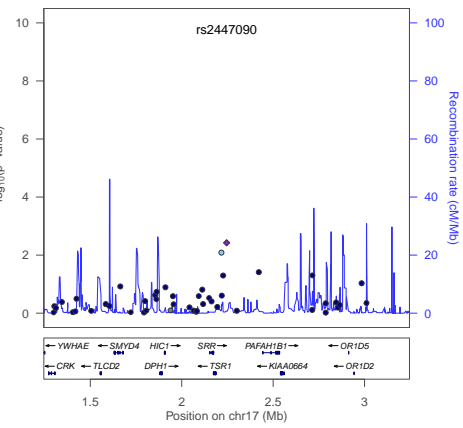
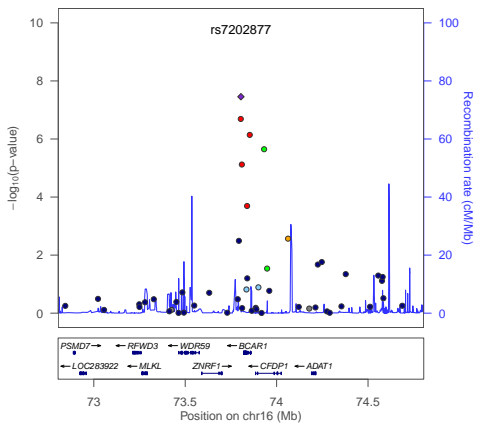
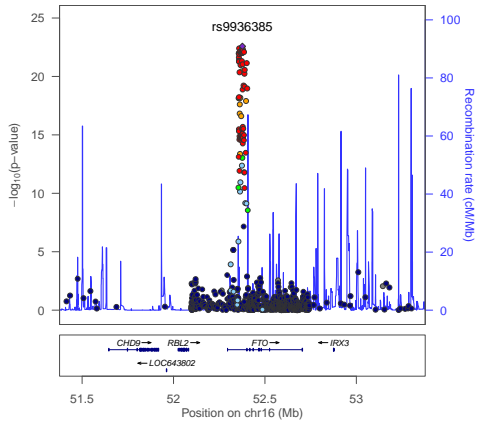
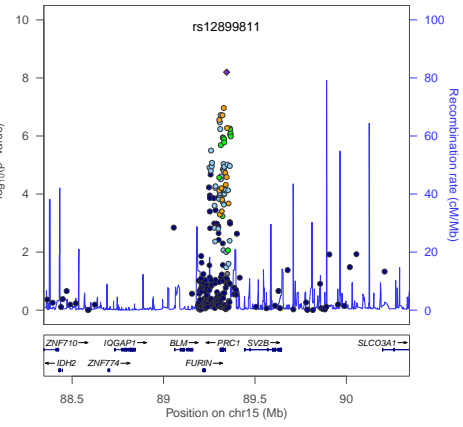
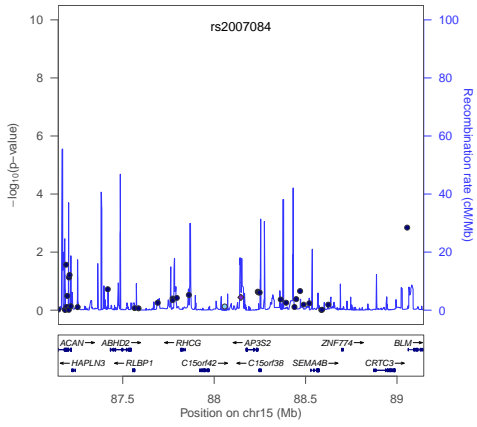
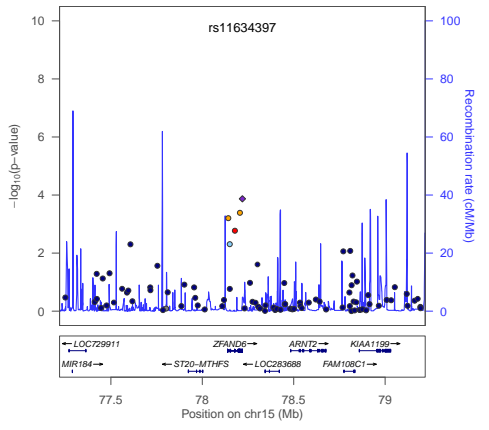
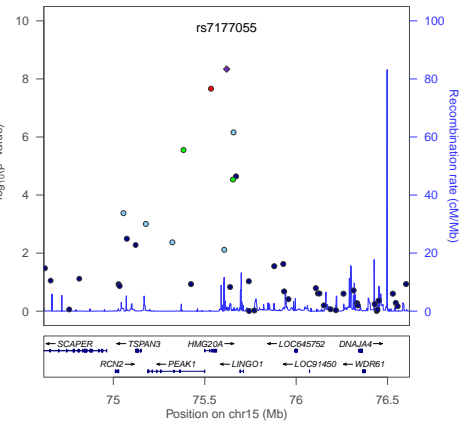
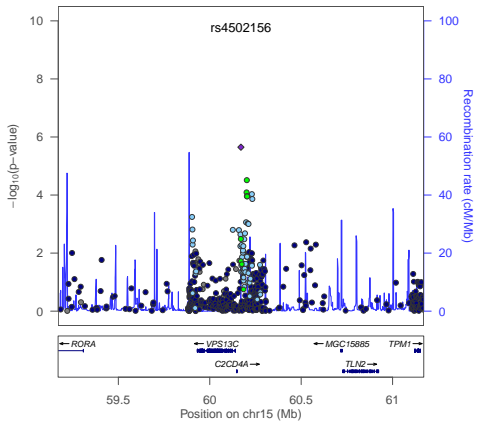
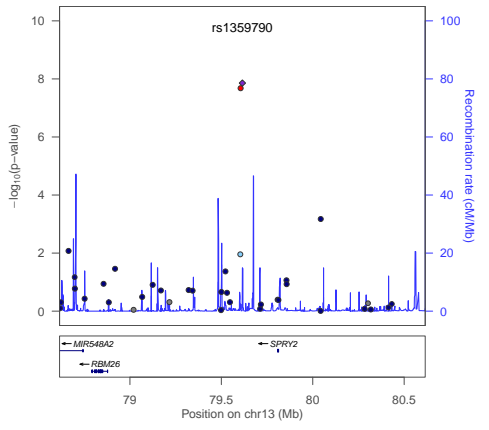
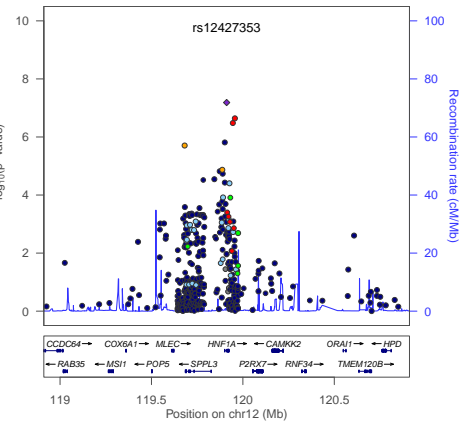
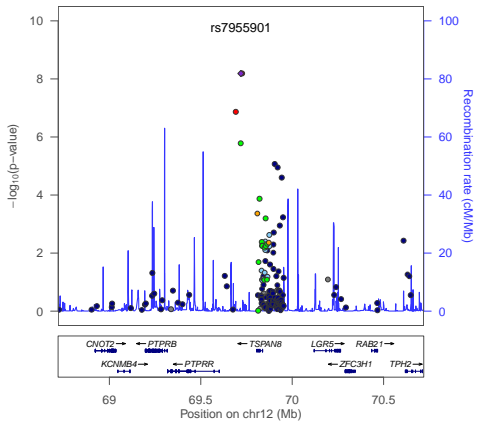
Supplementary Figure 3. Regional plots of novel and established T2D susceptibility loci. Each point represents a Metabochip SNP passing quality control in our combined meta-analysis, plotted with their p-value (on a $-\log_{10}$ scale) as a function of genomic position (NCBI Build 36). In each panel, the lead SNP is represented by the purple diamond. The colour coding of all other SNPs (circles) indicates LD with the lead SNP (estimated by CEU r^2 from the 1000 Genomes Project June 2010 release): red $r^2 \geq 0.8$; gold $0.6 \leq r^2 < 0.8$; green $0.4 \leq r^2 < 0.6$; cyan $0.2 \leq r^2 < 0.4$; blue $r^2 < 0.2$; grey r^2 unknown. Recombination rates are estimated from the International HapMap Project and gene annotations are taken from the University of California Santa Cruz genome browser.

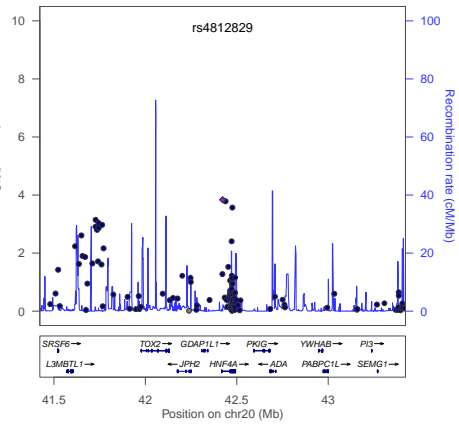
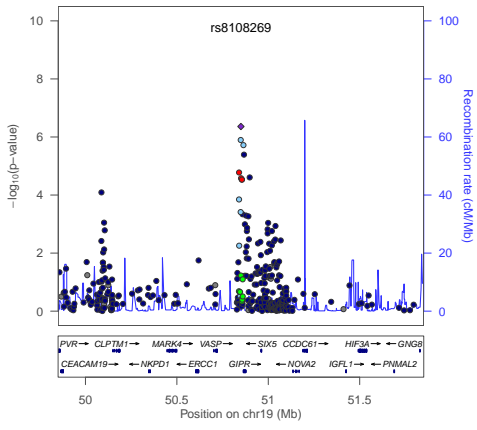
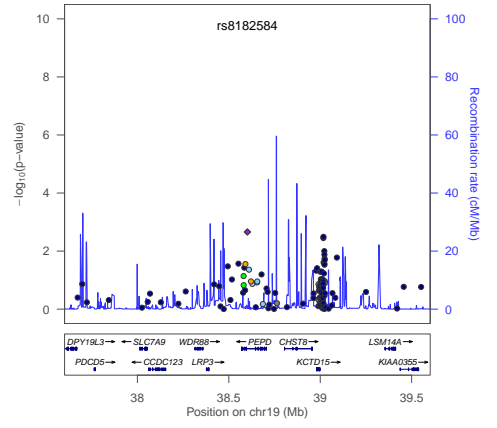
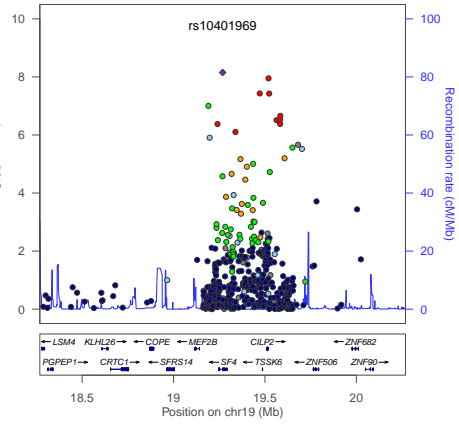
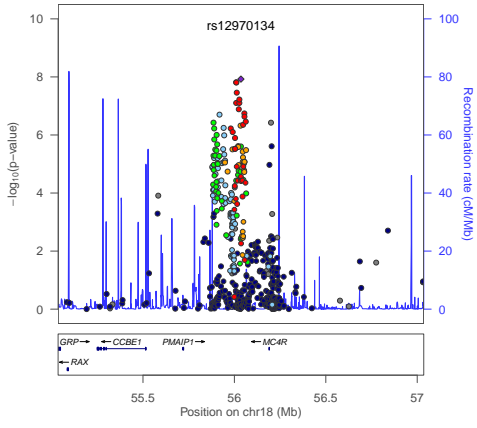


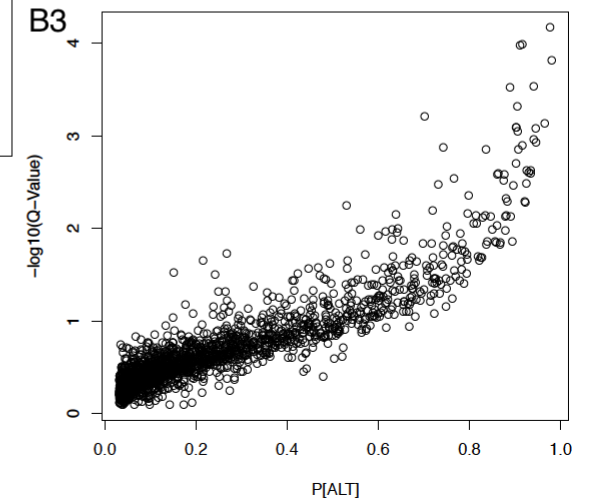
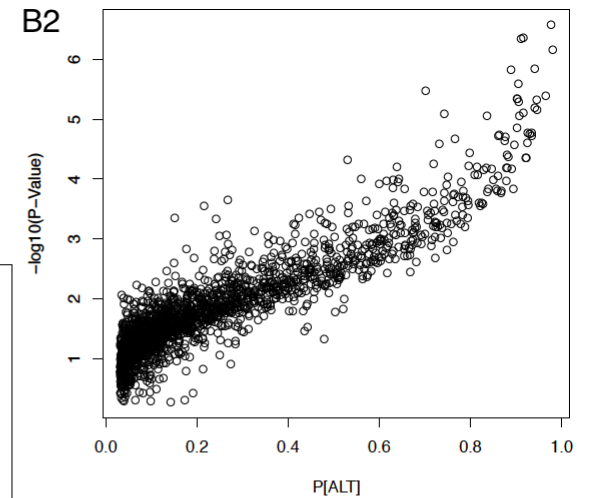
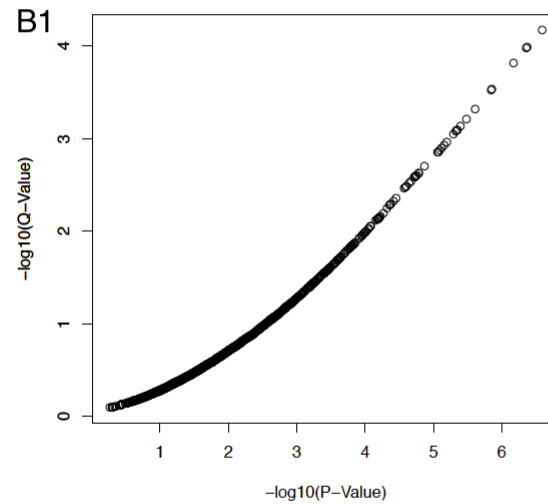
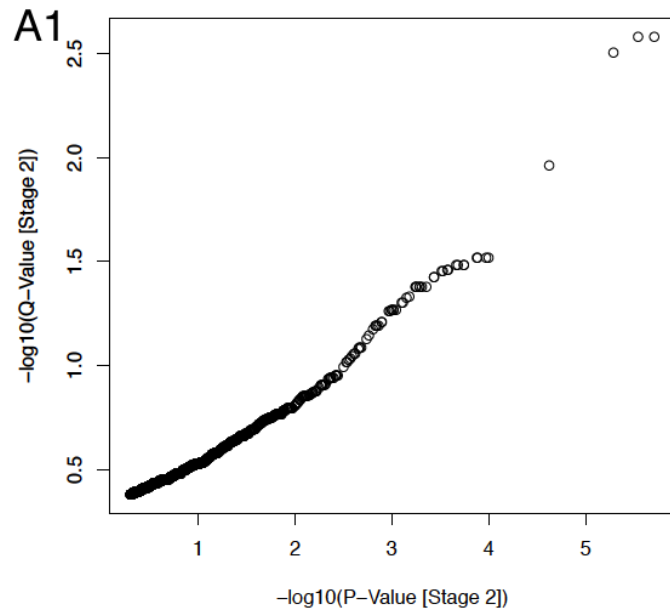






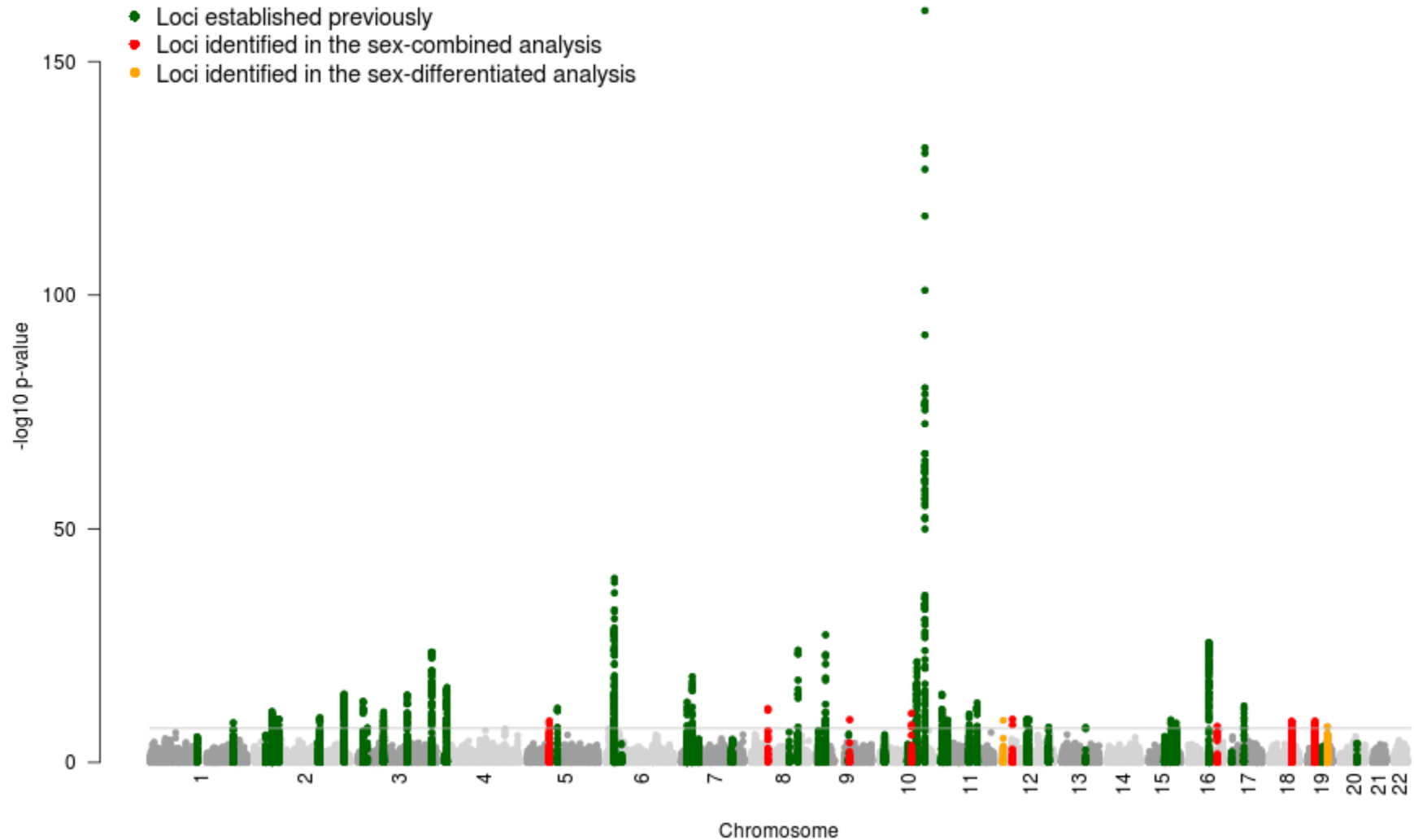




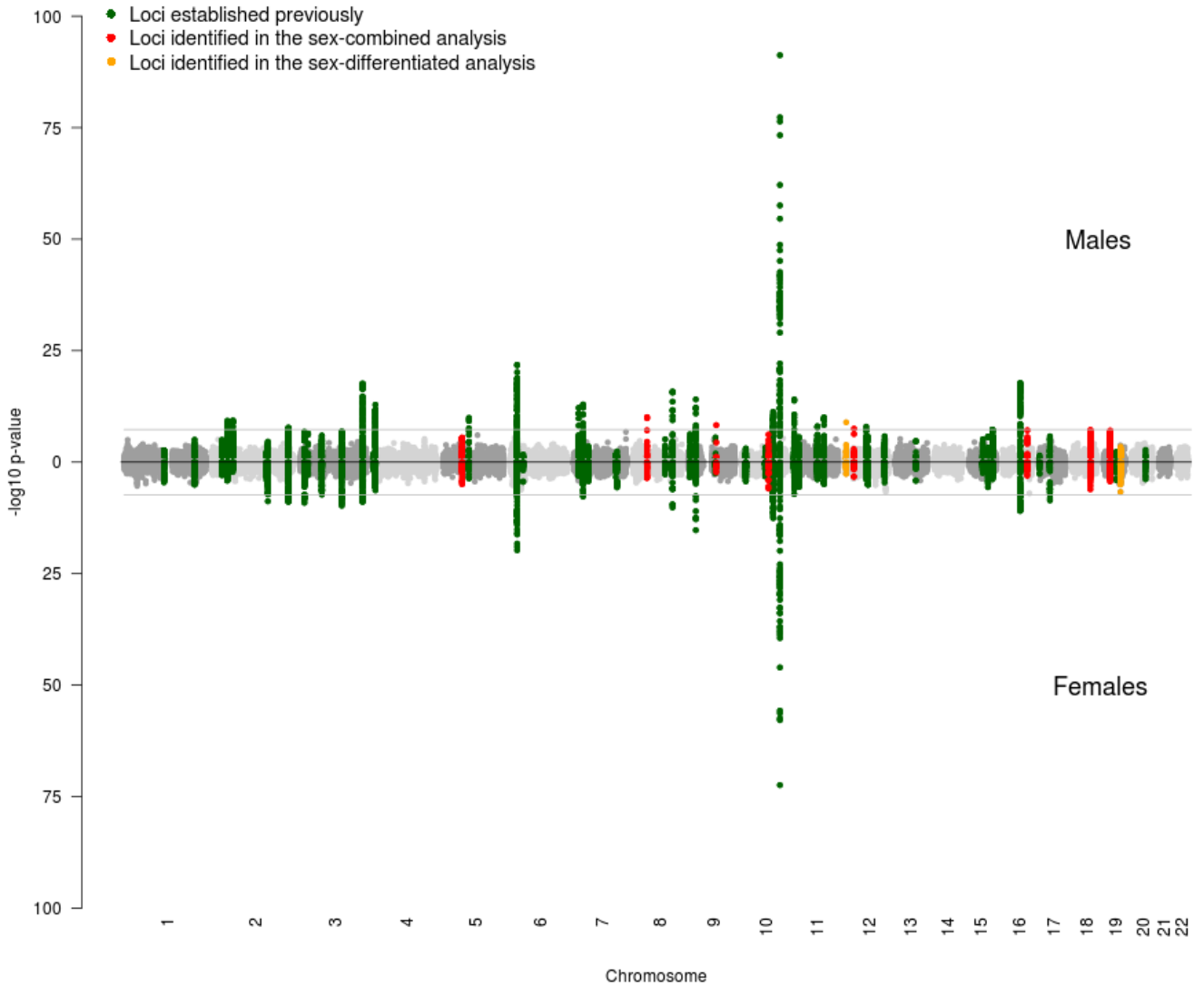


Supplementary Figure 4. Comparison of combined meta-analysis, FDR analysis and mixture modelling. (A1) Plot of estimated Q-values from FDR analysis and p-value using data only from 3,412 SNPs and samples contributing to Stage 2 meta-analysis. We note that because this set of SNPs is strongly enriched in departures from the null, the resultant Q-values do not appear well calibrated (i.e., estimates of π -hat was 0.532 and note the axis for Q-values do not range from 0-1 as expected with significant constraint in the range). Given this, we do not advocate this strategy for SNP and sample selection for FDR analysis on these data. (B1-B3) Plotted are pair-wise comparisons between combined meta-analysis p-value, estimated Q-value from FDR analysis using combined meta-analysis data, and probability of membership to the alternative distribution from mixture modelling of Stage 2 meta-analysis data alone ($P[ALT]$). Results are plotted for 2,172 T2D replication SNPs with consistent direction of effect between Stage 1 and 2 meta-analyses. In these figures, FDR Q-values were estimated using the set of 64,646 replication SNPs for all traits on Metabochip.

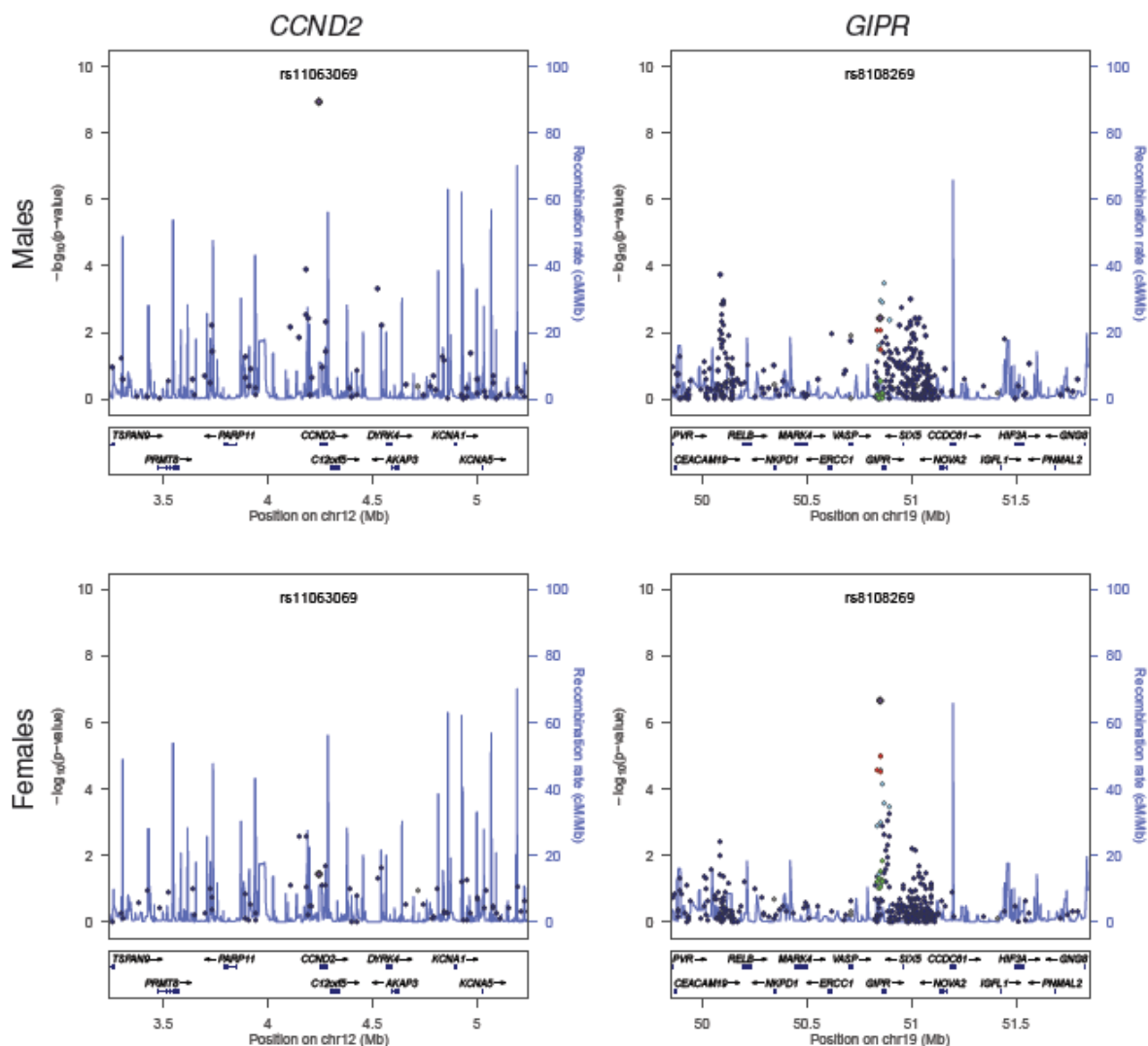
Supplementary Figure 5. Manhattan plot for the sex-differentiated meta-analysis. Previously established loci are highlighted in green. Novel loci achieving genome-wide significance in the sex-combined meta-analysis are highlighted in red. Novel loci achieving genome-wide significance in the sex-differentiated meta-analysis are highlighted in gold.



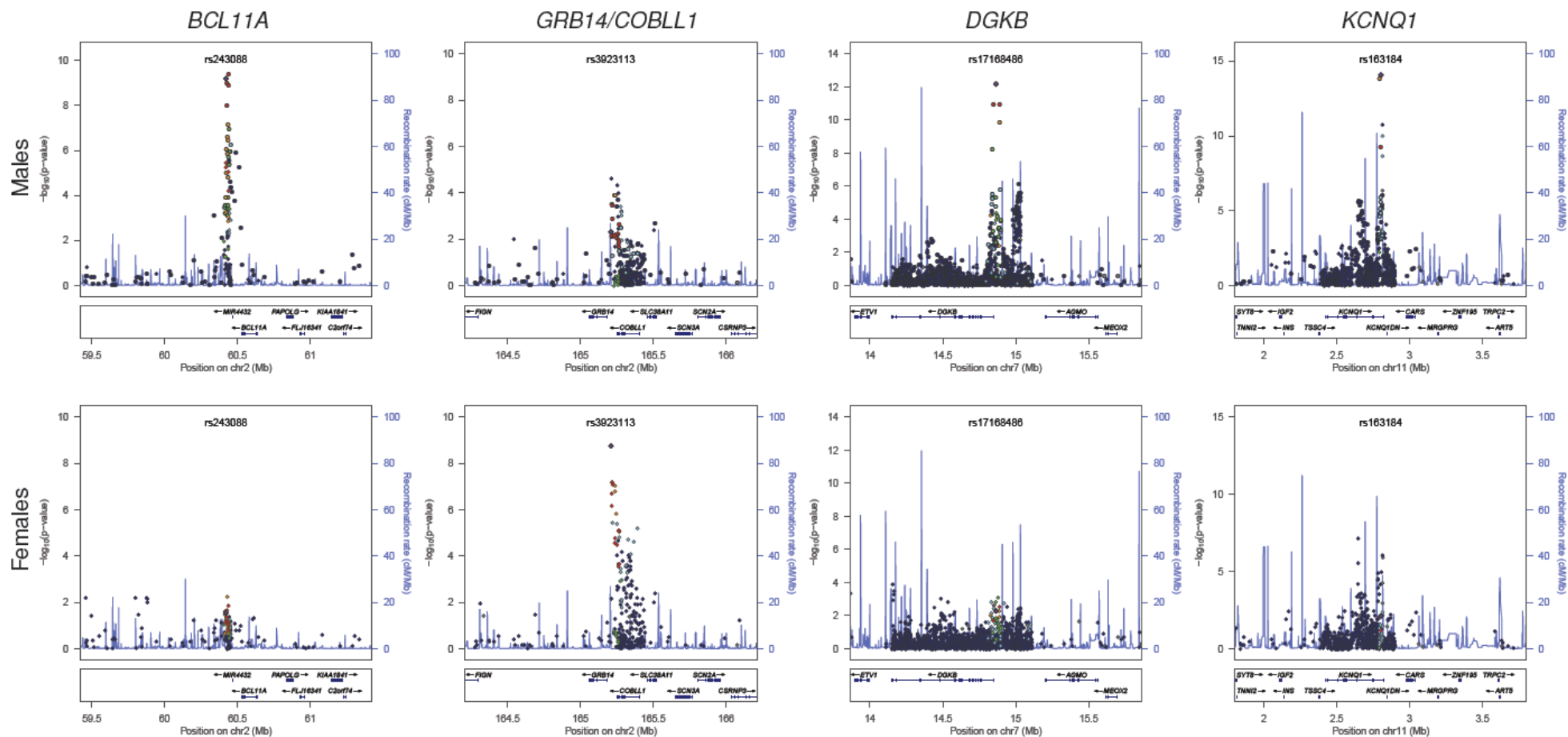
Supplementary Figure 6. Miami plot for the sex-specific meta-analyses. The top and bottom panels summarise the results of the male- and female-specific meta-analyses. Previously established loci are highlighted in green. Novel loci achieving genome-wide significance in the sex-combined meta-analysis are highlighted in red. Novel loci achieving genome-wide significance in the sex-differentiated meta-analysis are highlighted in gold.



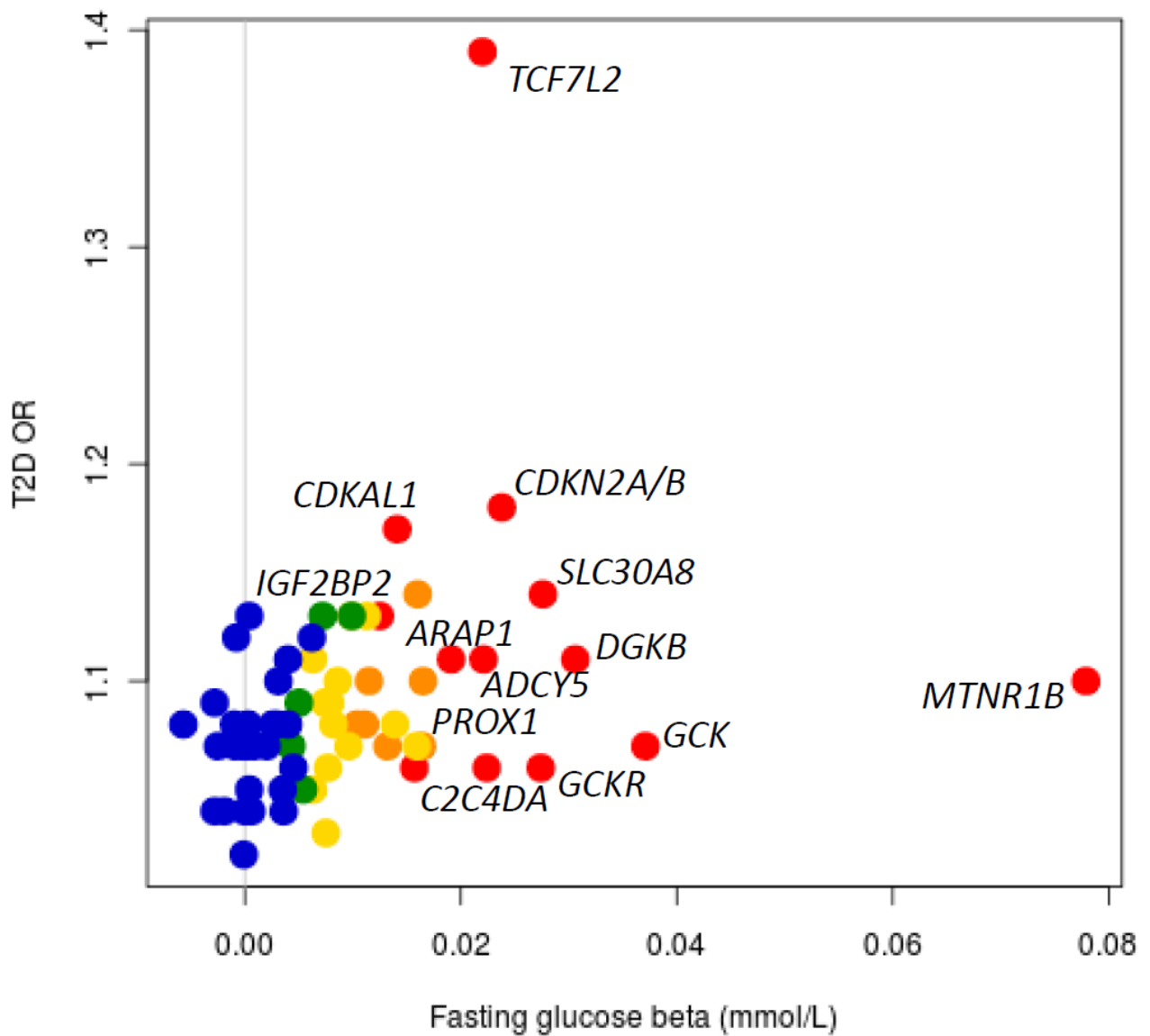
Supplementary Figure 7. Regional plots of novel T2D susceptibility loci identified through sex-differentiated meta-analysis. Each point represents a MetaboChip SNP passing quality control in our combined meta-analysis, plotted with their p-value (on a $-\log_{10}$ scale) as a function of genomic position (NCBI Build 36). In each panel, the lead sex-differentiated SNP is represented by the purple diamond. The colour coding of all other SNPs (circles) indicates LD with the lead SNP (estimated by CEU r^2 from the 1000 Genomes Project June 2010 release): red $r^2 \geq 0.8$; gold $0.6 \leq r^2 < 0.8$; green $0.4 \leq r^2 < 0.6$; cyan $0.2 \leq r^2 < 0.4$; blue $r^2 < 0.2$; grey r^2 unknown. Recombination rates are estimated from the International HapMap Project and gene annotations are taken from the University of California Santa Cruz genome browser.



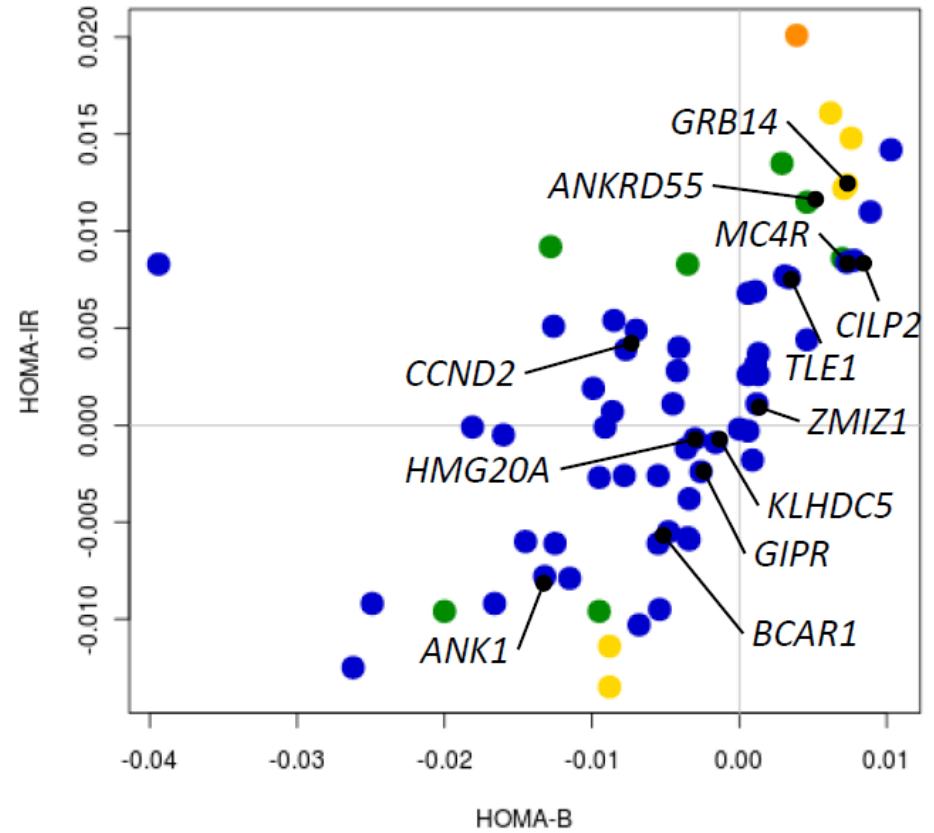
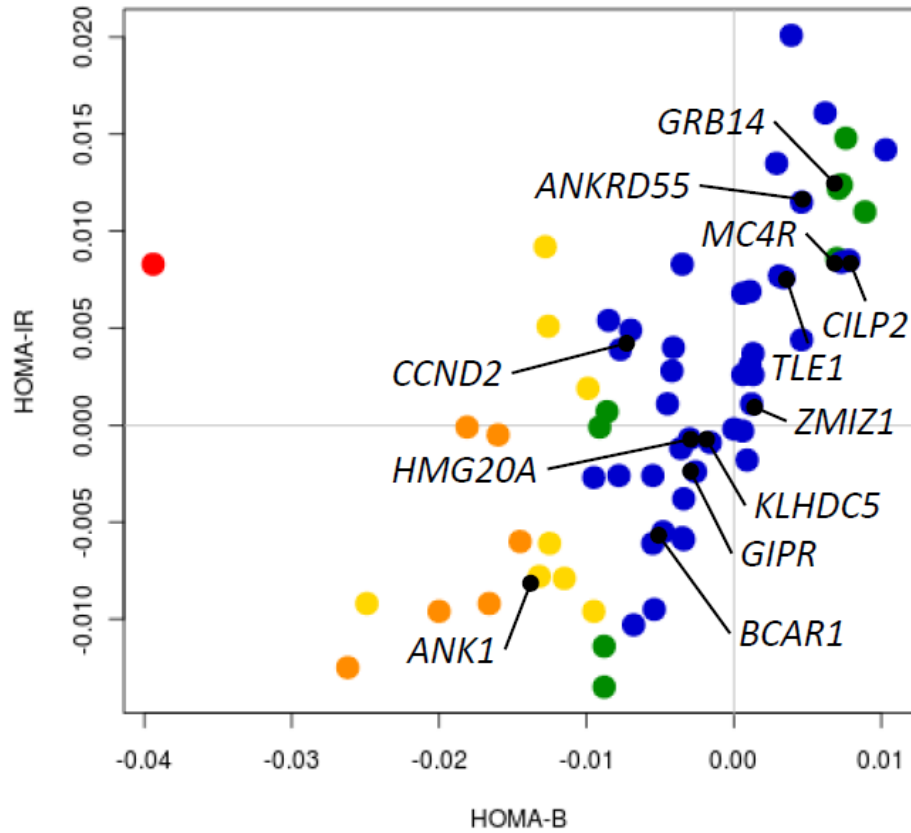
Supplementary Figure 8. Regional plots of T2D susceptibility loci demonstrating nominal heterogeneity in allelic effects between sexes. Each point represents a Metabochip SNP passing quality control in our combined meta-analysis, plotted with their p-value (on a $-\log_{10}$ scale) as a function of genomic position (NCBI Build 36). In each panel, the lead sex-differentiated SNP is represented by the purple diamond. The colour coding of all other SNPs (circles) indicates LD with the lead SNP (estimated by CEU r^2 from the 1000 Genomes Project June 2010 release): red $r^2 \geq 0.8$; gold $0.6 \leq r^2 < 0.8$; green $0.4 \leq r^2 < 0.6$; cyan $0.2 \leq r^2 < 0.4$; blue $r^2 < 0.2$; grey r^2 unknown. Recombination rates are estimated from the International HapMap Project and gene annotations are taken from the University of California Santa Cruz genome browser.



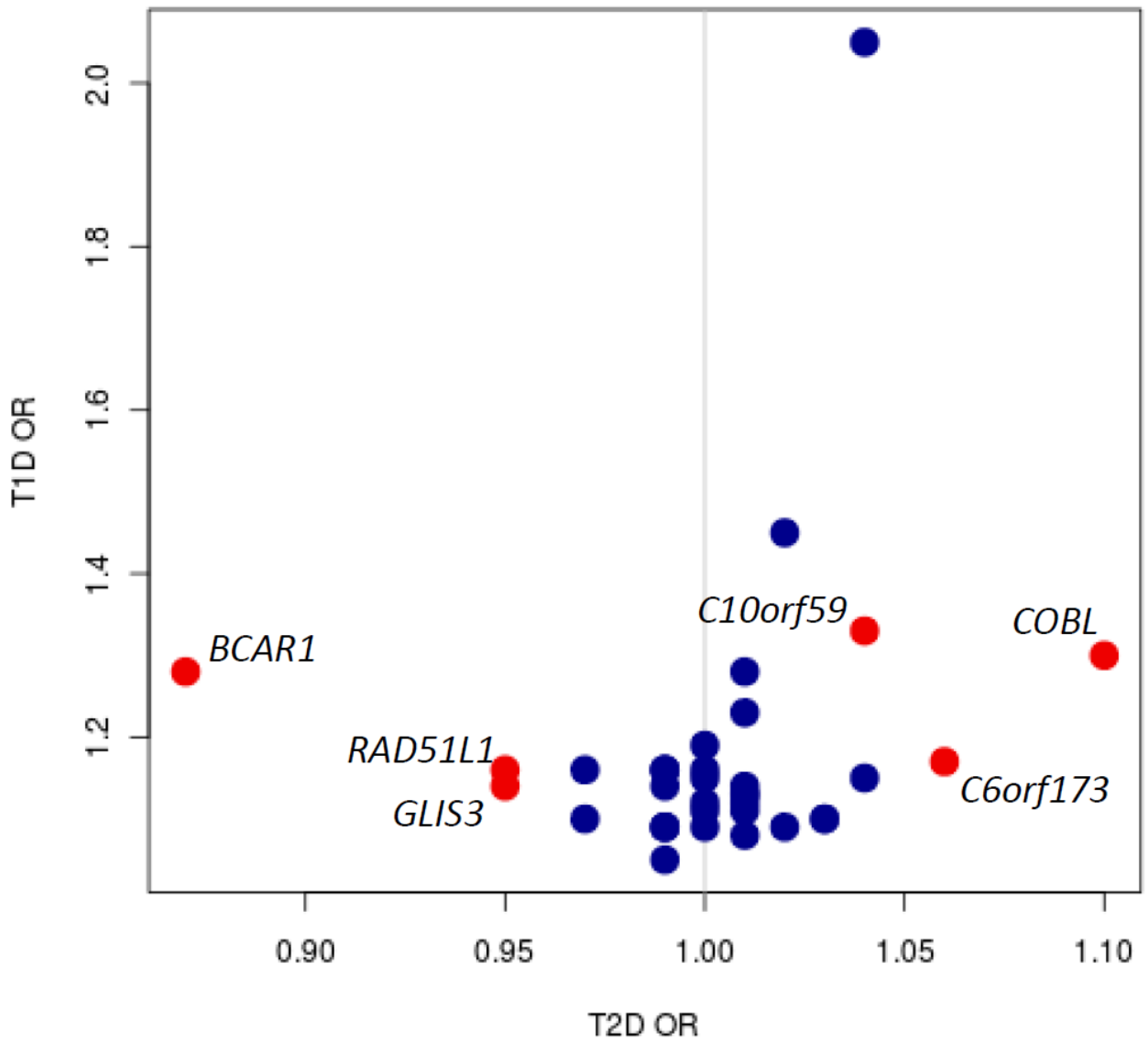
Supplementary Figure 9. Plot of FG and T2D risk at novel and established T2D susceptibility loci obtained from the present meta-analysis and up to 133,010 non-diabetic individuals from the MAGIC Investigators. Each point represents a lead T2D SNP, aligned to the risk allele, coloured according to the significance of association with FG: red $p < 5 \times 10^{-8}$; orange $5 \times 10^{-8} \leq p < 10^{-4}$; yellow $10^{-4} \leq p < 0.01$; green $0.01 \leq p < 0.05$; blue $p \geq 0.05$.



Supplementary Figure 10. Plots of indices of beta-cell function (HOMA-B) and insulin sensitivity (HOMA-IR) at novel and established T2D susceptibility loci obtained from up to 37,037 individuals from the MAGIC Investigators. Each point represents a lead T2D SNP, aligned to the risk allele, coloured according to the significance of association with HOMA-B (left panel) and HOMA-IR (right panel): red $p < 5 \times 10^{-8}$; orange $5 \times 10^{-8} \leq p < 10^{-4}$; yellow $10^{-4} \leq p < 0.01$; green $0.01 \leq p < 0.05$; blue $p \geq 0.05$.

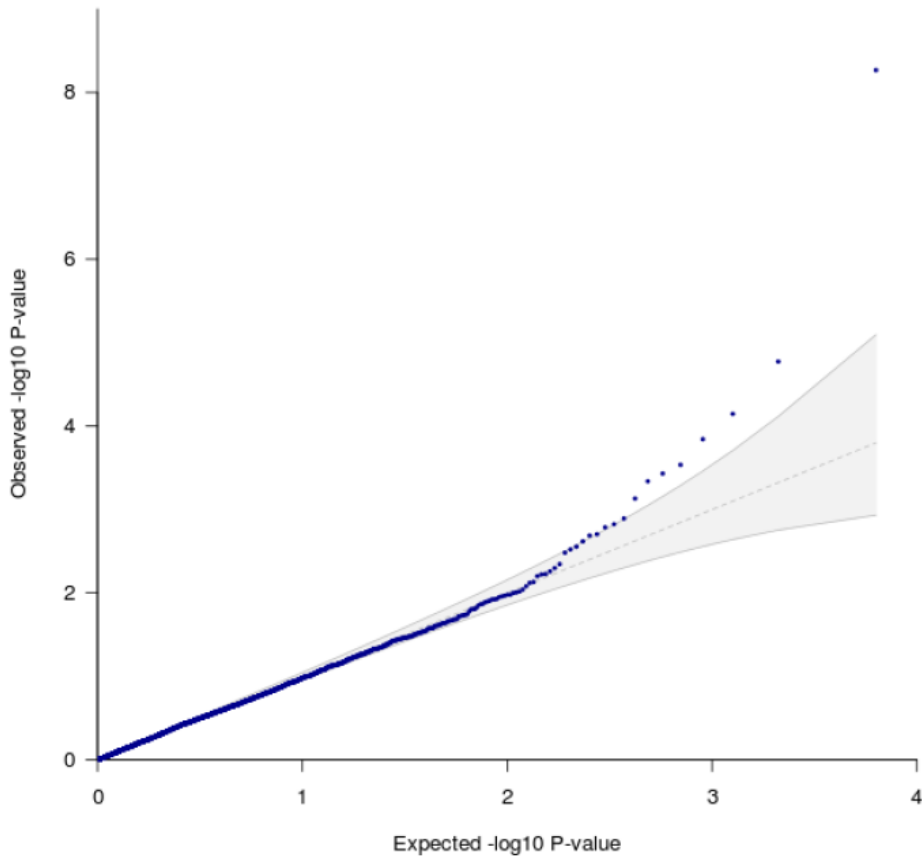


Supplementary Figure 11. Plot of T2D and T1D risk at 37 established T1D susceptibility loci obtained from the present meta-analysis and up to 7,514 T1D cases and 9,045 population controls from the Type 1 Diabetes Genetics Consortium. Each point represents a lead T1D SNP, aligned to the risk allele, coloured according to the significance of association with T2D: red $p < 0.05$; blue $p \geq 0.05$.

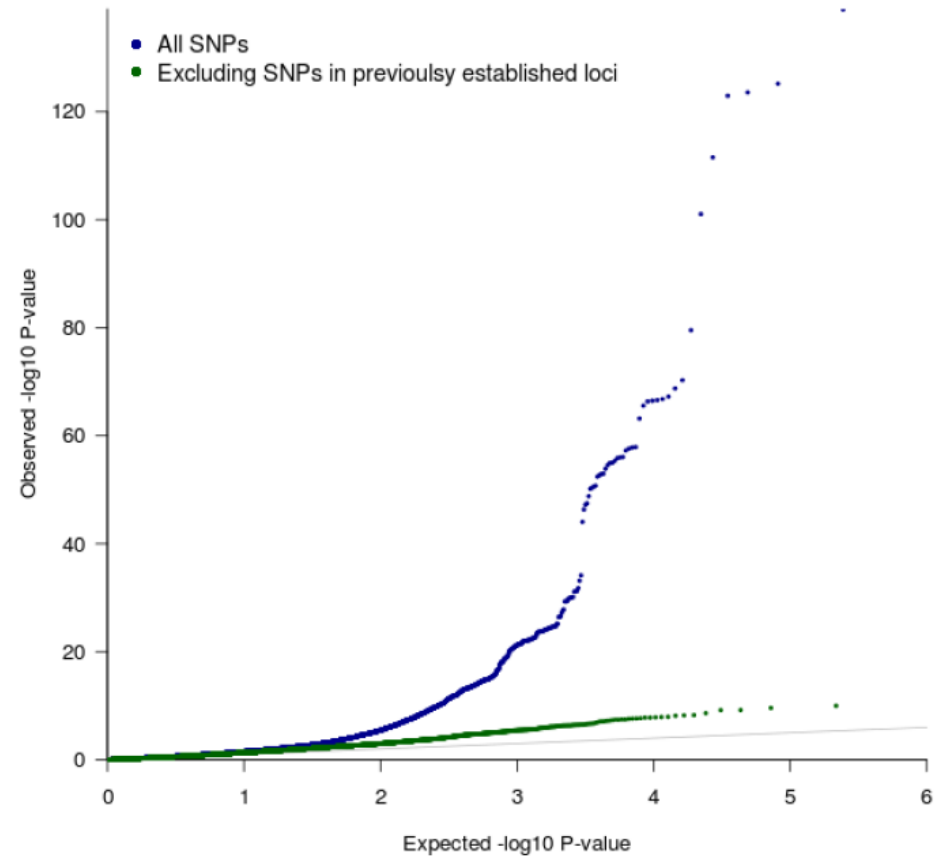


Supplementary Figure 12. QQ-plots of association statistics from the combined meta-analysis. Each point represents a MetaboChip SNP passing quality control in the combined meta-analysis. The y-axis corresponds to the observed \log_{10} p-value for association from the meta-analysis. The x-axis corresponds to the corresponding expected \log_{10} p-value under the null hypothesis of no association with T2D. The grey funnel represents 95% confidence limits for the expected p-values. Panel (a) includes 3,155 QT-interval replication SNPs, not expected to be associated with T2D, used for genomic control correction. Panel (b) includes all MetaboChip SNPs (in blue) and after excluding established T2D loci (in green).

(a) QT-interval SNPs

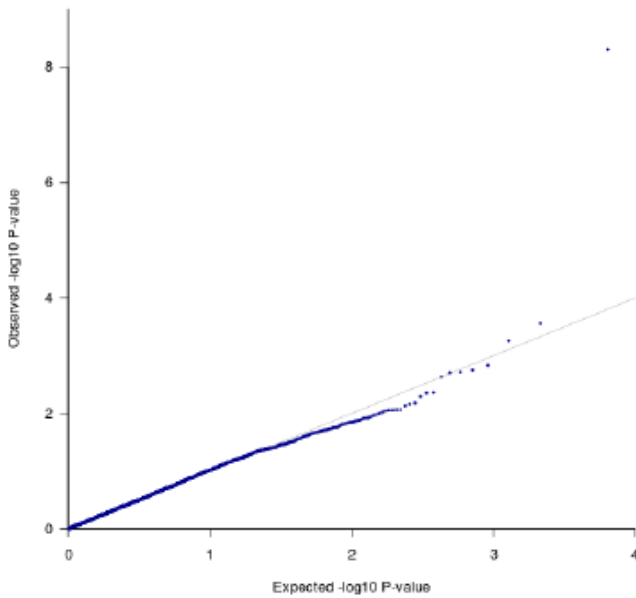


(b) MetaboChip SNPs

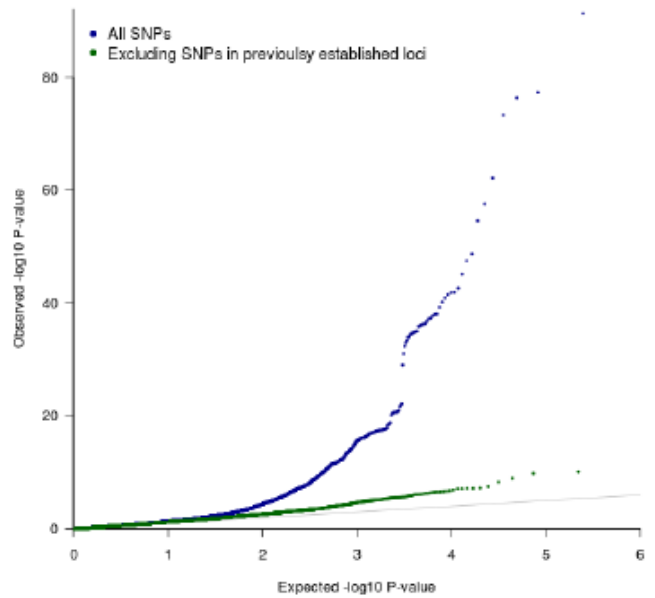


Supplementary Figure 13. QQ-plots of association statistics from sex-specific meta-analyses. Each point represents a Metabochip SNP passing quality control in the sex-differentiated meta-analysis. The y-axis corresponds to the observed \log_{10} p-value for association from the meta-analysis. The x-axis corresponds to the corresponding expected \log_{10} p-value under the null hypothesis of no association with T2D. The grey funnel represents 95% confidence limits for the expected p-values. Results are presented for the male-specific meta-analysis in panels (a) and (b), whilst those for the female-specific meta-analysis are presented in panels (c) and (d). Panels (a) and (c) include 3,155 QT-interval replication SNPs, not expected to be associated with T2D, used for genomic control correction. Panels (b) and (d) include all Metabochip SNPs (in blue) and after excluding established T2D loci (in green).

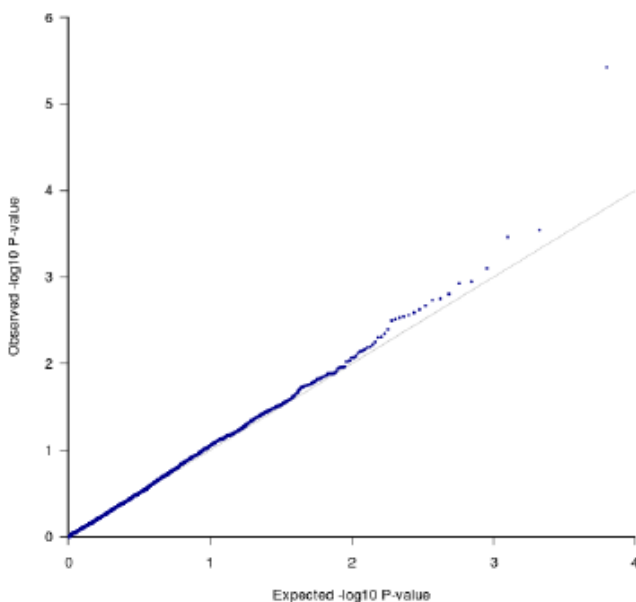
(a) Male QT-interval SNPs



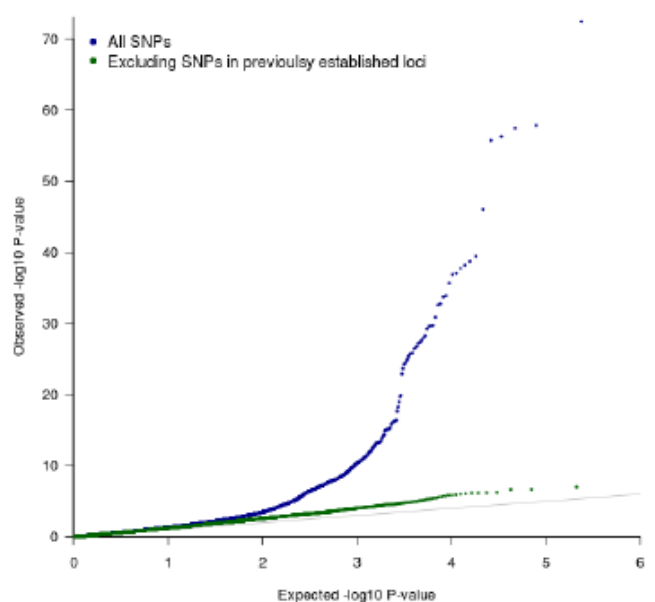
(b) Male Metabochip SNPs



(c) Female QT-interval SNPs



(d) Female Metabochip SNPs



Supplementary Table 2. Summary of combined meta-analysis for 65 novel and established T2D susceptibility loci.

Please see attached spreadsheet.

Supplementary Table 3. Summary statistics for lead SNPs at novel loci in meta-analyses of: (i) 5,561 T2D cases and 14,458 controls from GWAS of South Asian descent populations, excluding 1,958 overlapping samples from PROMIS; and (ii) 6,952 T2D cases and 11,865 controls from GWAS of East Asian descent populations.

SNP	Chr	Position (Build 36 bp)	Alleles ^a		Locus	South Asian meta-analysis			East Asian meta-analysis		
			Risk ^b	Other		Risk allele frequency	OR (95% CI)	<i>p</i> -value	Risk allele frequency	OR (95% CI)	<i>p</i> -value
rs13389219	2	165,237,122	C	T	<i>GRB14</i>	0.74	1.13 (1.06-1.20)	4.9E-05	0.86	1.02 (0.94-1.10)	6.6E-01
rs459193	5	55,842,508	G	A	<i>ANKRD55</i>	0.64	1.02 (0.97-1.08)	4.2E-01	0.49	1.04 (1.00-1.10)	7.3E-02
rs516946	8	41,638,405	C	T	<i>ANK1</i>	0.80	1.08 (1.02-1.15)	1.2E-02	0.86	1.04 (0.97-1.11)	2.8E-01
rs2796441	9	83,498,768	G	A	<i>TLE1</i>	0.52	1.05 (1.00-1.11)	6.2E-02	0.34	1.08 (1.02-1.15)	1.5E-02
rs12571751	10	80,612,637	A	G	<i>ZMIZ1</i>	0.57	1.07 (1.01-1.13)	1.3E-02	0.54	1.06 (1.00-1.12)	4.8E-02
rs10842994	12	27,856,417	C	T	<i>KLHDC5</i>	0.88	1.11 (1.02-1.20)	1.2E-02	0.75	1.02 (0.95-1.11)	5.4E-01
rs7177055	15	75,619,817	A	G	<i>HMG20A</i>	0.53	1.10 (1.05-1.16)	2.0E-04	0.38	1.06 (1.01-1.12)	2.6E-02
rs7202877	16	73,804,746	T	G	<i>BCAR1</i>	0.93	1.09 (0.99-1.20)	7.4E-02	0.79	0.99 (0.93-1.05)	7.3E-01
rs12970134	18	56,035,730	A	G	<i>MC4R</i>	0.36	1.08 (1.03-1.14)	3.8E-03	0.17	1.11 (1.05-1.18)	2.9E-04
rs10401969	19	19,268,718	C	T	<i>CILP2</i>	0.09	1.01 (0.92-1.10)	8.8E-01	0.06	0.98 (0.88-1.08)	6.6E-01

Chr: chromosome. OR: odds-ratio. CI: confidence interval.

^aAlleles are aligned to the forward strand of NCBI Build 36.

^bRisk allele for T2D from our primarily European descent meta-analysis combined meta-analysis.

Supplementary Table 4. Overlap of novel T2D susceptibility loci with related metabolic traits.

Locus	Trait	Lead SNP	CEU r^2 with lead T2D SNP	Reference
<i>GRB14</i>	Waist-hip ratio	rs10195252	0.933	Heid et al. (2010)
	Triglycerides	rs10195252	0.933	Teslovich et al. (2010)
	High-density lipoprotein cholesterol	rs12328675	0.163	Teslovich et al. (2010)
<i>ANK1</i>	Hemoglobin A _{1c}	rs6474359	0.006	Soranzo et al. (2010)
	Hemoglobin A _{1c}	rs4737009	0.004	Soranzo et al. (2010)
<i>MC4R</i>	Body mass index	rs17782313	0.802	Loos et al. (2008)
	High-density lipoprotein cholesterol	rs12967135	0.840	Teslovich et al. (2010)
	Waist circumference	rs12970134 ^a	1.000	Chambers et al. (2008)
	Insulin resistance	rs12970134 ^a	1.000	Chambers et al. (2008)
<i>CILP2</i>	Total cholesterol	rs10401969 ^a	1.000	Teslovich et al. (2010)
	Triglycerides	rs10401969 ^a	1.000	Teslovich et al. (2010)
	Low-density lipoprotein cholesterol	rs10401969 ^a	1.000	Teslovich et al. (2010)
<i>GIPR</i>	2-hour glucose	rs10423928	0.069	Saxena et al. (2010)
	Body mass index	rs2287019	0.064	Speliotes et al. (2010)

^aSame lead SNP for T2D and trait

Supplementary Table 5. Contribution of lead SNPs at novel and established T2D susceptibility loci to the sibling relative risk and explained liability-scale variance explained.

Locus	Lead SNP	Chr	Position (Build 36 bp)	Combined meta-analysis p-value	Stage 2 risk allele frequency	Stage 2 OR (95% CI)	Sibling relative risk ^a	Explained liability-scale variance (%) ^b
Previously established susceptibility loci								
<i>TCF7L2</i>	rs7903146	10	114,748,339	1.2E-139	0.27	1.38 (1.34-1.42)	1.023	1.351
<i>CDKAL1</i>	rs7756992	6	20,787,688	7.0E-35	0.29	1.15 (1.11-1.18)	1.004	0.247
<i>CDKN2A/B</i>	rs10811661	9	22,124,094	3.7E-27	0.82	1.19 (1.14-1.23)	1.004	0.226
<i>IGF2BP2</i>	rs4402960	3	186,994,381	2.4E-23	0.33	1.13 (1.10-1.17)	1.003	0.198
<i>FTO</i>	rs9936385	16	52,376,670	2.6E-23	0.41	1.13 (1.10-1.16)	1.004	0.213
<i>SLC30A8</i>	rs3802177	8	118,254,206	1.3E-21	0.66	1.13 (1.09-1.16)	1.003	0.185
<i>HHEX/IDE</i>	rs1111875	10	94,452,862	2.0E-19	0.58	1.09 (1.06-1.12)	1.002	0.103
<i>JAZF1</i>	rs849135	7	28,162,938	3.1E-17	0.52	1.10 (1.07-1.13)	1.002	0.131
<i>WFS1</i>	rs4458523	4	6,340,887	2.0E-15	0.57	1.10 (1.07-1.13)	1.002	0.127
<i>IRS1</i>	rs2943640	2	226,801,829	2.7E-14	0.63	1.10 (1.07-1.13)	1.002	0.119
<i>ADCY5</i>	rs11717195	3	124,565,088	6.5E-14	0.77	1.12 (1.09-1.16)	1.002	0.123
<i>MTNR1B</i>	rs10830963	11	92,348,358	5.3E-13	0.31	1.10 (1.06-1.13)	1.002	0.116
<i>PPARG</i>	rs1801282	3	12,368,125	1.1E-12	0.86	1.11 (1.07-1.16)	1.001	0.073
<i>THADA</i>	rs10203174	2	43,543,534	9.5E-12	0.89	1.14 (1.09-1.20)	1.001	0.085
<i>KCNQ1</i>	rs163184	11	2,803,645	1.2E-11	0.50	1.09 (1.06-1.12)	1.002	0.107
<i>HNF1B (TCF2)</i>	rs11651052	17	33,176,494	2.0E-11	0.44	1.10 (1.07-1.13)	1.002	0.131
<i>ZBED3</i>	rs6878122	5	76,463,067	5.0E-11	0.28	1.09 (1.05-1.12)	1.002	0.090
<i>DGKB</i>	rs17168486	7	14,864,807	5.9E-11	0.19	1.09 (1.06-1.13)	1.001	0.071
<i>ADAMTS9</i>	rs6795735	3	64,680,405	7.4E-11	0.59	1.09 (1.06-1.12)	1.002	0.102
<i>ARAP1 (CENTD2)</i>	rs1552224	11	72,110,746	1.8E-10	0.81	1.09 (1.06-1.13)	1.001	0.062
<i>KCNJ11</i>	rs5215	11	17,365,206	8.5E-10	0.41	1.07 (1.04-1.10)	1.001	0.065
<i>HMGA2</i>	rs2261181	12	64,498,585	1.2E-09	0.10	1.10 (1.05-1.16)	1.001	0.052
<i>UBE2E2</i>	rs1496653	3	23,429,794	3.6E-09	0.75	1.09 (1.05-1.12)	1.001	0.077
<i>HMG20A</i>	rs7177055	15	75,619,817	4.6E-09	0.68	1.08 (1.05-1.11)	1.001	0.073
<i>PRC1</i>	rs12899811	15	89,345,080	6.3E-09	0.31	1.07 (1.04-1.10)	1.001	0.058
<i>TSPAN8/LGR5</i>	rs7955901	12	69,719,560	6.5E-09	0.45	1.06 (1.03-1.09)	1.001	0.049
<i>PROX1</i>	rs2075423	1	212,221,342	8.1E-09	0.62	1.07 (1.04-1.10)	1.001	0.061
<i>GRB14</i>	rs13389219	2	165,237,122	1.0E-08	0.60	1.09 (1.06-1.12)	1.002	0.101
<i>SPRY2</i>	rs1359790	13	79,615,157	1.4E-08	0.72	1.06 (1.03-1.10)	1.001	0.039
<i>BCL11A</i>	rs243088	2	60,422,249	1.8E-08	0.45	1.06 (1.03-1.09)	1.001	0.049
<i>HNF1A (TCF1)</i>	rs12427353	12	119,911,284	6.5E-08	0.79	1.07 (1.03-1.10)	1.001	0.042
<i>TLE4</i>	rs17791513	9	81,095,410	2.8E-07	0.91	1.08 (1.03-1.14)	1.000	0.026
<i>GCKR</i>	rs780094	2	27,594,741	5.4E-07	0.61	1.08 (1.05-1.11)	1.001	0.080
<i>CDC123/CAMK1D</i>	rs11257655	10	12,347,900	2.1E-06	0.23	1.08 (1.04-1.11)	1.001	0.064
<i>C2CD4A</i>	rs4502156	15	60,170,447	2.3E-06	0.52	1.05 (1.03-1.08)	1.001	0.034

<i>TP53INP1</i>	rs7845219	8	96,006,678	4.6E-06	0.52	1.04 (1.02-1.07)	1.000	0.022
<i>GCK</i>	rs10278336	7	44,211,888	6.4E-06	0.50	1.09 (1.05-1.13)	1.002	0.107
<i>GLIS3</i>	rs10758593	9	4,282,083	1.0E-05	0.42	1.06 (1.04-1.09)	1.001	0.048
<i>NOTCH2</i>	rs10923931	1	120,319,482	1.3E-05	0.12	1.07 (1.03-1.12)	1.001	0.030
<i>RBMS1</i>	rs7569522	2	161,054,693	4.1E-05	0.44	1.03 (1.01-1.06)	1.000	0.013
<i>ZFAND6</i>	rs11634397	15	78,219,277	1.4E-04	0.64	1.03 (1.00-1.06)	1.000	0.012
<i>FTITM2/R3HDML/HNF4A</i>	rs4812829	20	42,422,681	1.5E-04	0.19	1.06 (1.02-1.10)	1.001	0.032
<i>KLF14</i>	rs13233731	7	130,088,229	2.3E-04	0.51	1.01 (0.98-1.04)	1.000	0.001
<i>PEPD</i>	rs8182584	19	38,601,550	4.8E-04	0.38	1.05 (1.02-1.09)	1.001	0.033
<i>DUSP8</i>	rs2334499	11	1,653,425	1.2E-03	0.43	1.03 (1.00-1.06)	1.000	0.012
<i>PTPRD</i>	rs16927668	9	8,359,533	2.8E-03	0.24	1.05 (1.01-1.08)	1.000	0.026
<i>SRR</i>	rs2447090	17	2,245,724	3.8E-03	0.62	1.04 (1.01-1.07)	1.000	0.021
<i>VPS26A</i>	rs12242953	10	70,535,348	3.9E-03	0.93	1.05 (0.99-1.11)	1.000	0.009
<i>ST64GAL1</i>	rs17301514	3	188,096,103	1.4E-02	0.13	1.03 (0.99-1.07)	1.000	0.006
<i>MAEA</i>	rs6819243	4	1,283,245	7.6E-02	0.96	1.07 (0.99-1.14)	1.000	0.011
<i>GCC1</i>	rs17867832	7	126,784,073	9.5E-02	0.91	1.07 (0.99-1.16)	1.000	0.021
<i>PSMD6</i>	rs12497268	3	64,065,403	9.8E-02	0.80	1.03 (0.99-1.07)	1.000	0.008
<i>ZFAND3</i>	rs4299828	6	38,285,645	1.4E-01	0.79	1.03 (0.99-1.06)	1.000	0.008
<i>KCNK16</i>	rs3734621	6	39,412,189	2.5E-01	0.03	1.05 (0.97-1.14)	1.000	0.004
<i>AP3S2</i>	rs2007084	15	88,146,339	3.6E-01	0.92	1.03 (0.98-1.09)	1.000	0.004
Total							1.093	5.156
Novel susceptibility loci achieving genome-wide significance in combined meta-analysis								
<i>ZMIZ1</i>	rs12571751	10	80,612,637	1.0E-10	0.52	1.07 (1.04-1.10)	1.001	0.066
<i>ANK1</i>	rs516946	8	41,638,405	2.5E-10	0.76	1.08 (1.05-1.12)	1.001	0.059
<i>KLHDC5</i>	rs10842994	12	27,856,417	6.1E-10	0.80	1.10 (1.07-1.14)	1.001	0.079
<i>TLE1</i>	rs2796441	9	83,498,768	5.4E-09	0.57	1.07 (1.04-1.10)	1.001	0.064
<i>ANKRD55</i>	rs459193	5	55,842,508	6.0E-09	0.70	1.10 (1.06-1.13)	1.002	0.106
<i>CILP2</i>	rs10401969	19	19,268,718	7.0E-09	0.08	1.14 (1.08-1.20)	1.001	0.082
<i>MC4R</i>	rs12970134	18	56,035,730	1.2E-08	0.27	1.08 (1.05-1.11)	1.001	0.070
<i>BCAR1</i>	rs7202877	16	73,804,746	3.5E-08	0.89	1.10 (1.05-1.15)	1.001	0.047
Total							1.010	0.574
Combined total							1.104	5.730

Chr: chromosome. OR: odds-ratio. CI: confidence interval.

^aAssuming a multiplicative model across loci.

^bAssuming a liability threshold model and a disease prevalence of 8%.

Supplementary Table 6. Previously reported lead SNPs from GWAS and lead Metabochip SNPs from Stage 2 meta-analysis in 36 fine-mapping regions.

Locus	Fine-mapping trait	Previously reported lead GWAS SNP (* or best proxy on Metabochip): Stage 2 meta-analysis										Lead SNP from Stage 2 meta-analysis										CEU r^2	Reference
		SNP	Chr	Position	Risk allele	Other allele	Risk allele frequency	Cases	Controls	p-value	OR (95% CI)	SNP	Chr	Position	Risk allele	Other allele	Risk allele frequency	Cases	Controls	p-value	OR (95% CI)		
<i>NOTCH2</i>	T2D	rs10923931	1	120,319,482	T	G	0.11	22,162	55,566	1.3E-03	1.07 (1.03-1.12)	rs835575	1	120,258,086	T	G	0.11	22,669	58,119	1.0E-03	1.07 (1.03-1.12)	1.00	Voight et al. (2010)
<i>PROX1</i>	FG	rs340874	1	212,225,879	C	T	0.52	22,669	58,119	1.4E-05	1.06 (1.03-1.09)	rs17712208	1	212,217,068	T	A	0.03	21,387	56,604	3.9E-06	1.20 (1.11-1.30)	0.06	Dupuis et al. (2010)
<i>GCKR</i>	TG	rs780094	2	27,594,741	C	T	0.62	22,669	58,119	3.3E-07	1.08 (1.05-1.11)	rs780094	2	27,594,741	C	T	0.62	22,669	58,119	3.3E-07	1.08 (1.05-1.11)	Same SNP	Dupuis et al. (2010)
<i>THADA</i>	T2D	rs11899863	2	43,472,323	C	T	0.92	22,669	58,119	6.6E-08	1.16 (1.10-1.22)	rs10203174	2	43,543,534	C	T	0.90	22,669	58,119	2.0E-08	1.14 (1.09-1.20)	0.90	Voight et al. (2010)
<i>BCL11A</i>	T2D	rs243019*	2	60,439,310	C	T	0.46	22,669	58,119	3.7E-05	1.06 (1.03-1.09)	rs243083	2	60,427,374	G	A	0.46	22,669	58,119	1.1E-05	1.06 (1.03-1.09)	1.00	Voight et al. (2010)
<i>GRB14</i>	WHR and LDL-C	rs3923113	2	165,210,095	A	C	0.64	21,947	47,966	7.7E-09	1.09 (1.06-1.12)	rs1128249	2	165,236,870	G	T	0.61	22,669	58,119	1.7E-08	1.08 (1.05-1.12)	0.77	Kooner et al. (2011)
<i>IRS1</i>	T2D	rs7578326	2	226,728,897	A	G	0.64	22,669	58,119	8.4E-07	1.07 (1.04-1.11)	rs2943640	2	226,801,829	C	A	0.64	22,669	58,119	2.1E-11	1.10 (1.07-1.13)	0.65	Voight et al. (2010)
<i>PPARG</i>	T2D	rs13081389	3	12,264,800	A	G	0.93	22,669	58,119	2.0E-03	1.09 (1.03-1.15)	rs1899951	3	12,369,840	C	T	0.86	22,669	58,119	3.7E-07	1.11 (1.07-1.15)	0.34	Voight et al. (2010)
<i>ADAMTS9</i>	T2D	rs6795735	3	64,680,405	C	T	0.60	22,669	58,119	1.7E-09	1.09 (1.06-1.12)	rs6795735	3	64,680,405	C	T	0.60	22,669	58,119	1.7E-09	1.09 (1.06-1.12)	Same SNP	Voight et al. (2010)
<i>ADCY5</i>	T2D	rs11708067	3	124,548,468	A	G	0.79	22,669	58,119	3.6E-11	1.12 (1.08-1.16)	rs11717195	3	124,565,088	T	C	0.78	22,669	58,119	1.2E-11	1.12 (1.09-1.16)	0.80	Dupuis et al. (2010)
<i>IGFBP2</i>	T2D	rs6769511*	3	187,012,984	C	T	0.31	22,669	58,119	3.4E-16	1.13 (1.10-1.16)	rs4402960	3	186,994,381	T	G	0.31	21,942	57,192	4.8E-17	1.13 (1.10-1.17)	1.00	Voight et al. (2010)
<i>WFS1</i>	T2D	rs1801214	4	6,353,923	T	C	0.58	22,669	58,119	1.3E-10	1.09 (1.06-1.13)	rs4416547	4	6,344,868	A	G	0.59	22,669	58,119	9.6E-11	1.10 (1.07-1.13)	1.00	Voight et al. (2010)
<i>ZBED3</i>	T2D	rs4457053	5	76,460,705	G	A	0.27	22,669	58,119	5.0E-07	1.08 (1.05-1.11)	rs6878122	5	76,463,067	G	A	0.27	22,669	58,119	8.7E-08	1.09 (1.05-1.12)	1.00	Voight et al. (2010)
<i>CDKAL1</i>	T2D	rs9368222*	6	20,794,975	A	C	0.28	21,942	57,192	1.1E-18	1.14 (1.11-1.18)	rs7756992	6	20,787,688	G	A	0.28	22,669	58,119	9.9E-20	1.15 (1.11-1.18)	1.00	Voight et al. (2010)
<i>DGKB</i>	FG	rs2191349	7	15,030,834	T	G	0.52	22,669	58,119	3.9E-03	1.04 (1.01-1.07)	rs17168486	7	14,864,807	T	C	0.17	22,669	58,119	2.8E-07	1.09 (1.06-1.13)	0.00	Dupuis et al. (2010)
<i>JAZF1</i>	T2D	rs849134	7	28,162,747	A	G	-	-	-	-	-	rs849135	7	28,162,938	G	A	0.52	22,669	58,119	1.7E-11	1.10 (1.07-1.13)	1.00	Voight et al. (2010)
<i>GCKR</i>	FG and HbA _{1c}	rs4607517	7	44,202,193	A	G	0.15	21,947	47,966	4.6E-06	1.09 (1.05-1.14)	rs6975024	7	44,198,411	C	T	0.15	22,669	58,119	6.6E-06	1.09 (1.05-1.13)	1.00	Dupuis et al. (2010)
<i>KLF14</i>	T2D	rs972283	7	130,117,394	G	A	0.52	22,669	58,119	3.3E-01	1.01 (0.99-1.04)	7-130116320	7	130,116,320	A	G	0.02	21,491	45,519	4.5E-02	1.10 (1.00-1.21)	0.15	Voight et al. (2010)
<i>TP53INP1</i>	T2D	rs896854	8	96,029,687	T	C	0.50	22,669	58,119	1.3E-02	1.03 (1.01-1.06)	rs7845219	8	96,006,678	T	C	0.51	22,669	58,119	2.3E-03	1.04 (1.02-1.07)	0.85	Voight et al. (2010)
<i>SLC30A8</i>	T2D	rs3802177	8	118,254,206	G	A	0.67	22,669	58,119	2.1E-15	1.13 (1.09-1.16)	rs11558471	8	118,254,914	A	G	0.66	22,669	58,119	1.1E-15	1.13 (1.09-1.16)	0.96	Voight et al. (2010)
<i>GLIS3</i>	FG	rs7041847	9	4,277,466	A	G	0.49	21,947	47,966	8.4E-03	1.04 (1.01-1.07)	9-4284707	9	4,284,707	G	T	0.36	22,669	58,119	3.0E-06	1.07 (1.04-1.10)	0.39	Cho et al. (2012)
<i>CDKN2A/B</i>	T2D	rs10965250	9	22,123,284	G	A	0.83	22,669	58,119	8.1E-19	1.18 (1.14-1.23)	rs10811661	9	22,124,094	T	C	0.83	22,669	58,119	3.0E-19	1.19 (1.14-1.23)	0.92	Voight et al. (2010)
<i>CDC123/CAMK1D</i>	T2D	rs12779790	10	12,368,016	G	A	-	-	-	-	-	rs11257655	10	12,347,900	T	C	0.22	22,669	58,119	7.9E-06	1.08 (1.04-1.11)	0.75	Voight et al. (2010)
<i>HHEX/IDE</i>	T2D	rs5015480	10	94,455,539	C	T	-	-	-	-	-	rs7923837	10	94,471,897	G	A	0.62	22,669	58,119	6.4E-10	1.09 (1.06-1.12)	0.66	Voight et al. (2010)
<i>TCF7L2</i>	T2D	rs7903146	10	114,748,339	T	C	0.25	22,669	58,119	2.6E-99	1.38 (1.34-1.42)	rs7903146	10	114,748,339	T	C	0.25	22,669	58,119	2.6E-99	1.38 (1.34-1.42)	Same SNP	Voight et al. (2010)
<i>KCNQ1</i>	T2D	rs231362	11	2,648,047	G	A	0.52	18,660	52,922	1.6E-05	1.07 (1.04-1.10)	rs2237896	11	2,815,016	G	A	0.95	22,618	57,760	4.7E-11	1.25 (1.17-1.34)	0.00	Voight et al. (2010)
<i>KCNJ11</i>	T2D	rs5215	11	17,365,206	C	T	0.40	22,669	58,119	1.2E-06	1.07 (1.04-1.10)	rs5215	11	17,365,206	C	T	0.40	22,669	58,119	1.2E-06	1.07 (1.04-1.10)	Same SNP	Voight et al. (2010)
<i>ARAP1 (CENTD2)</i>	T2D	rs1552224	11	72,110,746	A	C	0.82	22,669	58,119	9.5E-07	1.09 (1.06-1.13)	11-72138046	11	72,138,046	A	C	0.82	22,669	58,119	1.3E-07	1.10 (1.06-1.14)	0.95	Voight et al. (2010)
<i>MTNR1B</i>	T2D	rs1387153	11	92,313,476	T	C	0.29	22,669	58,119	9.7E-07	1.08 (1.05-1.11)	rs10830963	11	92,348,358	G	C	0.29	21,866	56,045	1.9E-09	1.10 (1.06-1.13)	0.56	Voight et al. (2010)
<i>HMGA2</i>	T2D	rs2612035*	12	64,478,934	G	A	0.09	22,669	58,119	1.5E-05	1.10 (1.06-1.16)	rs7134682	12	64,454,418	T	G	0.12	22,669	58,119	1.5E-06	1.10 (1.06-1.15)	0.29	Voight et al. (2010)
<i>TSPAN8/LGR5</i>	T2D	rs4760915*	12	69,920,379	T	C	0.27	22,669	58,119	5.4E-03	1.04 (1.01-1.08)	rs7955901	12	69,719,560	C	T	0.43	22,669	58,119	1.1E-05	1.06 (1.03-1.09)	0.13	Voight et al. (2010)
<i>HNF1A (TCF1)</i>	T2D	rs7957197	12	119,945,069	T	A	0.79	22,162	55,566	9.4E-04	1.06 (1.02-1.10)	rs1169288	12	119,901,033	C	A	0.33	21,334	54,628	2.4E-05	1.07 (1.03-1.10)	0.07	Voight et al. (2010)
<i>C2CD4A</i>	FG and 2 hour glucose	rs7163757	15	60,178,900	C	T	-	-	-	-	-	rs4502156	15	60,170,447	T	C	0.53	22,669	58,119	1.2E-04	1.05 (1.03-1.08)	1.00	Yamauchi et al. (2010)
<i>PRC1</i>	T2D	rs8042680	15	89,322,341	A	C	0.31	21,947	47,966	4.2E-05	1.06 (1.03-1.10)	rs12899811	15	89,345,080	G	A	0.31	22,669	58,119	2.1E-06	1.07 (1.04-1.10)	0.62	Voight et al. (2010)
<i>FTO</i>	BMI	rs11642841	16	52,402,988	A	C	0.40	22,669	58,119	1.6E-13	1.11 (1.08-1.14)	rs1121980	16	52,366,748	A	G	0.43	22,669	58,119	8.2E-18	1.13 (1.10-1.16)	0.78	Voight et al. (2010)
<i>HNF1B (TCF2)</i>	T2D	rs11651755*	17	33,173,953	C	T	0.45	22,669	58,119	2.0E-11	1.10 (1.07-1.13)	rs11263763	17	33,177,678	G	A	0.44	22,669	58,119	1.8E-11	1.10 (1.07-1.13)	0.87	Voight et al. (2010)

Chr: chromosome. OR: odds-ratio. CI: confidence interval.

Supplementary Table 7. Summary of sex-differentiated meta-analysis for loci demonstrating heterogeneity in allelic effects between males and females.

SNP	Chr	Position (Build 36 bp)	Alleles ^a		Sex	Stage 1 meta-analysis				Stage 2 meta-analysis				Combined meta-analysis				Sex-differentiated meta-analysis				Locus	Rationale for inclusion in this table
			Risk ^b	Other		Cases	Controls	p-value	OR (95% CI)	Cases	Controls	p-value	OR (95% CI)	Cases	Controls	p-value	OR (95% CI)	Cases	Controls	p-value	Heterogeneity p-value		
rs243088	2	60,422,249	T	A	Male	5,253	20,945	2.6E-05	1.11 (1.06-1.17)	13,842	32,361	3.1E-06	1.09 (1.05-1.13)	19,095	53,306	6.5E-10	1.10 (1.06-1.13)	32,249	111,929	4.7E-10	1.2E-02	<i>BCL11A</i>	Lead SNP from sex-differentiated meta-analysis
					Female	4,327	32,865	1.0E-01	1.04 (0.99-1.10)	8,827	25,758	9.6E-02	1.03 (0.99-1.07)	13,154	58,623	2.8E-02	1.04 (1.00-1.07)						
rs3923113	2	165,210,095	A	C	Male	5,253	20,945	5.5E-01	1.02 (0.96-1.07)	13,409	25,757	2.2E-03	1.06 (1.02-1.10)	18,662	46,702	4.9E-03	1.05 (1.01-1.08)	31,527	101,776	2.6E-10	8.0E-03	<i>GRB14</i>	Lead SNP from sex-differentiated meta-analysis
					Female	4,327	32,865	1.1E-02	1.07 (1.02-1.14)	8,538	22,209	2.9E-09	1.14 (1.09-1.19)	12,865	55,074	1.8E-09	1.11 (1.08-1.15)						
rs17168486	7	14,864,807	T	C	Male	5,253	20,945	5.8E-10	1.23 (1.16-1.32)	13,842	32,361	4.9E-06	1.11 (1.06-1.16)	19,095	53,306	6.5E-13	1.15 (1.11-1.19)	32,249	111,929	1.2E-13	6.8E-03	<i>DGKB</i>	Lead SNP from sex-differentiated meta-analysis
					Female	4,327	32,865	3.3E-01	1.03 (0.97-1.11)	8,827	25,758	3.9E-03	1.08 (1.02-1.13)	13,154	58,623	5.2E-03	1.06 (1.02-1.11)						
rs6960043	7	15,019,385	C	T	Male	6,377	22,243	2.6E-03	1.07 (1.03-1.13)	13,613	31,718	7.5E-05	1.08 (1.04-1.11)	19,990	53,961	7.9E-07	1.07 (1.04-1.11)	34,513	113,801	1.9E-07	1.2E-01	<i>DGKB</i>	Lead SNP for putative secondary signal from sex-combined meta-analysis
					Female	5,794	34,619	7.2E-03	1.07 (1.02-1.12)	8,729	25,221	2.9E-01	1.02 (0.98-1.06)	14,523	59,840	1.5E-02	1.04 (1.01-1.07)						
rs163184	11	2,803,645	G	T	Male	5,253	20,945	2.3E-05	1.12 (1.06-1.18)	13,578	31,385	4.7E-11	1.13 (1.09-1.17)	18,831	52,330	8.5E-15	1.12 (1.09-1.16)	31,874	110,307	2.4E-15	1.3E-03	<i>KCNQ1</i>	Lead SNP from sex-differentiated meta-analysis
					Female	4,327	32,865	4.2E-02	1.06 (1.00-1.12)	8,716	25,112	5.0E-02	1.04 (1.00-1.08)	13,043	57,977	7.8E-03	1.05 (1.01-1.08)						
rs231361	11	2,648,076	A	G	Male	5,253	20,945	5.2E-03	1.09 (1.03-1.16)	13,842	32,361	1.4E-04	1.08 (1.04-1.12)	19,095	53,306	2.9E-06	1.08 (1.05-1.12)	32,249	111,929	1.8E-10	7.2E-01	<i>KCNQ1</i>	Lead SNP for putative secondary signal from sex-combined meta-analysis
					Female	4,327	32,865	1.7E-03	1.11 (1.04-1.18)	8,827	25,758	1.8E-04	1.09 (1.04-1.13)	13,154	58,623	2.9E-06	1.09 (1.05-1.13)						
rs11063069	12	4,244,634	G	A	Male	5,096	14,646	3.0E-06	1.16 (1.09-1.24)	13,338	30,361	2.3E-05	1.10 (1.05-1.15)	18,434	45,007	1.1E-09	1.12 (1.08-1.16)	31,756	86,881	9.8E-10	1.3E-02	<i>CCND2</i>	Lead SNP from sex-differentiated meta-analysis
					Female	4,931	18,325	7.5E-02	1.06 (0.99-1.13)	8,391	23,549	1.7E-01	1.04 (0.99-1.09)	13,322	41,874	3.6E-02	1.04 (1.00-1.09)						
rs8108269	19	50,850,353	G	T	Male	6,377	22,243	8.8E-02	1.05 (0.99-1.11)	13,842	32,361	1.7E-02	1.05 (1.01-1.09)	20,219	54,604	3.7E-03	1.05 (1.02-1.08)	34,840	114,981	2.1E-08	5.7E-02	<i>GIPR</i>	Lead SNP from sex-differentiated meta-analysis
					Female	5,794	34,619	4.1E-03	1.09 (1.03-1.15)	8,827	25,758	4.7E-06	1.10 (1.06-1.15)	14,621	60,377	2.2E-07	1.10 (1.06-1.14)						

Chr: chromosome. OR: odds-ratio. CI: confidence interval.

^aAlleles are aligned to the forward strand of NCBI Build 36.

^bRisk allele from sex-combined meta-analysis.

Supplementary Table 8. Lead SNPs from sex-differentiated meta-analysis for 65 novel and established T2D susceptibility loci.

SNP	Chr	Position (Build 36 bp)	Alleles		Male-specific meta-analysis				Female-specific meta-analysis				Sex-differentiated meta-analysis				Locus	Sex-combined meta-analysis	
			Risk	Other	Cases	Controls	p-value	OR (95% CI)	Cases	Controls	p-value	OR (95% CI)	Cases	Controls	p-value	Heterogeneity p-value		Lead SNP	CEU r ²
rs2641352	1	120,247,586	C	T	18,362	50,663	4.6E-03	1.07 (1.02-1.12)	12,718	56,414	3.1E-05	1.11 (1.06-1.17)	31,080	107,077	3.0E-06	2.2E-01	NOTCH2	rs10923931	1.00
rs2075423	1	212,221,342	G	T	20,219	54,604	9.3E-06	1.07 (1.04-1.10)	14,621	60,377	1.0E-05	1.08 (1.04-1.11)	34,840	114,981	3.2E-09	7.7E-01	PROX1	rs2075423	Same SNP
rs780094	2	27,594,741	C	T	20,219	54,604	4.7E-05	1.06 (1.03-1.09)	14,621	60,377	1.2E-03	1.05 (1.02-1.09)	34,840	114,981	1.3E-06	7.4E-01	GCKR	rs780094	Same SNP
rs13405158	2	43,558,790	T	C	20,219	54,604	5.2E-10	1.16 (1.11-1.22)	14,621	60,377	6.4E-04	1.10 (1.04-1.15)	34,840	114,981	1.2E-11	1.0E-01	THADA	rs10203174	1.00
rs243088	2	60,422,249	T	A	19,095	53,306	6.5E-10	1.10 (1.06-1.13)	13,154	58,623	2.8E-02	1.04 (1.00-1.07)	32,249	111,929	4.7E-10	1.2E-02	BCL11A	rs243088	Same SNP
rs7569522	2	161,054,693	A	G	20,219	54,604	3.1E-02	1.03 (1.00-1.06)	14,621	60,377	9.5E-05	1.06 (1.03-1.10)	34,840	114,981	4.8E-05	1.5E-01	RBMS1	rs7569522	Same SNP
rs3923113	2	165,210,095	A	C	18,662	46,702	4.9E-03	1.05 (1.01-1.08)	12,865	55,074	1.8E-09	1.11 (1.08-1.15)	31,527	101,776	2.6E-10	8.0E-03	GRB14	rs13389219	0.77
rs2943640	2	226,801,829	C	A	20,219	54,604	3.0E-08	1.09 (1.06-1.12)	14,621	60,377	1.3E-09	1.11 (1.07-1.14)	34,840	114,981	2.2E-15	4.5E-01	IRS1	rs2943640	Same SNP
rs11709077	3	12,311,507	G	A	20,219	54,604	1.5E-07	1.12 (1.07-1.17)	14,621	60,377	1.1E-08	1.14 (1.09-1.20)	34,840	114,981	8.7E-14	5.1E-01	PPARG	rs1801282	1.00
rs1496653	3	23,429,794	A	G	20,219	54,604	4.4E-07	1.09 (1.05-1.13)	14,621	60,377	3.3E-03	1.06 (1.02-1.10)	34,840	114,981	3.8E-08	2.3E-01	UBE2E2	rs1496653	Same SNP
rs12497268	3	64,065,403	G	C	20,219	54,604	6.9E-03	1.05 (1.01-1.09)	14,621	60,377	5.9E-01	1.01 (0.97-1.05)	34,840	114,981	2.2E-02	1.5E-01	PSMD6	rs12497268	Same SNP
rs4611812	3	64,674,485	C	T	19,095	53,306	1.1E-06	1.08 (1.05-1.11)	13,154	58,623	3.3E-07	1.09 (1.05-1.13)	32,249	111,929	1.6E-11	5.8E-01	ADAMTS9	rs6795735	0.94
rs11708067	3	124,548,468	A	G	20,219	54,604	4.1E-07	1.09 (1.06-1.13)	14,621	60,377	1.7E-10	1.13 (1.09-1.18)	34,840	114,981	3.8E-15	1.8E-01	ADCY5	rs11717195	0.80
rs7640539	3	186,995,990	A	T	18,866	52,663	1.5E-17	1.14 (1.11-1.18)	13,043	57,977	1.8E-09	1.11 (1.07-1.15)	31,909	110,640	2.3E-24	2.2E-01	IGF2BP2	rs4402960	1.00
rs17301514	3	188,096,103	A	G	18,227	45,990	1.9E-02	1.06 (1.01-1.11)	12,557	42,745	1.3E-01	1.04 (0.99-1.10)	30,784	88,735	2.0E-02	6.6E-01	ST64GAL1	rs17301514	Same SNP
rs2306248	4	850,146	G	A	19,095	53,306	2.0E-01	0.98 (0.95-1.01)	13,154	58,623	1.3E-02	1.04 (1.01-1.08)	32,249	111,929	2.0E-02	6.9E-03	MAEA	rs6819243	0.01
rs1801214	4	6,353,923	T	C	19,095	53,306	2.9E-12	1.11 (1.08-1.15)	13,154	58,623	5.0E-07	1.09 (1.05-1.13)	32,249	111,929	8.6E-17	3.6E-01	WFS1	rs4458523	1.00
rs459193	5	55,842,508	G	A	19,095	53,306	3.4E-06	1.08 (1.05-1.12)	13,154	58,623	1.1E-05	1.09 (1.05-1.13)	32,249	111,929	1.3E-09	8.4E-01	ANKRD55	rs459193	Same SNP
rs6878122	5	76,463,067	G	A	18,566	52,766	2.6E-10	1.12 (1.08-1.15)	12,661	58,088	2.3E-04	1.07 (1.03-1.12)	31,227	110,854	2.4E-12	1.4E-01	ZBED3	rs6878122	Same SNP
rs7756992	6	20,787,688	G	A	20,219	54,604	1.5E-22	1.17 (1.13-1.20)	14,621	60,377	1.9E-20	1.17 (1.14-1.22)	34,840	114,981	4.0E-40	7.7E-01	CDKAL1	rs7756992	Same SNP
rs4299828	6	38,285,645	A	G	20,219	54,604	1.9E-02	1.04 (1.01-1.08)	14,621	60,377	2.8E-01	1.02 (0.98-1.06)	34,840	114,981	3.5E-02	4.4E-01	ZFAND3	rs4299828	Same SNP
rs1537230	6	39,052,174	G	A	20,219	54,604	1.9E-01	1.02 (0.99-1.05)	14,621	60,377	3.8E-05	1.07 (1.04-1.11)	34,840	114,981	8.7E-05	3.0E-02	KCNK16	rs3734621	0.01
rs17168486	7	14,864,807	T	C	19,095	53,306	6.5E-13	1.15 (1.11-1.19)	13,154	58,623	5.2E-03	1.06 (1.02-1.11)	32,249	111,929	1.2E-13	6.8E-03	DGKB	rs17168486	Same SNP
rs849135	7	28,162,938	G	A	19,095	53,306	3.2E-13	1.11 (1.08-1.15)	13,154	58,623	2.0E-08	1.10 (1.06-1.13)	32,249	111,929	4.4E-19	4.7E-01	JAZF1	rs849135	Same SNP
rs4607517	7	44,202,193	A	G	18,662	46,702	9.2E-04	1.07 (1.03-1.11)	12,865	55,074	5.2E-04	1.08 (1.04-1.13)	31,527	101,776	9.9E-06	6.9E-01	GCK	rs10278336	0.18
rs17867832	7	126,784,073	T	G	11,770	32,695	1.8E-01	1.05 (0.98-1.12)	8,282	41,116	4.7E-04	1.14 (1.06-1.22)	20,052	73,811	8.8E-04	9.9E-02	GCC1	rs17867832	Same SNP
rs6467314	7	130,092,681	G	C	19,095	53,306	5.6E-01	1.01 (0.98-1.04)	13,154	58,623	2.2E-06	1.09 (1.05-1.13)	32,249	111,929	1.1E-05	1.8E-03	KLF14	rs13233731	0.32
rs516946	8	41,638,405	C	T	20,219	54,604	7.8E-11	1.12 (1.08-1.16)	14,621	60,377	1.1E-03	1.06 (1.03-1.10)	34,840	114,981	3.1E-12	5.2E-02	ANK1	rs516946	Same SNP
rs7845219	8	96,006,678	T	C	19,095	53,306	7.2E-06	1.07 (1.04-1.10)	13,154	58,623	1.8E-03	1.05 (1.02-1.09)	32,249	111,929	3.2E-07	5.0E-01	TP53INP1	rs7845219	Same SNP
rs3802177	8	118,254,206	G	A	18,840	52,613	1.4E-16	1.15 (1.11-1.18)	12,976	57,878	7.2E-11	1.13 (1.09-1.17)	31,816	110,491	9.2E-25	5.1E-01	SLC30A8	rs3802177	Same SNP
rs10758593	9	4,282,083	A	G	18,797	51,826	5.8E-07	1.08 (1.05-1.11)	12,911	56,746	1.0E-02	1.04 (1.01-1.08)	31,708	108,572	1.4E-07	1.6E-01	GLIS3	rs10758593	Same SNP
rs16927668	9	8,359,533	T	C	19,095	53,306	1.0E-02	1.05 (1.01-1.08)	13,154	58,623	1.7E-02	1.05 (1.01-1.09)	32,249	111,929	2.1E-03	9.3E-01	PTPRD	rs16927668	Same SNP
rs10965250	9	22,123,284	G	A	19,095	53,306	8.5E-15	1.17 (1.13-1.22)	13,154	58,623	5.7E-16	1.20 (1.15-1.26)	32,249	111,929	4.9E-28	4.1E-01	CDKN2A/B	rs10811661	0.92
rs17791513	9	81,095,410	A	G	19,095	53,306	2.8E-06	1.14 (1.10-1.20)	13,108	58,283	1.5E-02	1.08 (1.02-1.15)	32,203	111,589	8.8E-07	2.1E-01	TLE4	rs17791513	Same SNP
rs2796441	9	83,498,768	G	A	19,690	54,064	4.9E-09	1.09 (1.06-1.13)	14,128	59,842	5.0E-03	1.05 (1.01-1.08)	33,818	113,906	7.2E-10	6.4E-02	TLE1	rs2796441	Same SNP
rs11257655	10	12,347,900	T	C	18,761	52,172	8.3E-04	1.06 (1.02-1.10)	13,154	58,623	5.9E-05	1.08 (1.04-1.13)	31,915	110,795	1.2E-06	4.5E-01	CDC123/CAMK1D	rs11257655	Same SNP
rs5030913	10	70,676,137	T	G	20,219	54,604	6.7E-01	1.01 (0.98-1.04)	14,621	60,377	1.1E-03	1.06 (1.02-1.10)	34,840	114,981	4.4E-03	3.4E-02	VPS26A	rs12242953	0.02
rs12571751	10	80,612,637	A	G	20,219	54,604	6.4E-07	1.07 (1.04-1.11)	14,621	60,377	1.2E-06	1.08 (1.05-1.12)	34,840	114,981	3.1E-11	7.8E-01	ZMIZ1	rs12571751	Same SNP
rs1111875	10	94,452,862	C	T	20,219	54,604	4.9E-12	1.11 (1.07-1.14)	14,621	60,377	6.7E-13	1.12 (1.09-1.16)	34,840	114,981	2.7E-22	4.9E-01	HHEX/IDE	rs1111875	Same SNP
rs7903146	10	114,748,339	T	C	19,095	53,306	5.6E-92	1.39 (1.35-1.44)	13,154	58,623	4.0E-73	1.39 (1.34-1.44)	32,249	111,929	1.3E-161	8.7E-01	TCF7L2	rs7903146	Same SNP
rs2334499	11	1,653,425	T	C	19,095	53,306	8.5E-04	1.05 (1.02-1.08)	13,154	58,623	1.1E-01	1.03 (0.99-1.06)	32,249	111,929	1.1E-03	2.9E-01	DUSP8	rs2334499	Same SNP
rs163184	11	2,803,645	G	T	18,831	52,330	8.5E-15	1.12 (1.09-1.16)	13,043	57,977	7.8E-03	1.05 (1.01-1.08)	31,874	110,307	2.4E-15	1.3E-03	KCNQ1	rs163184	Same SNP
rs757110	11	17,375,053	C	A	19,095	53,306	2.5E-06	1.07 (1.04-1.11)	13,154	58,623	9.7E-06	1.08 (1.04-1.11)	32,249	111,929	8.6E-10	8.9E-01	KCNJ11	rs5215	0.87
rs1552224	11	72,110,746	A	C	19,095	53,306	8.7E-09	1.12 (1.08-1.16)	13,154	58,623	1.3E-04	1.09 (1.04-1.14)	32,249	111,929	4.4E-11	3.3E-01	ARAP1 (CENTD2)	rs1552224	Same SNP
rs10830963	11	92,348,358	G	C	19,955	53,628	2.7E-10	1.11 (1.07-1.14)	13,141	58,514	1.4E-05	1.08 (1.05-1.12)	33,096	112,142	1.8E-13	3.7E-01	MTNR1B	rs10830963	Same SNP
rs11063069	12	4,244,634	G	A	19,715	52,604	1.1E-09	1.12 (1.08-1.16)	14,185	58,168	3.6E-02	1.04 (1.00-1.09)	33,900	110,772	9.8E-10	1.3E-02	CCND2	rs11063069	Same SNP
rs10842994	12	27,856,417	C	T	20,219	54,604	3.2E-08	1.11 (1.07-1.15)	14,621	60,377	5.3E-04	1.07 (1.03-1.12)	34,840	114,981	5.6E-10	2.4E-01	KLHDC5	rs10842994	Same SNP
rs2261181	12	64,498,585	T	C	19,955	53,628	1.1E-07	1.14 (1.09-1.19)	14,510	59,731	1.3E-04	1.11 (1.05-1.17)	34,465	113,359	5.1E-10	4.7E-01	HMGA2	rs2261181	Same SNP
rs7138300	12	69,725,856	C	T	20,219	54,604	1.8E-06	1.07 (1.04-1.10)	14,621	60,377	1.0E-05	1.07 (1.04-1.11)	34,840	114,981	6.8E-10	9.7E-01	TSPAN8/LGR5	rs7955901	0.90
rs12427353	12	119,911,284	G	C	19,095	53,306	3.5E-05	1.08 (1.04-1.12)	13,154	58,623	2.5E-05	1.09 (1.05-1.14)	32,249	111,929	2.7E-08	7.6E-01	HNF1A (TCF1)	rs12427353	Same SNP
rs1359790	13	79,615,157	G	A	19,885	53,470	1.6E-05	1.07 (1.04-1.11)	14,448	58,958	6.7E-05	1.07 (1.04-1.11)	34,333	112,428	3.3E-08	9.6E-01	SPRY2	rs1359790	Same SNP
rs4502156	15	60,170,447	T	C	19,095	53,306	3.3E-05	1.06 (1.03-1.10)	13,154	58,623	3.7E-03	1.05 (1.02-1.08)	32,249	111,929	2.7E-06				

Supplementary Table 9. Meta-analysis summary statistics for loci demonstrating genome-wide significant evidence ($p < 5 \times 10^{-8}$) of association for both T2D and FG (or FG adjusted for BMI) in (i): the present study for T2D; and (ii) up to 133,010 non-diabetic individuals of European descent from the MAGIC Investigators for FG.

Locus	Lead SNP for FG	Chr	Position	Alleles ^a		Combined meta-analysis (T2D)					MAGIC meta-analysis (FG or FG adjusted for BMI)				
				Risk ^b	Other	Risk allele frequency	Cases	Controls	<i>p</i> -value	OR (95% CI)	Risk allele frequency	Sample size	<i>p</i> -value	Beta	SE
Previously reported loci for both T2D and FG															
<i>MTNR1B</i>	rs10830963	11	92,348,358	G	C	0.29	21,866	56,045	5.3E-13	1.10 (1.07-1.13)	0.29	124,513	1.1E-215	0.078	0.002
<i>GCK</i>	rs2908289	7	44,190,467	A	G	0.15	22,669	58,119	2.2E-05	1.07 (1.04-1.10)	0.16	128,047	3.3E-88	0.057	0.003
<i>DGKB</i>	rs2191349	7	15,030,834	T	G	0.52	22,669	58,119	3.0E-05	1.05 (1.03-1.08)	0.53	123,378	1.3E-42	0.029	0.002
<i>GCKR</i>	rs780094	2	27,594,741	C	T	0.62	22,669	58,119	5.4E-07	1.06 (1.04-1.09)	0.61	127,460	2.6E-37	0.027	0.002
<i>SLC30A8</i>	rs11558471	8	118,254,914	A	G	0.66	22,669	58,119	1.1E-20	1.13 (1.10-1.16)	0.68	127,858	7.8E-37	0.029	0.002
<i>C2CD4A</i>	rs4502156	15	60,170,447	T	C	0.53	22,669	58,119	2.3E-06	1.06 (1.03-1.08)	0.55	128,155	1.4E-25	0.022	0.002
<i>TCF7L2</i>	rs7903146	10	114,748,339	T	C	0.25	22,669	58,119	1.2E-139	1.39 (1.35-1.42)	0.28	127,477	2.7E-20	0.022	0.002
<i>ADCY5</i>	rs11708067	3	124,548,468	A	G	0.79	22,669	58,119	7.2E-14	1.11 (1.08-1.14)	0.79	128,599	1.3E-18	0.023	0.003
<i>PROX1</i>	rs340874	1	212,225,879	C	T	0.52	22,669	58,119	1.1E-07	1.07 (1.04-1.09)	0.52	127,021	4.1E-10	0.013	0.002
Novel loci for both T2D and FG															
<i>CDKN2A/B</i>	rs10811661	9	22,124,094	T	C	0.83	22,669	58,119	3.7E-27	1.18 (1.15-1.22)	0.82	128,488	5.7E-18	0.024	0.003
<i>ARAP1 (CENTD2)</i>	rs1783598	11	72,529,111	T	C	0.76	22,669	58,119	8.2E-08	1.08 (1.05-1.11)	0.79	127,480	1.2E-10	0.017	0.003
<i>IGF2BP2</i>	rs7651090	3	186,996,086	G	A	0.31	22,669	58,119	3.4E-23	1.13 (1.10-1.16)	0.31	128,548	1.8E-08	0.013	0.002
<i>CDKAL1</i>	rs2328548	6	20,824,937	A	G	0.18	22,669	58,119	1.9E-23	1.16 (1.13-1.20)	0.18	123,391	2.0E-08	0.015	0.003
Novel loci for both T2D and FG adjusted for BMI															
<i>ZBED3</i>	rs7708285	5	76,461,623	G	A	0.27	22,342	56,939	1.5E-10	1.10 (1.07-1.13)	0.27	117,931	1.2E-08	0.015	0.003

Chr: chromosome. OR: odds-ratio. CI: confidence interval. SE: standard error.

^aAlleles are aligned to the forward strand of NCBI Build 36.

^bRisk allele for T2D from our combined meta-analysis.

Supplementary Table 10. Summary statistics for lead SNPs at novel and established T2D susceptibility loci in a meta-analysis of glycaemic traits in up to 133,010 non-diabetic individuals of European descent from the MAGIC Investigators.

SNP	Chr	Position (Build 36 bp)	Alleles ^a		Locus	Fasting glucose				Fasting insulin				HOMA-IR				HOMA-B			
			Risk ^b	Other		Beta	SE	p-value	Sample size	Beta	SE	p-value	Sample size	Beta	SE	p-value	Sample size	Beta	SE	p-value	Sample size
rs10923931	1	120,319,482	T	G	NOTCH2	0.0139	0.0053	8.7E-03	53,569	0.0018	0.0057	7.5E-01	42,854	0.0011	0.0064	8.7E-01	36,848	-0.0045	0.0052	3.8E-01	36,277
rs2075423	1	212,221,342	G	T	PROX1	0.0164	0.0036	7.1E-06	52,627	-0.0108	0.0039	5.8E-03	41,998	-0.0061	0.0044	1.6E-01	35,895	-0.0125	0.0035	3.9E-04	35,429
rs780094	2	27,594,741	C	T	GCKR	0.0274	0.0021	2.6E-37	127,460	0.0187	0.0025	7.1E-14	103,026	0.0201	0.0041	7.6E-07	35,899	0.0039	0.0034	2.5E-01	35,433
rs10203174	2	43,543,534	C	T	THADA	0.0160	0.0036	8.7E-06	128,571	-0.0109	0.0043	1.1E-02	104,031	-0.0125	0.0070	7.5E-02	37,020	-0.0262	0.0059	9.8E-06	36,449
rs243088	2	60,422,249	T	A	BCL11A	0.0096	0.0034	4.4E-03	53,312	0.0040	0.0036	2.6E-01	42,608	0.0026	0.0040	5.1E-01	36,602	0.0006	0.0033	8.6E-01	36,031
rs7569522	2	161,054,693	A	G	RBMS1	0.0063	0.0021	2.4E-03	132,848	0.0068	0.0024	4.7E-03	108,413	0.0068	0.0041	9.3E-02	36,933	0.0006	0.0034	8.6E-01	36,362
rs13389219	2	165,237,122	C	T	GRB14	0.0002	0.0034	9.4E-01	53,754	0.0133	0.0036	2.7E-04	43,028	0.0124	0.0041	2.2E-03	37,021	0.0073	0.0034	3.0E-02	36,451
rs2943640	2	226,801,829	C	A	IRS1	0.0031	0.0022	1.5E-01	128,565	0.0134	0.0025	1.4E-07	104,040	0.0086	0.0041	3.6E-02	37,022	0.0070	0.0034	3.7E-02	36,451
rs1801282	3	12,368,125	C	G	PPARG	0.0099	0.0049	4.2E-02	53,770	0.0185	0.0051	3.3E-04	43,043	0.0161	0.0058	5.6E-03	37,037	0.0062	0.0047	1.8E-01	36,466
rs1496653	3	23,429,794	A	G	UBE2E2	0.0050	0.0024	3.7E-02	131,768	-0.0120	0.0028	1.7E-05	103,956	-0.0135	0.0047	3.8E-03	35,839	-0.0088	0.0038	1.9E-02	35,373
rs12497268	3	64,065,403	G	C	PSMD6	0.0075	0.0027	4.9E-03	132,966	0.0032	0.0031	2.9E-01	108,517	0.0040	0.0052	4.5E-01	37,034	-0.0041	0.0042	3.3E-01	36,463
rs6795735	3	64,680,405	C	T	ADAMTS9	0.0040	0.0021	6.0E-02	127,473	0.0000	0.0025	1.0E+00	103,032	0.0069	0.0040	8.6E-02	35,910	0.0011	0.0033	7.5E-01	35,444
rs11717195	3	124,565,088	T	C	ADCY5	0.0221	0.0026	1.7E-17	125,481	-0.0129	0.0030	1.8E-05	102,796	-0.0001	0.0051	9.8E-01	35,808	-0.0181	0.0043	2.7E-05	35,238
rs4402960	3	186,994,381	T	G	IGF2BP2	0.0125	0.0023	4.4E-08	127,307	-0.0009	0.0026	7.4E-01	102,883	-0.0079	0.0043	6.9E-02	35,770	-0.0115	0.0036	1.2E-03	35,304
rs17301514	3	188,096,103	A	G	ST6GAL1	0.0035	0.0036	3.3E-01	118,929	-0.0055	0.0041	1.9E-01	98,708	-0.0027	0.0078	7.3E-01	32,209	-0.0095	0.0065	1.4E-01	32,937
rs6819243	4	1,283,245	T	C	MAEA	0.0159	0.0060	8.4E-03	118,285	-0.0055	0.0062	3.8E-01	97,518	-0.0092	0.0121	4.4E-01	30,623	-0.0249	0.0096	9.5E-03	30,068
rs4458523	4	6,340,887	G	T	WFS1	0.0165	0.0034	1.0E-06	53,717	0.0021	0.0036	5.7E-01	42,993	0.0083	0.0041	4.2E-02	36,987	-0.0035	0.0034	3.0E-01	36,416
rs459193	5	55,842,508	G	A	ANKRD55	0.0111	0.0023	1.6E-06	132,989	0.0144	0.0027	6.6E-08	108,537	0.0115	0.0045	1.1E-02	37,034	0.0046	0.0037	2.1E-01	36,463
rs6878122	5	76,463,067	G	A	ZBED3	0.0115	0.0025	3.3E-06	128,033	0.0021	0.0029	4.7E-01	103,526	0.0049	0.0048	3.0E-01	32,498	-0.0070	0.0040	7.6E-02	31,945
rs7756992	6	20,787,688	G	A	CDKAL1	0.0141	0.0023	1.8E-09	127,467	-0.0095	0.0027	5.1E-04	99,562	-0.0096	0.0044	2.9E-02	35,896	-0.0095	0.0036	7.5E-03	35,430
rs4299828	6	38,285,645	A	G	ZFAND3	-0.0028	0.0026	2.8E-01	131,875	-0.0020	0.0030	4.9E-01	107,522	-0.0095	0.0050	5.6E-02	35,912	-0.0054	0.0041	1.8E-01	35,446
rs3734621	6	39,412,189	C	A	KCNK16	0.0020	0.0062	7.5E-01	130,537	-0.0002	0.0071	9.7E-01	105,934	0.0044	0.0122	7.2E-01	35,966	0.0046	0.0100	6.5E-01	35,454
rs17168486	7	14,864,807	T	C	DGKB	0.0306	0.0028	3.2E-28	127,472	0.0016	0.0032	6.3E-01	103,034	0.0051	0.0053	3.4E-01	35,902	-0.0126	0.0043	3.0E-03	35,436
rs849135	7	28,162,938	G	A	JAZF1	0.0063	0.0021	2.6E-03	128,602	-0.0021	0.0025	3.9E-01	100,600	-0.0012	0.0040	7.7E-01	37,032	-0.0036	0.0033	2.7E-01	36,461
rs10278336	7	44,211,888	A	G	GCK	0.0371	0.0035	1.9E-26	53,080	0.0074	0.0037	4.8E-02	42,388	0.0092	0.0042	2.7E-02	36,382	-0.0128	0.0034	2.1E-04	35,811
rs17867832	7	126,784,073	T	G	GCC1	-0.0028	0.0044	5.3E-01	82,995	-0.0063	0.0050	2.0E-01	72,577	-0.0103	0.0069	1.4E-01	37,026	-0.0068	0.0057	2.3E-01	36,455
rs13233731	7	130,088,229	G	A	KLF14	0.0054	0.0022	1.2E-02	122,723	0.0049	0.0025	5.0E-02	98,823	0.0077	0.0040	5.1E-02	37,022	0.0031	0.0033	3.5E-01	36,451
rs516946	8	41,638,405	C	T	ANK1	0.0074	0.0024	1.7E-03	132,954	-0.0051	0.0028	6.3E-02	105,035	-0.0078	0.0045	8.6E-02	37,033	-0.0132	0.0038	5.3E-04	36,462
rs7845219	8	96,006,678	T	C	TP53BP1	0.0077	0.0020	1.8E-04	132,999	-0.0013	0.0024	6.0E-01	108,541	-0.0026	0.0040	5.2E-01	37,034	-0.0055	0.0033	9.4E-02	36,463
rs3802177	8	118,254,206	G	A	SLC30A8	0.0276	0.0023	1.8E-32	128,022	-0.0070	0.0027	1.1E-02	103,485	-0.0005	0.0047	9.2E-01	37,025	-0.0160	0.0038	2.0E-05	36,454
rs10758593	9	4,282,083	A	G	GLIS3	0.0157	0.0022	1.2E-12	119,145	-0.0110	0.0026	1.9E-05	94,789	-0.0060	0.0040	1.4E-01	35,908	-0.0145	0.0033	1.3E-05	35,442
rs16927668	9	8,359,533	T	C	PTPRD	0.0006	0.0025	8.1E-01	132,990	0.0009	0.0029	7.5E-01	108,536	0.0037	0.0048	4.4E-01	37,024	0.0013	0.0040	7.4E-01	36,453
rs10811661	9	22,124,094	T	C	CDKN2A/B	0.0238	0.0028	5.7E-18	128,488	-0.0044	0.0032	1.8E-01	103,955	0.0054	0.0052	3.0E-01	36,988	-0.0085	0.0043	5.1E-02	36,417
rs17791513	9	81,095,410	A	G	TLE4	-0.0008	0.0038	8.4E-01	132,888	-0.0045	0.0043	3.0E-01	108,553	0.0026	0.0075	7.3E-01	33,028	0.0013	0.0059	8.3E-01	32,473
rs2796441	9	83,498,768	G	A	TLE1	-0.0002	0.0022	9.3E-01	132,285	0.0030	0.0025	2.3E-01	107,832	0.0076	0.0045	9.4E-02	36,328	0.0034	0.0037	3.5E-01	35,757
rs11257655	10	12,347,900	T	C	CDC123/CAMK1D	0.0132	0.0026	4.4E-07	127,025	0.0004	0.0030	8.9E-01	102,606	-0.0001	0.0050	9.9E-01	35,479	-0.0091	0.0041	2.5E-02	35,013
rs12242953	10	70,535,348	G	A	VPS26A	-0.0009	0.0043	8.4E-01	131,865	0.0016	0.0050	7.5E-01	107,335	-0.0026	0.0084	7.6E-01	35,914	-0.0078	0.0070	2.6E-01	35,448
rs12571751	10	80,612,637	A	G	ZMIZ1	0.0003	0.0021	8.9E-01	129,435	-0.0024	0.0024	3.1E-01	105,043	0.0011	0.0040	7.9E-01	37,035	0.0012	0.0033	7.2E-01	36,464
rs1111875	10	94,452,862	C	T	HHEX/IDE	0.0040	0.0021	6.2E-02	127,461	-0.0037	0.0025	1.4E-01	99,561	0.0028	0.0040	4.9E-01	35,912	-0.0042	0.0033	2.0E-01	35,446
rs7903146	10	114,748,339	T	C	TCF7L2	0.0220	0.0024	2.7E-20	127,477	-0.0181	0.0028	6.1E-11	103,037	-0.0096	0.0045	3.4E-02	35,903	-0.0200	0.0038	1.4E-07	35,437
rs2334499	11	1,653,425	T	C	DUSP8	0.0000	0.0021	9.9E-01	131,414	-0.0007	0.0025	7.7E-01	103,619	-0.0002	0.0042	9.7E-01	35,478	0.0000	0.0034	9.9E-01	35,012
rs163184	11	2,803,645	G	T	KCNQ1	0.0079	0.0022	3.5E-04	125,677	-0.0017	0.0026	5.2E-01	101,869	0.0007	0.0044	8.7E-01	35,476	-0.0086	0.0035	1.6E-02	35,010
rs5215	11	17,365,206	C	T	KCNJ11	-0.0025	0.0022	2.6E-01	121,160	-0.0056	0.0026	3.0E-02	97,873	-0.0018	0.0041	6.6E-01	35,882	0.0009	0.0033	7.8E-01	35,416
rs1552224	11	72,110,746	A	C	ARAP1 (CENTD2)	0.0191	0.0028	1.5E-11	127,016	-0.0123	0.0033	1.7E-04	102,607	-0.0092	0.0054	8.5E-02	35,479	-0.0166	0.0043	9.4E-05	35,013
rs10830963	11	92,348,358	G	C	MTNR1B	0.0779	0.0025	1.1E-215	124,513	-0.0013	0.0029	6.6E-01	100,402	0.0083	0.0049	9.1E-02	37,031	-0.0394	0.0040	8.6E-23	36,460
rs11063069	12	4,244,634	G	A	CCND2	0.0082	0.0027	2.7E-03	127,579	-0.0006	0.										

Supplementary Table 11. Summary statistics for lead SNPs at novel loci in a meta-analysis of BMI in up to 249,796 individuals of European descent, excluding T2D cohorts, from the GIANT Consortium.

SNP	Chr	Position (Build 36 bp)	Alleles ^a		Locus	Beta	SE	p-value	Sample size
			Risk ^b	Other					
rs13389219	2	165,237,122	C	T	<i>GRB14</i>	-0.0116	0.0049	1.8E-02	119,537
rs459193	5	55,842,508	G	A	<i>ANKRD55</i>	-0.0051	0.0055	3.5E-01	119,547
rs516946	8	41,638,405	C	T	<i>ANK1</i>	-0.0035	0.0056	5.3E-01	119,130
rs2796441	9	83,498,768	G	A	<i>TLE1</i>	-0.0005	0.0053	9.2E-01	119,538
rs12571751	10	80,612,637	A	G	<i>ZMIZ1</i>	0.0062	0.0048	2.0E-01	119,516
rs11063069	12	4,244,634	G	A	<i>CCND2</i>	-0.0090	0.0066	1.7E-01	119,532
rs10842994	12	27,856,417	C	T	<i>KLHDC5</i>	-0.0044	0.0061	4.7E-01	119,398
rs7177055	15	75,619,817	A	G	<i>HMG20A</i>	0.0102	0.0053	5.2E-02	119,548
rs7202877	16	73,804,746	T	G	<i>BCAR1</i>	-0.0102	0.0081	2.1E-01	119,554
rs12970134	18	56,035,730	A	G	<i>MC4R</i>	0.0483	0.0054	2.3E-19	119,529
rs10401969	19	19,268,718	C	T	<i>CILP2</i>	-0.0074	0.0101	4.6E-01	119,303
rs8108269	19	50,850,353	G	T	<i>GIPR</i>	0.0001	0.0057	9.9E-01	118,633

Chr: chromosome. SE: standard error.

^aAlleles are aligned to the forward strand of NCBI Build 36.

^bRisk allele for T2D from our combined meta-analysis.

Supplementary Table 12. Summary statistics for lead SNPs at novel loci in a meta-analysis of lipid traits in up to 100,184 individuals of European descent from the Global Lipids Genetics Consortium.

SNP	Chr	Position (Build 36 bp)	Alleles ^a		Locus	High-density lipoprotein cholesterol			Low-density lipoprotein cholesterol			Total cholesterol			Triglycerides		
			Risk ^b	Other		Z-score	Sample size	p-value	Z-score	Sample size	p-value	Z-score	Sample size	p-value	Z-score	Sample size	p-value
rs13389219	2	165,237,122	C	T	<i>GRB14</i>	-5.20	99,892	2.0E-07	4.57	95,446	5.0E-06	4.14	100,176	3.4E-05	6.30	96,590	3.1E-10
rs459193	5	55,842,508	G	A	<i>ANKRD55</i>	-3.56	99,900	3.8E-04	-1.24	95,454	2.2E-01	-1.35	100,184	1.8E-01	4.07	96,598	4.7E-05
rs516946	8	41,638,405	C	T	<i>ANK1</i>	0.98	96,841	3.3E-01	0.11	92,441	9.1E-01	-0.07	97,081	9.4E-01	-0.55	93,495	5.8E-01
rs2796441	9	83,498,768	G	A	<i>TLE1</i>	0.18	99,897	8.6E-01	1.95	95,451	5.1E-02	1.27	100,181	2.0E-01	-1.72	96,595	8.5E-02
rs12571751	10	80,612,637	A	G	<i>ZMIZ1</i>	-2.18	96,900	2.9E-02	0.31	92,495	7.6E-01	0.60	97,140	5.5E-01	2.73	93,554	6.4E-03
rs11063069	12	4,244,634	G	A	<i>CCND2</i>	-0.36	99,890	7.2E-01	2.25	95,444	2.4E-02	2.71	100,174	6.6E-03	2.61	96,588	9.0E-03
rs10842994	12	27,856,417	C	T	<i>KLHDC5</i>	-0.99	99,872	3.2E-01	1.57	95,427	1.2E-01	0.90	100,154	3.7E-01	-1.03	96,568	3.0E-01
rs7177055	15	75,619,817	A	G	<i>HMG20A</i>	-1.21	98,370	2.3E-01	0.32	93,962	7.5E-01	-0.24	98,617	8.1E-01	0.45	95,031	6.6E-01
rs7202877	16	73,804,746	T	G	<i>BCAR1</i>	-2.13	98,409	3.3E-02	-0.27	93,999	7.9E-01	-0.82	98,656	4.2E-01	0.48	95,070	6.3E-01
rs12970134	18	56,035,730	A	G	<i>MC4R</i>	-4.42	98,409	9.7E-06	-0.63	93,999	5.3E-01	-0.75	98,656	4.5E-01	4.51	95,070	6.4E-06
rs10401969	19	19,268,718	C	T	<i>CILP2</i>	0.56	98,393	5.8E-01	-9.62	93,983	6.7E-22	-12.93	98,640	2.9E-38	-11.28	95,054	1.6E-29
rs8108269	19	50,850,353	G	T	<i>GIPR</i>	-3.41	98,337	6.6E-04	-1.63	93,933	1.0E-01	-2.54	98,583	1.1E-02	-9.64	84,180	5.4E-22

Chr: chromosome.

^aAlleles are aligned to the forward strand of NCBI Build 36.

^bRisk allele for T2D from our combined meta-analysis.

Supplementary Table 13. Evidence for *cis*-eQTL expression with lead T2D SNPs (and proxies) at novel T2D susceptibility loci in multiple tissues from public databases and unpublished resources.

Locus	SNP ID	Lead T2D SNP or proxy?	CEU r2 with lead SNP	Transcript	Tissue	<i>p</i> -value	Strongest association with expression		
							<i>cis</i> -eQTL SNP	CEU r2	<i>p</i> -value
<i>GRB14</i>	rs13389219	Lead	Same SNP	<i>GRB14</i>	Adipose	1.1E-10	rs10195252	0.93	6.8E-11
	rs10195252	Proxy	0.93	<i>GRB14</i>	Omental fat	4.2E-13	rs10195252	Same SNP	4.2E-13
<i>ANK1</i>	rs516946	Lead	Same SNP	<i>ANK1</i>	Subcutaneous fat	1.5E-21	rs516946	Same SNP	1.5E-21
	rs516946	Lead	Same SNP	<i>ANK1</i>	Omental fat	3.8E-09	rs6989203	1.00	1.9E-20
	rs516946	Lead	Same SNP	<i>ANK1</i>	Adipose	5.2E-34	rs6989203	1.00	1.9E-34
	rs515071	Proxy	1.00	<i>ANK1</i>	Liver	2.2E-02	rs515071	Same SNP	2.2E-02
	rs13266210	Proxy	0.80	<i>ANK1</i>	Prefrontal cortex	2.4E-06	rs13266210	Same SNP	2.4E-06
<i>KLHDC5</i>	rs3751235	Proxy	0.94	<i>KLHDC5</i>	Blood	3.2E-05	rs3751235	Same SNP	3.2E-05
	rs3751235	Proxy	0.94	<i>KLHDC5</i>	CD4+ lymphocytes	2.8E-05	rs3751235	Same SNP	2.8E-05
	rs12578595	Proxy	1.00	<i>KLHDC5</i>	T cells	4.0E-06	rs12578595	Same SNP	4.0E-06
<i>HMG20A</i>	rs7177055	Lead	Same SNP	<i>LINGO1</i>	Adipose	9.1E-06	rs907372	0.73	7.3E-09
	rs7178572	Proxy	0.89	<i>AL355738</i>	Liver	4.5E-05	rs7178572	Same SNP	4.5E-05
	rs7178572	Proxy	0.89	<i>HMG20A</i>	Liver	7.5E-05	rs7178572	Same SNP	7.5E-05
<i>CILP2</i>	rs16996185	Proxy	0.91	<i>ATP13A1</i>	Monocytes	2.9E-141	rs16996185	Same SNP	2.9E-141
	rs12610185	Proxy	0.91	<i>ATP13A1</i>	Blood	3.0E-05	rs2304130	0.55	1.1E-97
<i>BCAR1</i>	rs7202877	Lead	Same SNP	<i>BCAR1</i>	Blood	2.0E-70	rs13331385	1.00	6.1E-74

Supplementary Table 14. Evidence for *cis*-eQTL expression with lead T2D SNPs at novel T2D susceptibility loci in adipose tissue and blood in individuals from the Icelandic population.

T2D Lead SNP	Chr	Position (Build 36 bp)	Alleles ^a		Locus	Gene (transcript)	Tissue	Beta	SE	<i>p</i> -value	Adjusted <i>p</i> -value	Strongest association with expression			
			Risk ^b	Other								<i>cis</i> -eQTL SNP	CEU <i>r</i> ²	<i>p</i> -value	Conditional <i>p</i> -value
rs13389219	2	165,237,122	C	T	<i>GRB14</i>	<i>GRB14</i> (NM_004490)	Adipose	0.367	0.055	1.1E-10	8.6E-01	rs10195252	1.00	6.8E-11	3.5E-01
						<i>SLC38A11</i> (NM_173512)	Adipose	-0.341	0.055	2.2E-09	3.7E-01	rs10184126	0.18	1.6E-92	1.2E-79
rs516946	8	41,638,405	C	T	<i>ANK1</i>	<i>ANK1</i> (NM_020475)	Adipose	0.491	0.075	3.1E-10	5.3E-01	rs6989203	1.00	2.6E-10	4.0E-01
						<i>ANK1</i> (NM_020477)	Adipose	0.517	0.075	2.8E-11	9.8E-02	rs6989203	1.00	1.8E-11	5.8E-02
						<i>ANK1</i> (NM_020481)	Adipose	0.850	0.068	5.2E-34	1.1E-01	rs6989203	1.00	1.9E-34	4.4E-02
						N/A (NM_152568)	Blood	0.327	0.070	6.2E-06	8.1E-03	rs10110166	0.00	1.6E-51	1.2E-47
rs7177055	15	75,619,817	A	G	<i>HMG20A</i>	<i>LINGO1</i> (NM_032808)	Adipose	0.311	0.068	9.1E-06	4.7E-01	rs907372	0.73	7.3E-09	2.0E-04
rs7202877	16	73,804,746	T	G	<i>BCAR1</i>	<i>CFDP1</i> (NM_006324)	Adipose	-0.470	0.098	3.4E-06	7.0E-03	rs4243111	0.18	4.6E-18	1.4E-14
						<i>CFDP1</i> (NM_006324)	Blood	-0.408	0.093	2.2E-05	9.2E-01	rs4888396	0.42	1.9E-14	3.3E-10
						<i>BCAR1</i> (NM_014567)	Blood	-1.390	0.076	2.0E-70	1.1E-03	rs13331385	1.00	6.1E-74	2.9E-06
						<i>TMEM170A</i> (NM_145254)	Adipose	-0.439	0.099	1.8E-05	1.7E-01	rs766522	0.43	1.3E-07	9.2E-04

Chr: chromosome. SE: standard error.

^aAlleles are aligned to the forward strand of NCBI Build 36.

^bRisk allele for T2D from our combined meta-analysis.

Supplementary Table 15. Primary and secondary lists of genes implicated in monogenic forms of T2D, and established and "probable" disease susceptibility loci, as used in pathway and protein-protein interaction analyses.

Category	(Nearest) Gene	Lead T2D SNP		
		SNP	Chr	Position (Build 36 bp)
Primary list				
Established locus	<i>NOTCH2</i>	rs10923931	1	120,319,482
Monogenic gene	<i>LMNA</i>			
Established locus	<i>PROX1</i>	rs2075423	1	212,221,342
Monogenic gene	<i>KLF11</i>			
Established locus	<i>GCKR</i>	rs780094	2	27,594,741
Established locus	<i>THADA</i>	rs10203174	2	43,543,534
Established locus	<i>BCL11A</i>	rs243088	2	60,422,249
Monogenic gene	<i>EIF2AK3</i>			
Established locus	<i>RBMS1</i>	rs7569522	2	161,054,693
Novel locus	<i>GRB14</i>	rs13389219	2	165,237,122
Monogenic gene	<i>NEUROD1</i>			
Established locus	<i>IRS1</i>	rs2943640	2	226,801,829
Monogenic gene and established locus	<i>PPARG</i>	rs1801282	3	12,368,125
Established locus	<i>UBE2E2</i>	rs1496653	3	23,429,794
Established locus	<i>ADAMTS9</i>	rs6795735	3	64,680,405
Established locus	<i>ADCY5</i>	rs11717195	3	124,565,088
Established locus	<i>IGF2BP2</i>	rs4402960	3	186,994,381
Monogenic gene and established locus	<i>WFS1</i>	rs4458523	4	6,340,887
Monogenic gene	<i>CISD2</i>			
Strongly associated locus	<i>TMEM154</i>	rs6813195	4	153,739,925
Novel locus	<i>ANKRD55</i>	rs459193	5	55,842,508
Established locus	<i>ZBED3</i>	rs6878122	5	76,463,067
Strongly associated locus	<i>SSR1</i>	rs9505118	6	7,235,436
Established locus	<i>CDKAL1</i>	rs7756992	6	20,787,688
Strongly associated locus	<i>POU5F1</i>	rs3130501	6	31,244,432
Monogenic gene	<i>PLAGL1</i>			
Monogenic gene	<i>HYMAI</i>			
Established locus	<i>DGKB</i>	rs17168486	7	14,864,807
Established locus	<i>JAZF1</i>	rs849135	7	28,162,938
Monogenic gene and established locus	<i>GCK</i>	rs10278336	7	44,211,888
Established locus	<i>KLF14</i>	rs13233731	7	130,088,229
Novel locus	<i>ANK1</i>	rs516946	8	41,638,405
Established locus	<i>TP53INP1</i>	rs7845219	8	96,006,678
Established locus	<i>SLC30A8</i>	rs3802177	8	118,254,206
Strongly associated locus	<i>GLIS3</i>	rs10758593	9	4,282,083
Established locus	<i>CDKN2B</i>	rs10811661	9	22,124,094
Established locus	<i>TLE4</i>	rs17791513	9	81,095,410
Novel locus	<i>TLE1</i>	rs2796441	9	83,498,768
Monogenic gene	<i>CEL</i>			
Monogenic gene	<i>AGPAT2</i>			
Established locus	<i>CDC123</i>	rs11257655	10	12,347,900
Monogenic gene	<i>PTF1A</i>			
Novel locus	<i>ZMIZ1</i>	rs12571751	10	80,612,637
Established locus	<i>HHEX</i>	rs1111875	10	94,452,862
Established locus	<i>TCF7L2</i>	rs7903146	10	114,748,339
Strongly associated locus	<i>PLEKHA1</i>	rs2421016	10	124,157,502
Established locus	<i>MOB2</i>	rs2334499	11	1,653,425

Monogenic gene	<i>INS</i>			
Established locus	<i>KCNQ1</i>	rs163184	11	2,803,645
Monogenic gene and established locus	<i>KCNJ11</i>	rs5215	11	17,365,206
Monogenic gene	<i>ABCC8</i>			
Monogenic gene	<i>BSCL2</i>			
Established locus	<i>ARAP1</i>	rs1552224	11	72,110,746
Established locus	<i>MTNR1B</i>	rs10830963	11	92,348,358
Strongly associated locus	<i>ETS1</i>	rs7931302	11	127,741,268
Novel locus	<i>CCND2</i>	rs11063069	12	4,244,634
Novel locus	<i>KLHDC5</i>	rs10842994	12	27,856,417
Established locus	<i>HMGA2</i>	rs2261181	12	64,498,585
Established locus	<i>TSPAN8</i>	rs7955901	12	69,719,560
Monogenic gene and established locus	<i>HNF1A</i>	rs12427353	12	119,911,284
Monogenic gene	<i>PDX1</i>			
Established locus	<i>SPRY2</i>	rs1359790	13	79,615,157
Established locus	<i>C2CD4A</i>	rs4502156	15	60,170,447
Novel locus	<i>HMG20A</i>	rs7177055	15	75,619,817
Established locus	<i>ZFAND6</i>	rs11634397	15	78,219,277
Established locus	<i>VPS33B</i>	rs12899811	15	89,345,080
Established locus	<i>FTO</i>	rs9936385	16	52,376,670
Novel locus	<i>CTRB1</i>	rs7202877	16	73,804,746
Monogenic gene and established locus	<i>HNF1B</i>	rs4430796	17	33,176,494
Novel locus	<i>MC4R</i>	rs12970134	18	56,035,730
Monogenic gene	<i>LMNB2</i>			
Monogenic gene	<i>INSR</i>			
Novel locus	<i>SUGP1</i>	rs10401969	19	19,268,718
Monogenic gene	<i>AKT2</i>			
Novel locus	<i>GIPR</i>	rs8108269	19	50,850,353
Monogenic gene	<i>HNF4A</i>			
Established locus	<i>DUSP9</i>			

Secondary list

Associated locus	<i>KLHL21</i>	rs1556036	1	6,574,315
Associated locus	<i>MACF1</i>	rs636083	1	39,594,268
Associated locus	<i>FAF1</i>	rs17106184	1	50,682,573
Associated locus	<i>LEPR</i>	rs11208660	1	65,756,214
Associated locus	<i>LRRC52</i>	rs169557	1	163,793,417
Associated locus	<i>LYPLAL1</i>	rs765751	1	217,735,849
Associated locus	<i>ABCB10</i>	rs927204	1	227,747,629
Associated locus	<i>BCL2L11</i>	rs11123406	2	111,667,012
Associated locus	<i>INHBB</i>	rs12617659	2	121,026,229
Associated locus	<i>TANC1</i>	rs17206971	2	159,636,566
Associated locus	<i>SLC38A11</i>	rs1869543	2	165,512,906
Associated locus	<i>PARD3B</i>	rs9288354	2	205,086,815
Associated locus	<i>ERBB4</i>	rs16825005	2	212,012,810
Associated locus	<i>EPHA4</i>	rs616355	2	221,481,792
Associated locus	<i>MINA</i>	rs17302349	3	99,117,155
Associated locus	<i>MECOM</i>	rs7635320	3	170,447,312
Associated locus	<i>LPP</i>	rs6808574	3	189,223,217
Associated locus	<i>FAM13A</i>	rs13147493	4	89,961,202
Associated locus	<i>UNC5C</i>	rs2241743	4	96,310,547
Associated locus	<i>NHEDC2</i>	rs7674212	4	104,208,348
Associated locus	<i>NDST3</i>	rs2389527	4	119,241,747
Associated locus	<i>TMEM155</i>	rs2706785	4	122,879,700
Associated locus	<i>PDGFC</i>	rs1464454	4	157,836,217
Associated locus	<i>ACSL1</i>	rs1996546	4	185,951,283

Associated locus	<i>ARL15</i>	rs702634	5	53,307,177
Associated locus	<i>MAP3K1</i>	rs3843467	5	55,892,132
Associated locus	<i>PDE4D</i>	rs986067	5	58,424,152
Associated locus	<i>MCC</i>	rs367943	5	112,837,627
Associated locus	<i>DTWD2</i>	rs6896169	5	118,041,959
Associated locus	<i>PHF15</i>	rs329122	5	133,892,498
Associated locus	<i>PHACTR1</i>	rs9349459	6	13,219,227
Associated locus	<i>MYLIP</i>	rs4716034	6	16,151,564
Associated locus	<i>C6orf204</i>	rs12199837	6	119,037,337
Associated locus	<i>CENPW</i>	rs4897182	6	126,797,335
Associated locus	<i>L3MBTL3</i>	rs6569648	6	130,390,812
Associated locus	<i>SNX13</i>	rs17138444	7	17,926,686
Associated locus	<i>POU6F2</i>	rs7779853	7	39,024,266
Associated locus	<i>OGDH</i>	rs6961567	7	44,692,594
Associated locus	<i>FAM185A</i>	rs10228495	7	102,227,420
Associated locus	<i>BRAF</i>	rs9648716	7	140,258,632
Associated locus	<i>PINX1</i>	rs6601534	8	10,729,403
Associated locus	<i>PURG</i>	rs2543622	8	30,983,146
Associated locus	<i>IL7</i>	rs2010128	8	79,922,054
Associated locus	<i>MYC</i>	rs1561927	8	129,637,260
Associated locus	<i>ZNF34</i>	rs2294120	8	145,974,371
Associated locus	<i>ELAVL2</i>	rs2150461	9	23,306,365
Associated locus	<i>PTPDC1</i>	rs10114341	9	95,959,003
Associated locus	<i>DNLZ</i>	rs10870149	9	138,374,718
Associated locus	<i>RPS24</i>	rs10824617	10	79,900,233
Associated locus	<i>APIP</i>	rs1326941	11	34,873,286
Associated locus	<i>MAP3K11</i>	rs11227234	11	65,121,747
Associated locus	<i>CACNA1C</i>	rs7306916	12	2,471,624
Associated locus	<i>CPNE8</i>	rs11170498	12	37,725,840
Associated locus	<i>SLC38A4</i>	rs17684703	12	45,510,592
Associated locus	<i>ANO4</i>	rs4764773	12	99,858,781
Associated locus	<i>SBNO1</i>	rs6488868	12	122,365,927
Associated locus	<i>ZNF664</i>	rs825461	12	123,127,756
Associated locus	<i>RNF6</i>	rs10507349	13	25,679,528
Associated locus	<i>OLFM4</i>	rs2039632	13	53,825,274
Associated locus	<i>DLL4</i>	rs4923889	15	39,022,224
Associated locus	<i>C16orf68</i>	rs8052543	16	8,405,759
Associated locus	<i>GRIN2A</i>	rs11645816	16	9,679,607
Associated locus	<i>IRX3</i>	rs9928968	16	53,010,700
Associated locus	<i>IRX6</i>	rs16954899	16	53,958,597
Associated locus	<i>RPL13</i>	rs12709089	16	88,157,812
Associated locus	<i>ZZEF1</i>	rs8068804	17	3,932,613
Associated locus	<i>RAI1</i>	rs1006656	17	17,623,209
Associated locus	<i>CBX1</i>	rs2240122	17	43,507,558
Associated locus	<i>GATA6</i>	rs2046058	18	17,891,792
Associated locus	<i>CCBE1</i>	rs17781351	18	55,583,528
Associated locus	<i>ZNF536</i>	rs7253628	19	35,739,109
Associated locus	<i>EIF2S2</i>	rs6059662	20	32,139,388
Associated locus	<i>PROCR</i>	rs6087685	20	33,241,273
Associated locus	<i>ZHX3</i>	rs17265513	20	39,266,042
Associated locus	<i>R3HDM1L</i>	rs4812829	20	42,422,681
Associated locus	<i>URB1</i>	rs11702306	21	32,687,431
Associated locus	<i>ASCC2</i>	rs5997539	22	28,567,706

Chr: chromosome.

Supplementary Table 16. Biological processes with most significant enrichment from modified two-step gene set enrichment analysis.

Resource	Biological process	Number of genes	MAGENTA applied to Stage 1 meta-analysis		Modified GSEA of primary T2D susceptibility loci using Stage 2 meta-analysis ^a		Modified GSEA of primary and secondary T2D susceptibility loci using Stage 2 meta-analysis ^a		Genes
			Enrichment <i>p</i> -value	FDR	Nearest gene	LD region	Nearest gene	LD region	
KEGG	Adipocytokine signalling pathway	67	6.2E-05	1.6E-03	1.4E-02	6.0E-02	7.0E-04	1.6E-04	<i>LEPR , RELA , RXRG , ACSL1 , IRS1 , NFKB1 , CAMKK1 , AKT2</i>
KEGG, REACTOME, BioCarta	Cell cycle regulation	40	1.1E-02	4.5E-02	4.0E-03	7.0E-04	5.0E-02	7.0E-04	<i>CDKN2B , CCND2 , CDKN1C , CDKN2C , CCNA2 , CCNE2</i>
Gene ontology	G1 phase of mitotic cell cycle	10	2.0E-04	1.0E-04	1.0E+00	3.0E-03	6.0E-02	3.0E-03	<i>MAP3K11 , CDC123 , CDKN1C</i>
REACTOME	G1 phase	16	4.4E-02	1.0E-01	1.0E+00	1.1E-02	1.0E+00	4.0E-02	<i>CCND2 , E2F3</i>
KEGG	PPAR signalling pathway	69	4.2E-02	1.7E-01	1.0E+00	1.0E+00	3.0E-02	3.4E-01	<i>RXRG , PPARG , ACSL1</i>
MitoCarta	Oxidative phosphorylation	106	3.6E-02	1.6E-01	-	3.5E-01	-	1.0E-01	<i>ATPAF2 , NDUFA13 , UQCR10 , NDUFS5 , C8orf38 , NDUFB2</i>
KEGG	Biosynthesis of unsaturated fatty acids	22	3.0E-03	1.4E-02	-	-	-	-	
Gene ontology	Negative regulation of inflammatory response	22	4.4E-03	1.9E-02	-	-	-	-	
Gene ontology	Positive regulation of inflammatory response	20	1.2E-02	3.5E-02	-	-	-	-	

^aBonferroni corrected cutoff for modified GSEA of Stage 2 meta-analysis: $p < 0.0014$.

"-" indicates that there was no transcript in the gene-set.