Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index

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Elizabeth K. Speliotes[1,2,*], **Cristen J. Willer**[3,*], **Sonja I. Berndt**[4,*], **Keri L. Monda**[5,*], **Gudmar Thorleifsson**[6,*], **Anne U. Jackson**[3], **Hana Lango Allen**[7], **Cecilia M. Lindgren**[8,9], **Jian'an Luan**[10], **Reedik Mägi**[8], **Joshua C. Randall**[8], **Sailaja Vedantam**[1,11], **Thomas W. Winkler**[12], **Lu Qi**[13,14], **Tsegaselassie Workalemahu**[13], **Iris M. Heid**[12,15], **Valgerdur Steinthorsdottir**[6], **Heather M. Stringham**[3], **Michael N. Weedon**[7], **Eleanor Wheeler**[16], **Andrew R. Wood**[7], **Teresa Ferreira**[8], **Robert J. Weyant**[3], **Ayellet V. Segré**[17,18,19], **Karol Estrada**[20,21,22], **Liming Liang**[23,24], **James Nemesh**[18], **Ju-Hyun Park**[4], **Stefan Gustafsson**[25], **Tuomas O. Kilpeläinen**[10], **Jian Yang**[26], **Nabila Bouatia-Naji**[27,28], **Tõnu Esko**[29,30,31], **Mary F. Feitosa**[32], **Zoltán Kutalik**[33,34], **Massimo Mangino**[35], **Soumya Raychaudhuri**[18,36], **Andre Scherag**[37], **Albert Vernon Smith**[38,39], **Ryan Welch**[3], **Jing Hua Zhao**[10], **Katja K. Aben**[40], **Devin M. Absher**[41], **Najaf Amin**[20], **Anna L. Dixon**[42], **Eva Fisher**[43], **Nicole L. Glazer**[44,45], **Michael E. Goddard**[46,47], **Nancy L. Heard-Costa**[48], **Volker Hoesel**[49], **Jouke-Jan Hottenga**[50], **Åsa Johansson**[51,52], **Toby Johnson**[33,34,53,54], **Shamika Ketkar**[32], **Claudia Lamina**[15,55], **Shengxu Li**[10], **Miriam F. Moffatt**[56], **Richard H. Myers**[57], **Narisu Narisu**[58], **John R.B. Perry**[7], **Marjolein J. Peters**[21,22], **Michael Preuss**[59], **Samuli Ripatti**[60,61], **Fernando Rivadeneira**[20,21,22], **Camilla Sandholt**[62], **Laura J. Scott**[3], **Nicholas J. Timpson**[63], **Jonathan P. Tyrer**[64], **Sophie van Wingerden**[20], **Richard M. Watanabe**[65,66], **Charles C. White**[67], **Fredrik Wiklund**[25], **Christina Barlassina**[68], **Daniel I. Chasman**[69,70], **Matthew N. Cooper**[71], **John-Olov Jansson**[72], **Robert W. Lawrence**[71], **Niina Pellikka**[60,61], **Inga Prokopenko**[8,9], **Jianxin Shi**[4], **Elisabeth Thiering**[15], **Helene Alavere**[29], **Maria T. S. Alibrandi**[73], **Peter Almgren**[74], **Alice M. Arnold**[75,76], **Thor Aspelund**[38,39], **Larry D. Atwood**[48], **Beverley Balkau**[77,78], **Anthony J. Balmforth**[79], **Amanda J. Bennett**[9], **Yoav Ben-Shlomo**[80], **Richard N. Bergman**[66], **Sven Bergmann**[33,34], **Heike Biebermann**[81], **Alexandra I.F. Blakemore**[82], **Tanja Boes**[37], **Lori L. Bonnycastle**[58], **Stefan R. Bornstein**[83], **Morris J. Brown**[84], **Thomas A. Buchanan**[66,85], **Fabio Busonero**[86], **Harry Campbell**[87], **Francesco P. Cappuccio**[88], **Christine Cavalcanti-Proença**[27,28], **Yii-Der Ida Chen**[89], **Chih-Mei Chen**[15], **Peter S. Chines**[58], **Robert Clarke**[90], **Lachlan Coin**[91], **John Connell**[92], **Ian N.M. Day**[63], **Martin den Heijer**[93,94], **Jubao Duan**[95], **Shah Ebrahim**[96,97], **Paul Elliott**[91,98], **Roberto Elosua**[99], **Gudny Eiriksdottir**[38], **Michael R. Erdos**[58], **Johan G. Eriksson**[100,101,102,103,104], **Maurizio F. Facheris**[105,106], **Stephan B. Felix**[107], **Pamela Fischer-Posovszky**[108], **Aaron R. Folsom**[109], **Nele Friedrich**[110], **Nelson B. Freimer**[111], **Mao Fu**[112], **Stefan Gaget**[27,28], **Pablo V. Gejman**[95], **Eco J.C. Geus**[50], **Christian Gieger**[15], **Anette P. Gjesing**[62], **Anuj Goel**[8,113], **Philippe Goyette**[114], **Harald Grallert**[15], **Jürgen Gräßler**[115], **Danielle M. Greenawalt**[116], **Christopher J. Groves**[9], **Vilmundur Gudnason**[38,39], **Candace Guiducci**[1], **Anna-Liisa Hartikainen**[117], **Neelam Hassanali**[9], **Alistair S. Hall**[79], **Aki S.**

Correspondence should be addressed to Michael Boehnke (boehnke@umich.edu), Kari Stefansson (kstefans@decode.is), Kari North (kari_north@unc.edu), Mark McCarthy (mark.mccarthy@drl.ox.ac.uk), Joel Hirschhorn (joelh@broadinstitute.org), Erik Ingelsson (erik.ingelsson@ki.se), and Ruth Loos (ruth.loos@mrc-epid.cam.ac.uk).
*These authors contributed equally to this work.

Author contributions
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Havulinna[118], **Caroline Hayward**[119], **Andrew C. Heath**[120], **Christian Hengstenberg**[121,122], **Andrew A. Hicks**[105], **Anke Hinney**[123], **Albert Hofman**[20,22], **Georg Homuth**[124], **Jennie Hui**[71,125,126], **Wilmar Igl**[51], **Carlos Iribarren**[127,128], **Bo Isomaa**[103,129], **Kevin B. Jacobs**[130], **Ivonne Jarick**[131], **Elizabeth Jewell**[3], **Ulrich John**[132], **Torben Jørgensen**[133,134], **Pekka Jousilahti**[118], **Antti Jula**[135], **Marika Kaakinen**[136,137], **Eero Kajantie**[101,138], **Lee M. Kaplan**[2,70,139], **Sekar Kathiresan**[17,18,140,141,142], **Johannes Kettunen**[60,61], **Leena Kinnunen**[143], **Joshua W. Knowles**[144], **Ivana Kolcic**[145], **Inke R. König**[59], **Seppo Koskinen**[118], **Peter Kovacs**[146], **Johanna Kuusisto**[147], **Peter Kraft**[23,24], **Kirsti Kvaløy**[148], **Jaana Laitinen**[149], **Olivier Lantieri**[150], **Chiara Lanzani**[73], **Lenore J. 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Groop**[74], **Talin Haritunians**[89], **David J. Hunter**[13,14,23], **Robert C. Kaplan**[240], **Karen L. Mohlke**[241], **Jeffrey R. O'Connell**[112], **Leena**

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[1] Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts 02142, USA [2] Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA [3] Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA [4] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, USA [5] Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514, USA [6] deCODE Genetics, 101 Reykjavik, Iceland [7] Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, EX1 2LU, UK [8] Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK [9] Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, OX3 7LJ, UK [10] MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK [11] Divisions of Genetics and Endocrinology and Program in Genomics, Children's Hospital, Boston, Massachusetts 02115, USA [12] Regensburg University Medical Center, Department of Epidemiology and Preventive Medicine, 93053 Regensburg, Germany [13] Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA [14] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA [15] Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany [16] Wellcome Trust Sanger Institute, Hinxton, Cambridge, CB10 1SA, UK [17] Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA [18] Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA [19] Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA [20] Department of Epidemiology, Erasmus MC, Rotterdam, 3015GE, The Netherlands [21] Department of Internal Medicine, Erasmus MC, Rotterdam, 3015GE, The Netherlands [22] Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA) [23] Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA [24] Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, USA [25] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden [26] Queensland Statistical Genetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia [27] CNRS UMR8199-IBL-Institut Pasteur de Lille, F-59019 Lille, France [28] University Lille Nord de France, 59000 Lille, France [29] Estonian Genome Center, University of Tartu, Tartu 50410, Estonia [30] Estonian Biocenter, Tartu 51010, Estonia [31] Institute of Molecular and Cell Biology, University of Tartu, Tartu 51010, Estonia [32] Department of Genetics, Washington University School of Medicine, St Louis, Missouri 63110, USA [33] Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland [34] Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland [35] Department of Twin Research and Genetic Epidemiology, King's College London, London, SE1 7EH, UK [36] Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115 USA [37] Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, 45122 Essen, Germany [38] Icelandic Heart Association, Kopavogur, Iceland [39] University of Iceland, Reykjavik, Iceland [40] Comprehensive Cancer Center East, 6501 BG Nijmegen, The Netherlands [41] Hudson Alpha Institute for Biotechnology, Huntsville, Alabama 35806, USA [42] Department of Pharmacy and Pharmacology, University of Bath, Bath, BA1 1RL, UK [43] Department of Epidemiology, German Institute of

Human Nutrition Potsdam-Rehbruecke, 14558 Nuthetal, Germany [44] Department of Medicine, University of Washington, Seattle, Washington 98101, USA [45] Cardiovascular Health Research Unit, University of Washington, Seattle, Washington 98101, USA [46] University of Melbourne, Parkville 3010, Australia [47] Department of Primary Industries, Melbourne, Victoria 3001, Australia [48] Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, USA [49] Technical University Munich, Chair of Biomathematics, Boltzmannstrasse 3, 85748 Garching [50] Department of Biological Psychology, VU University Amsterdam, 1081 BT Amsterdam, The Netherlands [51] Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, SE-75185 Uppsala, Sweden [52] Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, N-7489, Norway [53] Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK [54] Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK [55] Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, 6020 Innsbruck, Austria [56] National Heart and Lung Institute, Imperial College London, London SW3 6LY, UK [57] Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, USA [58] National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA [59] Institut fur Medizinische Biometrie und Statistik, Universitat zu Lubeck, Universitatsklinikum Schleswig-Holstein, Campus Lubeck, 23562 Lubeck, Germany [60] Institute for Molecular Medicine Finland (FIMM), University of Helsinki, 00014, Helsinki, Finland [61] National Institute for Health and Welfare, Department of Chronic Disease Prevention, Unit of Public Health Genomics, 00014, Helsinki, Finland [62] Hagedorn Research Institute, 2820 Gentofte, Denmark [63] MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, Oakfield House, Bristol, BS8 2BN, UK [64] Department of Oncology, University of Cambridge, Cambridge, CB1 8RN, UK [65] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California 90089, USA [66] Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA [67] Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA [68] University of Milan, Department of Medicine, Surgery and Dentistry, 20139 Milano, Italy [69] Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts 02215, USA [70] Harvard Medical School, Boston, Massachusetts 02115, USA [71] Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia 6009, Australia [72] Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden [73] University Vita-Salute San Raffaele, Division of Nephrology and Dialysis, 20132 Milan, Italy [74] Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden [75] Departments of Biostatistics, University of Washington, Seattle, Washington 98195, USA [76] Collaborative Health Studies Coordinating Center, Seattle, Washington 98115, USA [77] INSERM CESP Centre for Research in Epidemiology and Public Health U1018, Epidemiology of diabetes, obesity and chronic kidney disease over the lifecourse, 94807 Villejuif, France [78] University Paris Sud 11, UMRS 1018, 94807 Villejuif, France [79] Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds LS2 9JT, UK [80] Department of Social Medicine, University of Bristol, Bristol, BS8 2PS, UK [81] Institute of Experimental Paediatric Endocrinology, Charite Universitatsmedizin Berlin, 13353 Berlin, Germany [82] Department of Genomics of Common Disease, School of Public Health, Imperial College London, W12 0NN, London, UK [83] Department of Medicine III, University of Dresden, 01307 Dresden, Germany [84] Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK [85] Division of Endocrinology, Keck

School of Medicine, University of Southern California, Los Angeles, California 90033, USA [86] Istituto di Neurogenetica e Neurofarmacologia del CNR, Monserrato, 09042, Cagliari, Italy [87] Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland [88] University of Warwick, Warwick Medical School, Coventry, CV2 2DX, UK [89] Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA [90] Clinical Trial Service Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford, OX3 7LF, UK [91] Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London, W2 1PG, UK [92] University of Dundee, Ninewells Hospital & Medical School, Dundee, DD1 9SY, UK [93] Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands [94] Department of Endocrinology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands [95] Northshore University Healthsystem, Evanston, Ilinois 60201, USA [96] The London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK [97] South Asia Network for Chronic Disease [98] MRC-HPA Centre for Environment and Health, London W2 1PG, UK [99] Cardiovascular Epidemiology and Genetics, Institut Municipal D'investigacio Medica and CIBER Epidemiologia y Salud Publica, Barcelona, Spain [100] Department of General Practice and Primary health Care, University of Helsinki, Helsinki, Finland [101] National Institute for Health and Welfare, 00271 Helsinki, Finland [102] Helsinki University Central Hospital, Unit of General Practice, 00280 Helsinki, Finland [103] Folkhalsan Research Centre, 00250 Helsinki, Finland [104] Vasa Central Hospital, 65130 Vasa, Finland [105] Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano/Bozen, 39100, Italy. Affiliated Institute of the University of Lubeck, Lubeck, Germany [106] Department of Neurology, General Central Hospital, Bolzano, Italy [107] Department of Internal Medicine B, Ernst-Moritz-Arndt University, 17475 Greifswald, Germany [108] Pediatric Endocrinology, Diabetes and Obesity Unit, Department of Pediatrics and Adolescent Medicine, 89075 Ulm, Germany [109] Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis Minnesota 55454, USA [110] Institut fur Klinische Chemie und Laboratoriumsmedizin, Universitat Greifswald, 17475 Greifswald, Germany [111] Center for Neurobehavioral Genetics, University of California, Los Angeles, California 90095, USA [112] Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA [113] Department of Cardiovascular Medicine, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU [114] Montreal Heart Institute, Montreal, Quebec, H1T 1C8, Canada [115] Department of Medicine III, Pathobiochemistry, University of Dresden, 01307 Dresden, Germany [116] Merck Research Laboratories, Merck & Co., Inc., Boston, Massachusetts 02115, USA [117] Department of Clinical Sciences/Obstetrics and Gynecology, University of Oulu, 90014 Oulu, Finland [118] National Institute for Health and Welfare, Department of Chronic Disease Prevention, Chronic Disease Epidemiology and Prevention Unit, 00014, Helsinki, Finland [119] MRC Human Genetics Unit, Institute for Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU, Scotland, UK [120] Department of Psychiatry and Midwest Alcoholism Research Center, Washington University School of Medicine, St Louis, Missouri 63108, USA [121] Klinik und Poliklinik fur Innere Medizin II, Universitat Regensburg, 93053 Regensburg, Germany [122] Regensburg University Medical Center, Innere Medizin II, 93053 Regensburg, Germany [123] Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, 45147 Essen, Germany [124] Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany [125] PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands, Western Australia 6009, Australia [126] Busselton Population Medical Research Foundation Inc., Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia [127] Division of Research, Kaiser Permanente Northern California, Oakland, California 94612, USA [128] Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California 94107, USA [129] Department of Social Services and Health Care, 68601 Jakobstad, Finland [130] Core Genotyping Facility, SAIC-Frederick, Inc., NCI-

Frederick, Frederick, Maryland 21702, USA [131] Institute of Medical Biometry and Epidemiology, University of Marburg, 35037 Marburg, Germany [132] Institut fur Epidemiologie und Sozialmedizin, Universitat Greifswald, 17475 Greifswald, Germany [133] Research Centre for Prevention and Health, Glostrup University Hospital, 2600 Glostrup, Denmark [134] Faculty of Health Science, University of Copenhagen, 2100 Copenhagen, Denmark [135] National Institute for Health and Welfare, Department of Chronic Disease Prevention, Population Studies Unit, 20720 Turku, Finland [136] Institute of Health Sciences, University of Oulu, 90014 Oulu, Finland [137] Biocenter Oulu, University of Oulu, 90014 Oulu, Finland [138] Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, 00029 HUS, Finland [139] MGH Weight Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA [140] Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts 02114, USA [141] Framingham Heart Study of the National, Heart, Lung, and Blood Institute and Boston University, Framingham, Massachusetts 01702, USA [142] Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA [143] National Institute for Health and Welfare, Diabetes Prevention Unit, 00271 Helsinki, Finland [144] Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA [145] Andrija Stampar School of Public Health, Medical School, University of Zagreb, 10000 Zagreb, Croatia [146] Interdisciplinary Centre for Clinical Research, University of Leipzig, 04103 Leipzig, Germany [147] Department of Medicine, University of Kuopio and Kuopio University Hospital, 70210 Kuopio, Finland [148] HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, 7600 Levanger, Norway [149] Finnish Institute of Occupational Health, 90220 Oulu, Finland [150] Institut inter-regional pour la sante (IRSA), F-37521 La Riche, France [151] Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA [152] Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, 33520 Tampere, Finland [153] Department of Medicine, Universite de Montreal, Montreal, Quebec, H3T 1J4, Canada [154] Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore [155] Transplantation Laboratory, Haartman Institute, University of Helsinki, 00014, Helsinki, Finland [156] Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden [157] Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR, UK [158] On behalf of the MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium) investigators [159] Department of Endocrinology, Diabetology and Nutrition, Bichat-Claude Bernard University Hospital, Assistance Publique des Hopitaux de Paris, F-75018 Paris, France [160] Cardiovascular Genetics Research Unit, Universite Henri Poincare-Nancy 1, 54000, Nancy, France [161] Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia [162] Avon Longitudinal Study of Parents and Children (ALSPAC) Laboratory, Department of Social Medicine, University of Bristol, Bristol, BS8 2BN, UK [163] Division of Health, Research Board, An Bord Taighde Slainte, Dublin, 2, Ireland [164] Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universitat Munchen, 81675 Munich, Germany [165] Institute of Human Genetics, Helmholtz Zentrum Munchen - German Research Center for Environmental Health, 85764 Neuherberg, Germany [166] Department of Clinical Sciences, Lund University, 20502 Malmo, Sweden [167] Molecular Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia [168] Croatian Centre for Global Health, School of Medicine, University of Split, Split 21000, Croatia [169] Neurogenetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia [170] National, Lung, and Blood Institute, National Institutes of Health, Framingham, Massachusetts 01702, USA [171] University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK [172] Department of Clinical Genetics, Erasmus MC, Rotterdam, 3015GE, The Netherlands [173] Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario L8N3Z5, Canada [174] Amgen, Cambridge, Massachusetts 02139, USA [175]

Finnish Twin Cohort Study, Department of Public Health, University of Helsinki, 00014, Helsinki, Finland [176] Obesity Research unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland [177] Department of Medicine, Levanger Hospital, The Nord-Trøndelag Health Trust, 7600 Levanger, Norway [178] Gen-Info Ltd, 10000 Zagreb, Croatia [179] National Institute for Health and Welfare, 90101 Oulu, Finland [180] Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK [181] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, 20520 Turku, Finland [182] The Department of Clinical Physiology, Turku University Hospital, 20520 Turku, Finland [183] Clinical Psychology and Psychotherapy, University of Marburg, 35032 Marburg, Germany [184] Department of Clinical Sciences/Clinical Chemistry, University of Oulu, 90014 Oulu, Finland [185] Ludwig-Maximilians-Universität, Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, 81377 Munich, Germany [186] South Karelia Central Hospital, 53130 Lappeenranta, Finland [187] Department of Clinical Sciences/Internal Medicine, University of Oulu, 90014 Oulu, Finland [188] Institut für Community Medicine, 17489 Greifswald, Germany [189] Christian-Albrechts-University, University Hospital Schleswig-Holstein, Institute for Clinical Molecular Biology and Department of Internal Medicine I, 24105 Kiel, Germany [190] Universität zu Lübeck, Medizinische Klinik II, 23562 Lübeck, Germany [191] Division of Cardiology, Cardiovascular Laboratory, Helsinki University Central Hospital, 00029 Helsinki, Finland [192] Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington 98195, USA [193] Department of Psychiatry/EMGO Institute, VU University Medical Center, 1081 BT Amsterdam, The Netherlands [194] Department of Haematology, University of Cambridge, Cambridge CB2 0PT, UK [195] NHS Blood and Transplant, Cambridge Centre, Cambridge, CB2 0PT, UK [196] Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK [197] Department of Health Sciences, University of Leicester, University Road, Leicester, LE1 7RH, UK [198] Department of Medicine, University of Leipzig, 04103 Leipzig, Germany [199] Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16-18, 04103 Leipzig, Germany [200] Department of Medicine, Helsinki University Central Hospital, 00290 Helsinki, Finland [201] Research Program of Molecular Medicine, University of Helsinki, 00014 Helsinki, Finland [202] Department of Human Genetics, Leiden University Medical Center, 2333 ZC Leiden, the Netherlands [203] Center of Medical Systems Biology, Leiden University Medical Center, 2333 ZC Leiden, the Netherlands [204] Department of Medicine, University of Turku and Turku University Hospital, 20520 Turku, Finland [205] INSERM Cardiovascular Genetics team, CIC 9501, 54000 Nancy, France [206] Steno Diabetes Center, 2820 Gentofte, Denmark [207] Center for Human Genomics, Wake Forest University, Winston-Salem, North Carolina 27157, USA [208] Department of Physiatrics, Lapland Central Hospital, 96101 Rovaniemi, Finland [209] School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia 6009, Australia [210] Department of Internal Medicine, University of Oulu, 90014 Oulu, Finland [211] School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6009, Australia [212] Department of Clinical Physiology, University of Tampere and Tampere University Hospital, 33520 Tampere, Finland; [213] Stanford University School of Medicine, Stanford, California 93405, USA [214] Department of Psychiatry and Human Behavior, University of California, Irvine (UCI), Irvine, California 92617, USA [215] LIFE Study Centre, University of Leipzig, Leipzig, Germany [216] Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, 1011 Lausanne, Switzerland [217] Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas 77030, USA [218] Faculty of Health Science, University of Southern Denmark, 5000 Odense, Denmark [219] New York University Medical Center, New York, New York 10016, USA [220] National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Unit for Child and Adolescent Mental Health, 00271 Helsinki, Finland [221] NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LJ, UK [222] Department of Urology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands [223] Institute of

Biomedical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark [224] Faculty of Health Science, University of Aarhus, 8000 Aarhus, Denmark [225] Department of Psychiatry, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands [226] Department of Psychiatry, University Medical Centre Groningen, 9713 GZ Groningen, The Netherlands [227] Department of Neurology, University of Lübeck, Lübeck, Germany [228] Institute for Paediatric Nutrition Medicine, Vestische Hospital for Children and Adolescents, University of Witten-Herdecke, 45711 Datteln, Germany [229] Department of Medicine III, Prevention and Care of Diabetes, University of Dresden, 01307 Dresden, Germany [230] Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, Maryland 21201, USA [231] Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland [232] South Ostrobothnia Central Hospital, 60220 Seinajoki, Finland [233] Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) University Hospital, 1011 Lausanne, Switzerland [234] The Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02142, USA [235] Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA [236] Pacific Biosciences, Menlo Park, California 94025, USA [237] Sage Bionetworks, Seattle, Washington 98109, USA [238] Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri 63110, USA [239] Division of Intramural Research, National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, Massachusetts 01702, USA [240] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York 10461, USA [241] Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA [242] Department of Medical Genetics, University of Helsinki, 00014 Helsinki, Finland [243] Laboratory of Genetics, National Institute on Aging, Baltimore, Maryland 21224, USA [244] Division of Community Health Sciences, St George's, University of London, London, SW17 0RE, UK [245] Klinikum Grosshadern, 81377 Munich, Germany [246] Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland [247] University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, CB2 OQQ, Cambridge, UK [248] Carolina Center for Genome Sciences, School of Public Health, University of North Carolina Chapel Hill, Chapel Hill, North Carolina 27514, USA [249] Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA

Abstract

Obesity is globally prevalent and highly heritable, but the underlying genetic factors remain largely elusive. To identify genetic loci for obesity-susceptibility, we examined associations between body mass index (BMI) and ~2.8 million SNPs in up to 123,865 individuals, with targeted follow-up of 42 SNPs in up to 125,931 additional individuals. We confirmed 14 known obesity-susceptibility loci and identified 18 new loci associated with BMI ($P<5\times10^{-8}$), one of which includes a copy number variant near *GPRC5B.* Some loci (*MC4R, POMC, SH2B1, BDNF*) map near key hypothalamic regulators of energy balance, and one is near *GIPR*, an incretin receptor. Furthermore, genes in other newly-associated loci may provide novel insights into human body weight regulation.

Obesity is a major and increasingly prevalent risk factor for multiple disorders, including type 2 diabetes and cardiovascular disease[1,2]. While lifestyle changes have driven its prevalence to epidemic proportions, heritability studies provide evidence for a substantial genetic contribution (h^2~40–70%) to obesity risk[3,4]. BMI is an inexpensive, non-invasive measure of obesity that predicts the risk of related complications[5]. Identifying genetic determinants of BMI could lead to a better understanding of the biological basis of obesity.

Genome-wide association (GWA) studies of BMI have previously identified ten loci with genome-wide significant ($P < 5\times10^{-8}$) associations in or near *FTO, MC4R, TMEM18,*

GNPDA2, BDNF, NEGR1, SH2B1, ETV5, MTCH2, and KCTD15[6–10]. Many of these genes are expressed or known to act in the central nervous system, highlighting a likely neuronal component to the predisposition to obesity[9]. This pattern is consistent with results in animal models and studies of monogenic human obesity, where neuronal genes, particularly those expressed in the hypothalamus and involved in regulation of appetite or energy balance, are known to play a major role in susceptibility to obesity[11–13].

The ten previously identified loci account for only a small fraction of the variation in BMI. Furthermore, power calculations based on the effect sizes of established variants have suggested that increasing the sample size would likely lead to the discovery of additional variants[9]. To identify more loci associated with BMI, we expanded the GIANT (Genetic Investigation of ANtropometric Traits) consortium GWA meta-analysis to include a total of 249,769 individuals of European ancestry.

Results

Stage 1 GWA studies identify novel loci associated with BMI

We first conducted a meta-analysis of GWA studies of BMI and ~2.8 million imputed or genotyped SNPs using data from 46 studies including up to 123,865 individuals (Online Methods, Supplementary Fig. 1 and Supplementary Note). This stage 1 analysis revealed 19 loci associated with BMI at $P < 5\times10^{-8}$ (Table 1, Fig. 1a and Supplementary Table 1). These 19 loci included all ten loci from previous GWA studies of BMI[6–10], two loci previously associated with body weight[10] (*FAIM2 and SEC16B*) and one locus previously associated with waist circumference[14] (near *TFAP2B*). The remaining six loci, near *GPRC5B, MAP2K5/LBXCOR1, TNNI3K, LRRN6C, FLJ35779/HMGCR, and PRKD1,* have not previously been associated with BMI or other obesity-related traits.

Stage 2 follow-up leads to additional novel loci for BMI

To identify additional BMI-associated loci and to validate the loci that reached genome-wide significance in stage 1 analyses, we examined SNPs representing 42 independent loci (including the 19 genome-wide significant loci) with stage 1 $P < 5\times10^{-6}$. Variants were considered to be independent if the pair-wise linkage disequilibrium (LD; r^2) was less than 0.1 and if they were separated by at least 1 Mb. In stage 2, we examined these 42 SNPs in up to 125,931 additional individuals (79,561 newly genotyped individuals from 16 different studies and 46,370 individuals from 18 additional studies for which GWA data were available; Table 1, Supplementary Note, and Online Methods). In a joint analysis of stage 1 and stage 2 results, 32 of the 42 SNPs reached $P < 5\times10^{-8}$. Even after excluding SNPs within these 32 confirmed BMI loci, we still observed an excess of small *P*-values compared to the distribution expected under the null hypothesis (Fig. 1b), suggesting that more BMI loci remain to be uncovered.

The 32 confirmed associations included all 19 loci with $P < 5\times10^{-8}$ at stage 1, 12 additional novel loci near *RBJ/ADCY3/POMC*, *QPCTL/GIPR, SLC39A8, TMEM160, FANCL, CADM2, LRP1B, PTBP2, MTIF3/GTF3A, ZNF608, RPL27A/TUB, NUDT3/HMGA1*, and one locus (*NRXN3*) previously associated with waist circumference[15] (Table 1, Supplementary Table 1, Supplementary Fig. 1 and 2). In all, our study increased the number of loci robustly associated with BMI from 10 to 32. Four of the 22 new loci were previously associated with body weight[10] or waist circumference[14,15], whereas 18 loci had not previously associated with any obesity-related trait in the general population. Whilst we confirmed all loci previously established by large-scale GWA studies for BMI[6–10] and waist circumference[14,15], four loci identified by GWA studies for early-onset or adult morbid obesity[16,17] [at *NPC1* (rs1805081; $P = 0.0025$), *MAF* (rs1424233; $P = 0.25$), *PTER*

(rs10508503; $P = 0.64$), and *TNKS/MSRA* (rs473034; $P = 0.23$)] showed limited or no evidence of association with BMI in our study.

As expected, the effect sizes of the 18 newly discovered loci are slightly smaller, for a given minor allele frequency, than those of the previously identified variants (Table 1 and Fig. 1c). The increased sample size also brought out more signals with low minor allele frequency. The BMI-increasing allele frequencies for the 18 newly identified variants ranged from 4% to 87%, covering more of the allele frequency spectrum than previous, smaller GWA studies of BMI (24%–83%)[9,10] (Table 1 and Fig. 1c).

We tested for evidence of non-additive (dominant or recessive) effects, SNP×SNP interaction effects and heterogeneity by sex or study among the 32 BMI-associated SNPs (Online Methods). We found no evidence for any such effects ($P > 0.001$, no significant results after correcting for multiple testing) (Supplementary Tables 1 and Supplementary Note).

Impact of 32 confirmed loci on BMI, obesity, body size, and other metabolic traits

Together, the 32 confirmed BMI loci explained 1.45% of the inter-individual variation in BMI of the stage 2 samples, with the *FTO* SNP accounting for the largest proportion of the variance (0.34%) (Table 1). To estimate the cumulative effect of the 32 variants on BMI, we constructed a genetic-susceptibility score that sums the number of BMI-increasing alleles weighted by the overall stage 2 effect sizes in the ARIC study (N = 8,120), one of our largest population-based studies (Online Methods). For each unit increase in the genetic-susceptibility score, approximately equivalent to one additional risk allele, BMI increased by 0.17 kg/m^2, equivalent to a 435–551 g gain in body weight in adults of 160–180 cm in height. The difference in average BMI between individuals with a high genetic-susceptibility score (≥38 BMI-increasing alleles, 1.5% (n=124) of the ARIC sample) and those with a low genetic-susceptibility score (≤21 BMI-increasing alleles, 2.2% (n=175) of the ARIC sample) was 2.73 kg/m^2, equivalent to a 6.99 to 8.85 kg body weight difference in adults 160–180 cm in height (Fig. 2a). Still, we note that the predictive value for obesity risk and BMI of the 32 variants combined was modest, although statistically significant (Fig. 2b, Supplementary Fig. 4). The area under the receiver operating characteristic (ROC) curve for prediction of risk of obesity (BMI ≥ 30 kg/m^2) using age, age^2 and sex only was 0.515 ($P = 0.023$ compared to AUC of 0.50), which increased to 0.575 ($P < 10^{-5}$) when also the 32 confirmed SNPs were included in the model (Fig. 2b). The area under the ROC for the 32 SNPs only was 0.574 ($P < 10^{-5}$).

All 32 confirmed BMI-increasing alleles showed directionally consistent effects on risk of being overweight (BMI ≥25 kg/m^2) or obese (≥30 kg/m^2) in stage 2 samples, with 30 of 32 variants achieving at least nominally significant associations. The BMI-increasing alleles increased the odds of overweight by 1.013 to 1.138-fold, and the odds for being obese by 1.016- to 1.203-fold (Supplementary Table 2). In addition, 30 of the 32 loci also showed directionally consistent effects on the risk of extreme and early-onset obesity in a meta-analysis of seven case-control studies of adults and children (binomial sign test $P = 1.3\times10^{-7}$) (Supplementary Table 3). The BMI-increasing allele observed in adults also increased the BMI in children and adolescents with directionally consistent effects observed for 23 of the 32 SNPs (binomial sign test $P = 0.01$). Furthermore, in family-based studies, the BMI-increasing allele was over-transmitted to the obese offspring for 24 of the 32 SNPs (binomial sign test $P = 0.004$) (Supplementary Table 3). As these studies in extreme obesity cases, children and families were relatively small (N_{range} = 354 − 15,251) compared to the overall meta-analyses, their power was likely insufficient to confirm association for all 32 loci. Nevertheless, these results show that the effects are unlikely to reflect population stratification and that they extend to BMI differences throughout the life course.

All BMI-increasing alleles were associated with increased body weight, as expected from the correlation between BMI and body weight (Supplementary Table 2). To confirm an effect of the loci on adiposity rather than general body size, we tested association with body fat percentage, which was available in a subset of the stage 2 replication samples (n = 5,359–28,425) (Supplementary Table 2). The BMI-increasing allele showed directionally consistent effects on body fat percentage at 31 of the 32 confirmed loci (binomial sign test $P = 1.54\times10^{-8}$) (Supplementary Table 2).

We also examined the association of the BMI loci with metabolic traits (type 2 diabetes[18], fasting glucose, fasting insulin, indices of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR)[19], and blood lipid levels[20]) and with height (Supplementary Tables 2 and 4). Although many nominal associations are expected because of known correlations between BMI and most of these traits and because of overlap in samples, several associations stand out as possible examples of pleiotropic effects of the BMI-associated variants. Particularly interesting is the variant in the *GIPR* locus where the BMI-increasing allele is also associated with increased fasting glucose levels and lower 2-hour glucose levels (Supplementary Table 4)[19,21]. The direction of the effect is opposite to what would be expected due to the correlation between obesity and glucose intolerance, but is consistent with the suggested roles of *GIPR* in glucose and energy metabolism (see below)[22]. Three loci show strong associations ($P < 10^{-4}$) with height (*MC4R*, *RBJ/ADCY3/POMC* and *MTCH2/NDUFS3*). Because BMI is weakly correlated with height (and indeed, the BMI-associated variants as a group show no consistent effect on height), these associations are also suggestive of pleiotropy. Interestingly, analogous to the effects of severe mutations in *POMC* and *MC4R* on height and weight[23,24], the BMI-increasing alleles of the variants near these genes were associated with decreased (*POMC*) and increased (*MC4R*) height, respectively (Supplementary Table 2).

Potential functional roles and pathways analyses

Although associated variants typically implicate genomic regions rather than individual genes, we note that some of the 32 loci include candidate genes with established connections to obesity. Several of the 10 previously identified loci are located in or near genes that encode neuronal regulators of appetite or energy balance, including *MC4R*[12,25], *BDNF*[26], and *SH2B1*[11,27]. Each of these genes has been tied to obesity, not only in animal models, but also by rare human variants that disrupt each of these genes and lead to severe obesity[24,28,29]. Using the automated literature search programme, Snipper (Online Methods), we identified various genes within the novel loci with potential biological links to obesity-susceptibility (Supplementary Note). Among the novel loci, the location of rs713586 near *POMC* provides further support for a role of neuroendocrine circuits that regulate energy balance in susceptibility to obesity. *POMC* encodes several polypeptides including α-MSH, a ligand of the *MC4R* gene product[30], and rare mutations in *POMC* also cause human obesity[23,29,31].

In contrast, the locus near *GIPR,* which encodes a receptor of gastric inhibitory polypeptide (GIP), suggests a role for peripheral biology in obesity. GIP, which is expressed in the K cell of the duodenum and intestine, is an incretin hormone that mediates incremental insulin secretion in response to oral intake of glucose. The variant associated with BMI is in strong LD ($r^2 = 0.83$) with a missense SNP in *GIPR* (rs1800437, Glu354Gln) that has recently been shown to influence the glucose and insulin response to an oral glucose challenge [21]. Although no human phenotype is known to be caused by mutations in *GIPR*, mice with disruption of *Gipr* are resistant to diet-induced obesity[32]. The association of a variant in *GIPR* with BMI suggests that there may be a link between incretins/insulin secretion and body weight regulation in humans as well.

To systematically identify biological connections among the genes located near the 32 confirmed SNPs, and to potentially identify new pathways associated with BMI, we performed pathway-based analyses using MAGENTA[33]. Specifically, we tested for enrichment of BMI genetic associations in biological processes or molecular functions that contain at least one gene from the 32 confirmed BMI loci (Online Methods). Using annotations from the KEGG, Ingenuity, PANTHER, and Gene Ontology databases, we found evidence of enrichment for pathways involved in the platelet-derived growth factor (PDGF) signaling (PANTHER, P = 0.0008, FDR = 0.0061), translation elongation (PANTHER, P = 0.0008, FDR = 0.0066), hormone or nuclear hormone receptor binding (Gene Ontology, P < 0.0005, FDR < 0.0085), homeobox transcription (PANTHER, P = 0.0001, FDR = 0.011), regulation of cellular metabolism (Gene Ontology, P = 0.0002, FDR = 0.031), neurogenesis and neuron differentiation (Gene Ontology, P < 0.0002, FDR < 0.034), protein phosphorylation (PANTHER, P = 0.0001, FDR = 0.045) and numerous other pathways related to growth, metabolism, immune and neuronal processes (Gene Ontology, P < 0.002, FDR < 0.046) (Supplementary Table 5).

Identifying possible functional variants

We used data from the 1000 Genomes Project and the HapMap Consortium to explore whether the 32 confirmed BMI SNPs were in LD ($r^2 \geq 0.75$) with common missense SNPs or copy number variants (CNVs) (Online Methods). Non-synonymous variants in LD with our signals were present in the *BDNF, SLC39A8, FLJ35779/HMGCR, QPCTL/GIPR, MTCH2, ADCY3,* and *LBXCOR1* genes. In addition, the rs7359397 signal was in LD with coding variants in several genes including *SH2B1, ATNX2L, APOB48R, SULT1A2,* and *AC138894.2* (Table 1, Fig. 3, Supplementary Table 6 and Supplementary Fig. 2). Furthermore, two SNPs tagged common CNVs. The first CNV was previously identified and is a 45-kb deletion near *NEGR1*[9]. The second CNV is a 21-kb deletion that lies 50kb upstream of *GPRC5B;* the deletion allele is tagged by the T-allele of rs12444979 ($r^2 = 1$) (Fig. 3). Although the correlations with potentially functional variants does not prove that these variants are indeed causal, these provide first clues as to which genes and variants at these loci might be prioritized for fine-mapping and functional follow-up.

As many of the 32 BMI loci harbor multiple genes, we examined whether gene expression (eQTL) analyses could also direct us to positional candidates. Gene expression data were available for human brain, lymphocytes, blood, subcutaneous and visceral adipose tissue, and liver[34–36] (Online Methods, Table 1 and Supplementary Table 7). Significant *cis*-associations, defined at the tissue-specific level, were observed between 14 BMI-associated alleles and expression levels (Table 1 and Supplementary Table 7). In several cases, the BMI-associated SNP was the most significant SNP or explained a substantial proportion of the association with the most significant SNP for the gene transcript in conditional analyses (P_{adj}>0.05). These significant associations included *NEGR1, ZC3H4*, *TMEM160*, *MTCH2*, *NDUFS3*, *GTF3A, ADCY3*, *APOB48R*, *SH2B1*, *TUFM*, *GPRC5B*, *IQCK*, *SLC39A8*, *SULT1A1*, and *SULT1A2* (Table 1 and Supplementary Table 7), making these genes higher priority candidates within the associated loci. However, we note that some BMI-associated variants were correlated with the expression of multiple nearby genes, making it difficult to determine the most relevant gene.

Evidence for the existence of additional associated variants

Because the variants identified by this large study explain only 1.45% of the variance in BMI (2–4% of genetic variance based on an estimated heritability of 40–70%), we considered how much the explained phenotypic variance could be increased by including more SNPs at various degrees of significance in a polygene model using an independent validation set (Online Methods)[37]. We found that including SNPs associated with BMI at

lower significance levels (up to $P > 0.05$) increased the explained phenotypic variance in BMI to 2.5%, or 4% to 6% of genetic variance (Fig. 4a). In a separate analysis, we estimated the total number of independent BMI-associated variants that are likely to exist with similar effect sizes to the 32 confirmed here (Online Methods)[38]. Based on the effect size and allele frequencies of the 32 replicated loci observed in stage 2 and the power to detect association in the combined stage 1 and stage 2, we estimated that there are 284 (95% CI: 132–510) loci with similar effect sizes as the currently observed ones, which together would account for 4.5% (95% CI: 3.1–6.8%) of the variation in BMI or 6–11% of the genetic variation (based on an estimated heritability of 40–70%) (Supplementary Table 8). In order to detect 95% of these loci, a sample size of approximately 730,000 subjects would be needed (Fig. 4b). This method does not account for the potential of loci of smaller effect than those identified here to explain even more of the variance and thus provides an estimated lower bound of explained variance. These two analyses strongly suggest that larger GWA studies will continue to identify additional novel associated loci, but also indicate that even extremely large studies focusing on variants with allele frequencies above 5% will not account for a large fraction of the genetic contribution to BMI.

We examined whether selecting only a single variant from each locus for follow-up led us to underestimate the fraction of phenotypic variation explained by the associated loci. To search for additional independent loci at each of the 32 associated BMI loci, we repeated our GWA meta-analysis, conditioning on the 32 confirmed SNPs. Using a significance threshold of 5×10^{-6} for SNPs at known loci, we identified one apparently independent signal at the *MC4R* locus; rs7227255 was associated with BMI ($P = 6.56 \times 10^{-7}$) even after conditioning for the most strongly associated variant near *MC4R* (rs571312) (Fig. 5). Interestingly, rs7227255 is in perfect LD ($r^2 = 1$) with a relatively rare *MC4R* missense variant (rs2229616, V103I, minor allele frequency = 1.7%) that has been associated with BMI in two independent meta-analyses[39,40]. Furthermore, mutations at the *MC4R* locus are known to influence early-onset obesity[24,41], supporting the notion that allelic heterogeneity may be a frequent phenomenon in the genetic architecture of obesity.

Discussion

Using a two-stage genome-wide association meta-analysis of up to 249,796 individuals of European descent, we have identified 18 additional loci that are associated with BMI at genome-wide significance, bringing the total number of such loci to 32. We estimate that more than 250 (i.e. 284 predicted loci – 32 confirmed loci) common variant loci with effects on BMI similar to those described here remain to be discovered, and even larger numbers of loci with smaller effects. A substantial proportion of these loci should be identifiable through larger GWA studies and/or by targeted follow-up of top signals selected from our stage 1 analysis. The latter approach is already being implemented through large-scale genotyping of samples informative for BMI using a custom array (the Metabochip) designed to support follow-up of thousands of promising variants in hundreds of thousands of individuals.

The combined effect on BMI of the associated variants at the 32 loci is modest, and even when we try to account for as-yet-undiscovered variants with similar properties, we estimate that these common variant signals account for only 6–11% of the genetic variation in BMI. There is a strong expectation that additional variance and biology will be explained using complementary approaches that capture variants not examined in the current study, such as lower frequency variants and short insertion-deletion polymorphisms. There is good reason to believe (based on our findings at *MC4R* and other loci – *POMC, BDNF, SH2B1* – which feature both common and rare variant associations) that a proportion of such low-frequency and rare causal variation will map to the loci already identified by GWA studies.

A primary goal of human genetic discovery is to improve understanding of the biology of conditions such as obesity[42]. One particularly interesting finding in this regard is the association between BMI and common variants near *GIPR*, which may indicate a causal contribution of variation in postprandial insulin secretion to the development of obesity. In most cases, the loci identified by the present study harbor few, if any, annotated genes with clear connections to the biology of weight regulation. This reflects our still limited understanding of the biology of BMI and obesity-related traits and is in striking contrast with the results from equivalent studies of certain other traits (such as autoimmune diseases or lipid levels). Thus, these results suggest that much novel biology remains to be uncovered, and that GWA studies may provide an important entry point. In particular, further examination of the associated loci through a combination of resequencing and fine-mapping to find causal variants, and genomic and experimental studies designed to assign function, could uncover novel insights into the biology of obesity.

In conclusion, we have performed GWA studies in large samples to identify numerous genetic loci associated with variation in BMI, a common measure of obesity. Because current lifestyle interventions are largely ineffective in addressing the challenges of growing obesity[43,44], new insights into biology are critically needed to guide the development and application of future therapies and interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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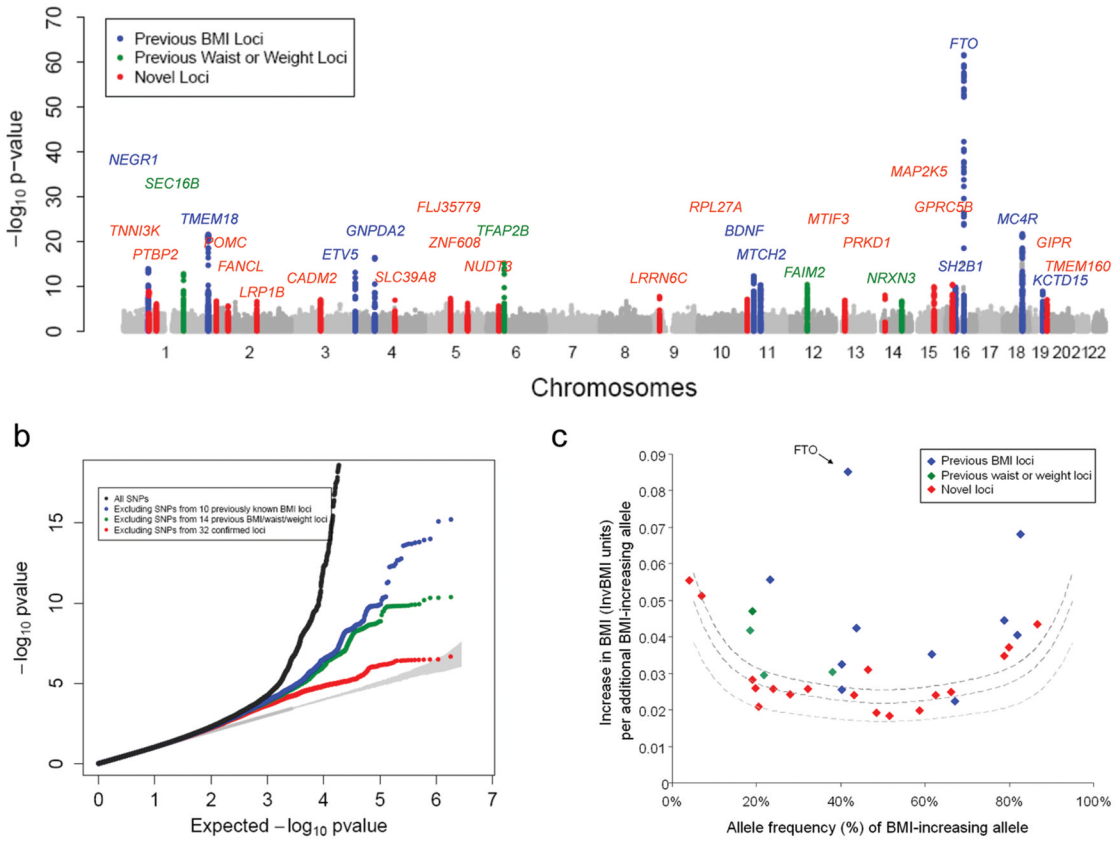

Figure 1. Genome-wide association results for the BMI meta-analysis

(**a**) Manhattan plot showing the significance of association between all SNPs and BMI in the stage 1 meta-analysis, highlighting SNPs previously reported to show genome-wide significant association with BMI (blue), weight or waist circumference (green), and the 18 new regions described here (red). The 19 SNPs that reached genome-wide significance at Stage 1 (13 previously reported and 6 new) are listed in Table 1). (**b**) Quantile-quantile (Q-Q) plot of SNPs in stage 1 meta-analysis (black) and after removing any SNPs within 1 Mb of the 10 previously reported genome-wide significant hits for BMI (blue), after additionally excluding SNPs from the four loci for waist/weight (green) and after excluding SNPs from all 32 confirmed loci (red). The plot was abridged at the Y-axis (at $P < 10^{-20}$) to better visualise the excess of small *P*-values after excluding the 32 confirmed loci (Supplementary Fig. 3 shows full-scale Q-Q plot). The shaded region is the 95% concentration band. (**c**) Plot of effect size (in inverse normally transformed units (invBMI)) versus effect allele frequency of newly identified and previously identified BMI variants after stage 1 + stage 2 analysis; including the 10 previously identified BMI loci (blue), the four previously identified waist and weight loci (green) and the 18 newly identified BMI loci (blue). The dotted lines represent the minimum effect sizes that could be identified for a given effect-allele frequency with 80% (upper line), 50% (middle line), and 10% (lower line) power, assuming a sample size of 123,000 individuals and a α-level of 5×10^{-8}.

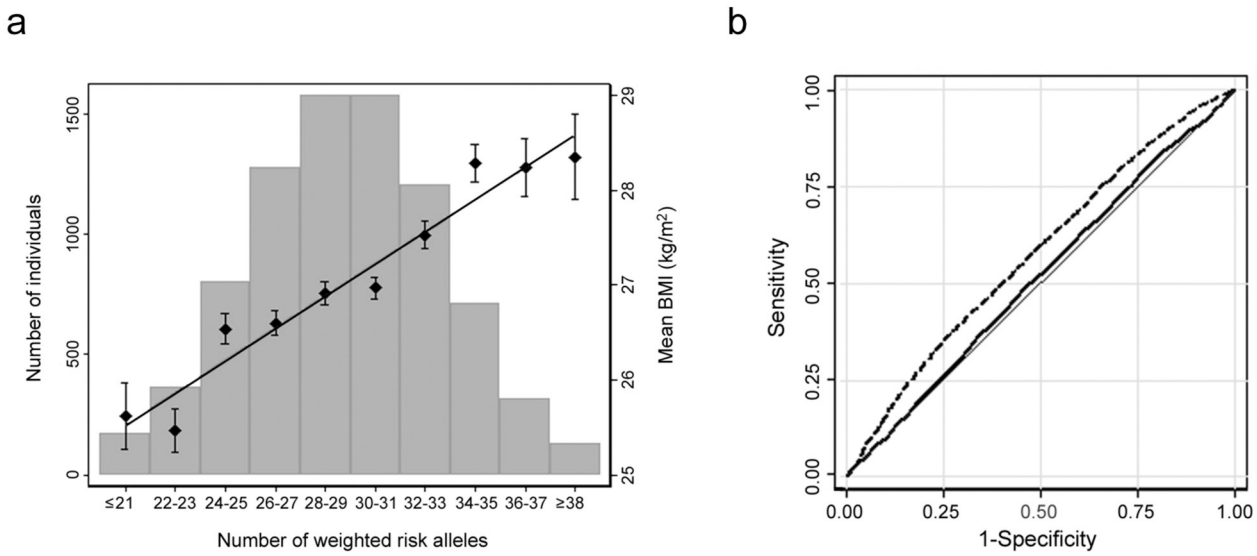

Figure 2. Combined impact of risk alleles on BMI/obesity

(**a**) Combined effect of risk alleles on average BMI in the population-based Atherosclerosis Risk in Communities (ARIC) study (n = 8,120 individuals of European descent). For each individual, the number of "best guess" replicated (n = 32) risk alleles from imputed data (0,1,2) per SNP was weighted for their relative effect sizes estimated from the stage 2 data. Weighted risk alleles were summed for each individual and the overall individual sum was rounded to the nearest integer to represent the individual's risk allele score (range 16–44). Along the x-axis, individuals in each risk allele category are shown (grouped ≤21 and ≥38 at the extremes), and the mean BMI (+/− SEM) is plotted (y axis on right), with the line representing the regression of the mean BMI values across the risk-allele scores. The histogram (y-axis on left) represents the number of individuals in each risk-score category. (**b**) The area under the ROC curve (AUC) of two different models predicting the risk of obesity (BMI = ≥30 kg/m^2) in the n = 8,120 genotyped individuals of European descent in the ARIC Study. Model 1, represented by the solid line, includes age, age^2, and sex (AUC = 0.515, $P = 0.023$ for difference from $AUC_{null} = 0.50$). Model 2, represented by the dashed line, includes age, age^2, sex, and the n = 32 confirmed BMI SNPs (AUC = 0.0575, $P < 10^{-5}$ for difference from $AUC_{null} = 0.50$). The difference between both AUCs is significant ($P < 10^{-4}$).

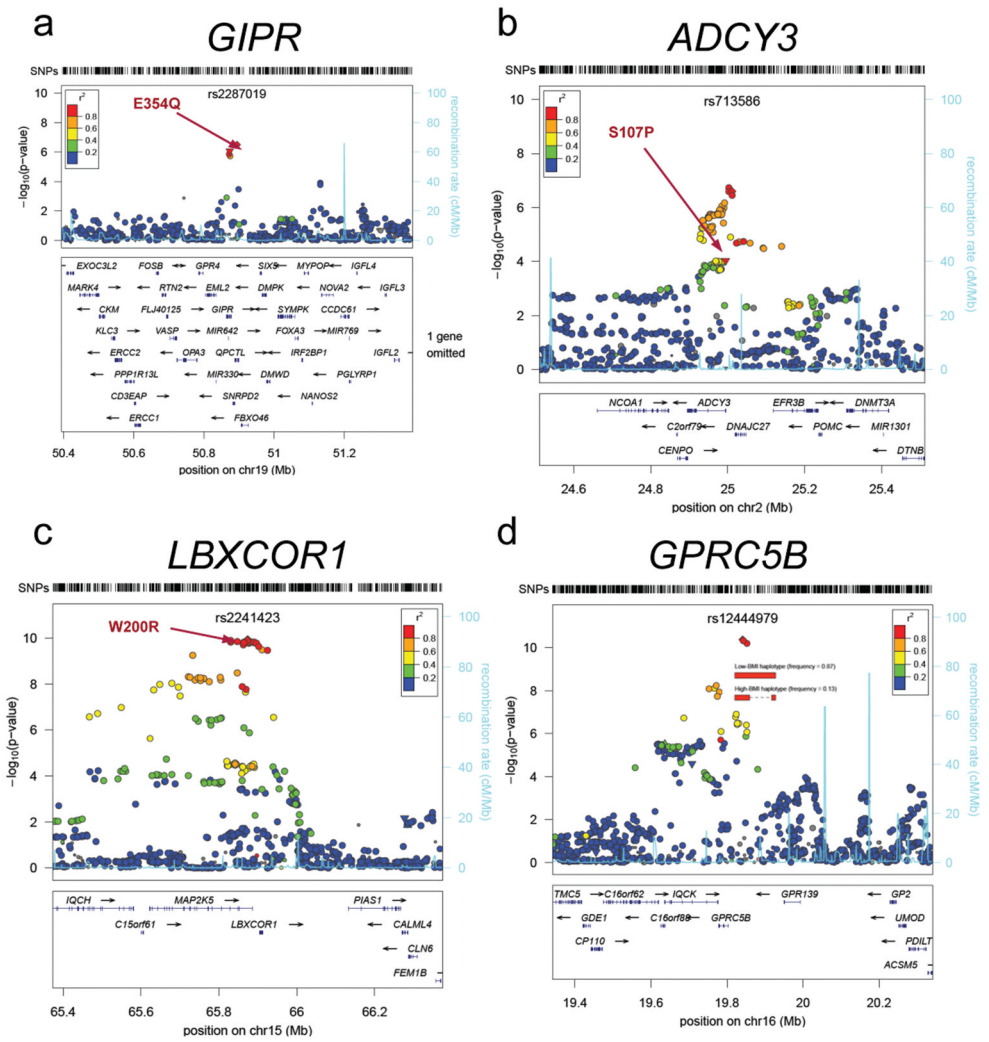

Figure 3. Regional plots of selected replicating BMI loci with missense and CNV variants

SNPs are plotted by position on chromosome against association with BMI ($-\log_{10}$ *P*-value). The SNP name shown on the plot was the most significant SNP after stage 1 meta-analysis. Estimated recombination rates (from HapMap) are plotted in cyan to reflect the local LD structure. The SNPs surrounding the most significant SNP are color-coded to reflect their LD with this SNP (taken from pairwise r^2 values from the HapMap CEU database, www.hapmap.org). Genes, position of exons, and direction of transcription from UCSC genome browser (http://genome.ucsc.edu) are noted. Hashmarks represent SNP positions available in the meta-analysis. (**a, b, c**) Missense variants noted with their amino acid change for the gene noted above the plot. (**d**) Structural haplotypes and BMI association signal in the *GPRC5B* region. A 21 kb deletion polymorphism is associated with 4 SNPs (r^2=1.0) that comprise the best haplogroup associating with BMI. Plots were generated using LocusZoom (http://csg.sph.umich.edu/locuszoom).

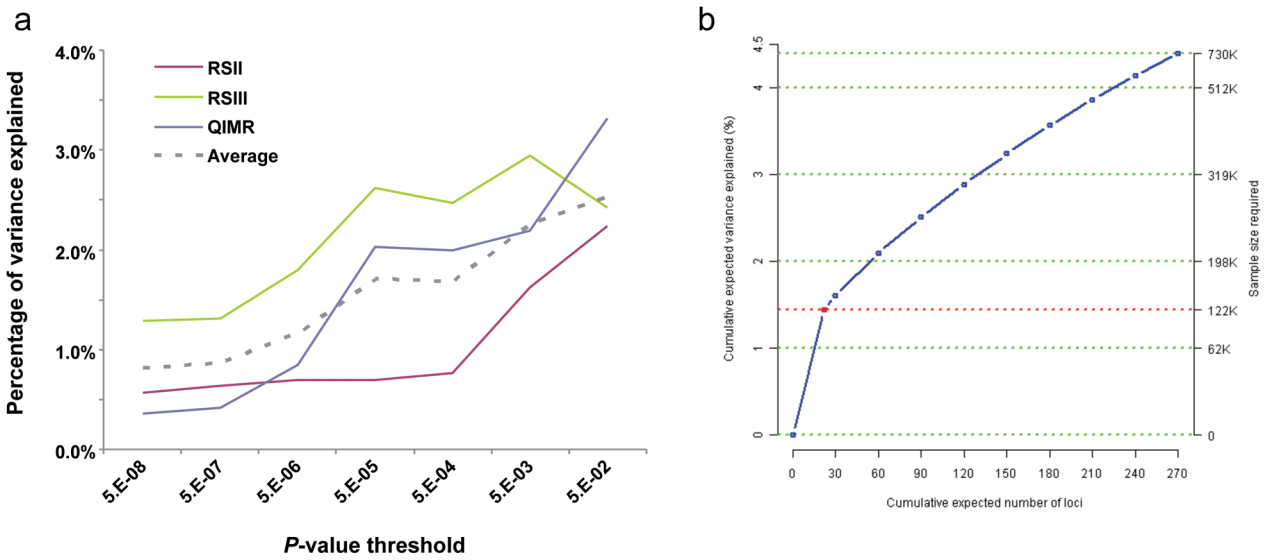

Figure 4. Phenotypic variance explained by common variants

(**a**) Variance explained is higher when SNPs not reaching genome-wide significance are included in the prediction model. The y-axis represents the proportion of variance explained at different *P*-value thresholds from stage 1 meta-analysis. Results are given for three studies (RSII, RSIII, QIMR), which were not included in the meta-analysis, after exclusion of all samples from The Netherlands (for RSII and RSIII) and the United Kingdom (for QIMR) from the discovery analysis for this sub-analysis. The dotted line represents the weighted average of the explained variance of three validation sets. (**b**) Cumulative number of susceptibility loci expected to be discovered, including those we have already identified and others that have yet to be detected, by the expected percentage of phenotypic variation explained and sample size required for a one-stage GWA study assuming a GC correction is utilized. The projections are based on loci that achieved a significance level of $P < 5\times10^{-8}$ in the joint analysis of stage 1 and stage 2 and the distribution of their effect sizes in stage 2. The dotted red line corresponds to the expected phenotypic variance explained by the 22 loci that are expected to be discovered in a one-stage GWAS with the sample size of stage 1 of this study.

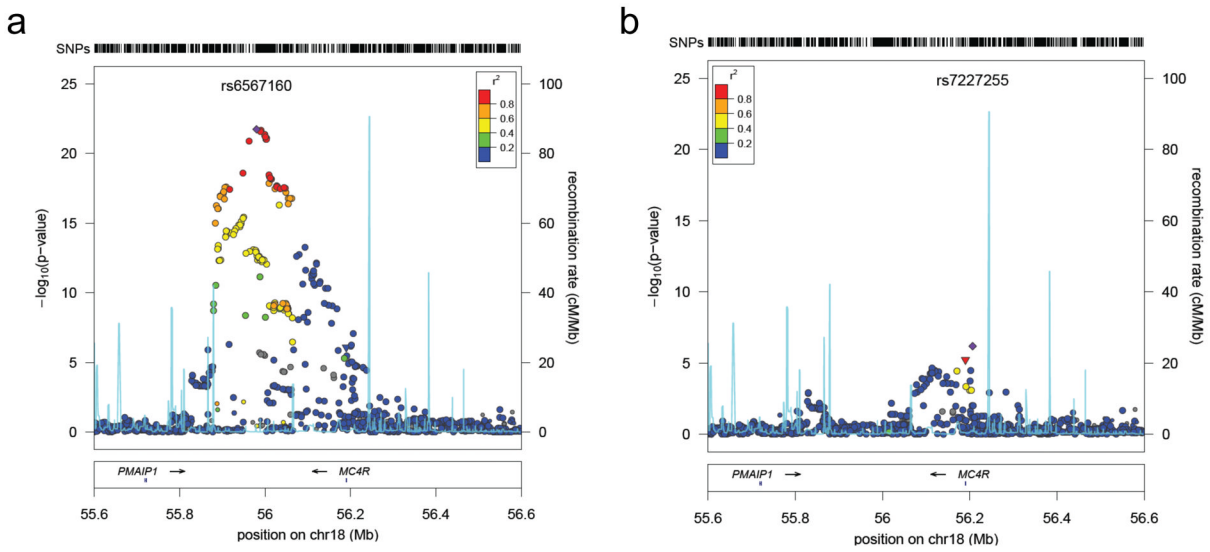

Figure 5. Second signal at the MC4R locus contributing to BMI

SNPs are plotted by position in a 1 Mb window of chromosome 18 against association with BMI ($\log_{10}$ *P*-value). Panel (**a**) highlights the most significant SNP in stage 1 meta-analysis, panel (**b**) the most significant SNP after conditional analysis where the model included the most strongly associated SNP from panel A as a covariate. Estimated recombination rates (from HapMap) are plotted in cyan to reflect the local LD structure. The SNPs surrounding the most significant SNP are color-coded to reflect their LD with this SNP (taken from pairwise r^2 values from the HapMap CEU database, www.hapmap.org). Genes, exons, and direction of transcription from UCSC genome browser (genome.ucsc.edu) are noted. Hashmarks at the top of the figure represent positions of SNPs in the meta-analysis. Regional plots were generated using LocusZoom (http://csg.sph.umich.edu/locuszoom).

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Table 1

Stage 1 and stage 2 results of the 32 SNPs that were associated with BMI at genome-wide significance ($P < 5.10^{-8}$) levels.

SNP	Nearest gene	Other nearby genes*	Chr	Position** (bp)	Alleles**		Frequency effect allele (%)	Per allele change in BMI beta (se)***	Explained variance (%)	Stage 1 *P*-value	Stage 2 *P*-value	Stage 1 + 2	
					Effect	Other						n	*P*-value
Previous BMI loci													
rs1558902	*FTO*		16	52,361,075	a	t	42%	0.39 (0.02)	0.34%	2.05E-62	1.007E-60	192,344	4.8E-120
rs2867125	*TMEM18*		2	612,827	c	t	83%	0.31 (0.03)	0.15%	2.42E-22	4.42E-30	197,806	2.77E-49
rs571312	*MC4R* [B]		18	55,990,749	a	c	24%	0.23 (0.03)	0.10%	1.82E-22	3.19E-21	203,600	6.43E-42
rs10938397	*GNPDA2*		4	44,877,284	g	a	43%	0.18 (0.02)	0.08%	4.35E-17	1.45E-15	197,008	3.78E-31
rs10767664	*BDNF*[B,M]		11	27,682,562	a	t	78%	0.19 (0.03)	0.07%	5.53E-13	1.17E-14	204,158	4.69E-26
rs2815752	*NEGR1*[C,Q]		1	72,585,028	a	g	61%	0.13 (0.02)	0.04%	1.17E-14	2.29E-09	198,380	1.61E-22
rs7359397	*SH2B1*[Q,B,M]	*APOB48R*[Q,M], *SULT1A2*[Q,M], *AC138894.2*[M], *ATXN2L*[M], *TUFM*[Q]	16	28,793,160	t	c	40%	0.15 (0.02)	0.05%	1.75E-10	7.89E-12	204,309	1.88E-20
rs9816226	*ETV5*		3	187,317,193	t	a	82%	0.14 (0.03)	0.03%	7.61E-14	1.15E-06	196,221	1.69E-18
rs3817334	*MTCH2*[Q,M]	*NDUFS3* [Q], *CUGBP1* [Q]	11	47,607,569	t	c	41%	0.06 (0.02)	0.01%	4.79E-11	1.10E-03	191,943	1.59E-12
rs29941	*KCTD15*		19	39,001,372	g	a	67%	0.06 (0.02)	0.00%	1.31E-09	2.40E-02	192,872	3.01E-09
Previous waist & weight loci													
rs543874	*SEC16B*		1	176,156,103	g	a	19%	0.22 (0.03)	0.07%	1.66E-13	2.41E-11	179,414	3.56E-23
rs987237	*TFAP2B*		6	50,911,009	g	a	18%	0.13 (0.03)	0.03%	5.97E-16	2.40E-06	195,776	2.90E-20
rs7138803	*FAIM2*		12	48,533,735	a	g	38%	0.12 (0.02)	0.04%	3.96E-11	7.82E-08	200,064	1.82E-17
rs10150332	*NRXN3*		14	79,006,717	c	t	21%	0.13 (0.03)	0.02%	2.03E-07	2.86E-05	183,022	2.75E-11
Newly identified BMI loci													
rs713586	*RBJ*	*ADCY3*[Q, M], *POMC*[Q,B]	2	25,011,512	c	t	47%	0.14 (0.02)	0.06%	1.80E-07	1.44E-16	230,748	6.17E-22
rs12444979	*GPRC5B*[C,Q]	*IQCK* [Q]	16	19,841,101	c	t	87%	0.17 (0.03)	0.04%	4.20E-11	8.13E-12	239,715	2.91E-21
rs2241423	*MAP2K5*	*LBXCOR1* [M]	15	65,873,892	g	a	78%	0.13 (0.02)	0.03%	1.15E-10	1.59E-09	227,950	1.19E-18
rs2287019	*QPCTL*	*GIPR*[B,M]	19	50,894,012	c	t	80%	0.15 (0.03)	0.04%	3.18E-07	1.40E-10	194,564	1.88E-16
rs1514175	*TNNI3K*		1	74,764,232	a	g	43%	0.07 (0.02)	0.02%	1.36E-09	7.04E-06	227,900	8.16E-14
rs13107325	*SLC39A8*[Q,M]		4	103,407,732	t	c	7%	0.19 (0.04)	0.03%	1.37E-07	1.93E-07	245,378	1.50E-13
rs2112347	*FLJ35779* [M]	*HMGCR* [B]	5	75,050,998	t	g	63%	0.10 (0.02)	0.02%	4.76E-08	8.29E-07	231,729	2.17E-13

SNP	Nearest gene	Other nearby genes*	Chr	Position** (bp)	Alleles**		Frequency effect allele (%)	Per allele change in BMI beta (se)***	Explained variance (%)	Stage 1 *P*-value	Stage 2 *P*-value	Stage 1 + 2	
					Effect	Other						n	*P*-value
rs10968576	*LRRN6C*		9	28,404,339	g	a	31%	0.11 (0.02)	0.02%	1.88E-08	3.19E-06	216,916	2.65E-13
rs3810291	*TMEM160* [Q]	*ZC3H4* [Q]	19	52,260,843	a	g	67%	0.09 (0.02)	0.02%	1.04E-07	1.59E-06	233,512	1.64E-12
rs887912	*FANCL*		2	59,156,381	t	c	29%	0.10 (0.02)	0.03%	2.69E-06	1.72E-07	242,807	1.79E-12
rs13078807	*CADM2*		3	85,966,840	g	a	20%	0.10 (0.02)	0.02%	9.81E-08	5.32E-05	237,404	3.94E-11
rs11847697	*PRKD1*		14	29,584,863	t	c	4%	0.17 (0.05)	0.01%	1.11E-08	2.25E-04	241,667	5.76E-11
rs2890652	*LRP1B*		2	142,676,401	c	t	18%	0.09 (0.03)	0.02%	2.38E-07	9.47E-05	209,068	1.35E-10
rs1555543	*PTBP2*		1	96,717,385	c	a	59%	0.06 (0.02)	0.01%	7.65E-07	4.48E-05	243,013	3.68E-10
rs4771122	*MTIF3*	*GTF3A* [Q]	13	26,918,180	g	a	24%	0.09 (0.03)	0.02%	1.20E-07	8.24E-04	198,577	9.48E-10
rs4836133	*ZNF608*		5	124,360,002	a	c	48%	0.07 (0.02)	0.01%	7.04E-07	1.88E-04	241,999	1.97E-09
rs4929949	*RPL27A*	*TUB* [B]	11	8,561,169	c	t	52%	0.06 (0.02)	0.01%	7.57E-08	1.00E-03	249,791	2.80E-09
rs206936	*NUDT3*	*HMGA1* [B]	6	34,410,847	g	a	21%	0.06 (0.02)	0.01%	2.81E-06	7.39E-04	249,777	3.02E-08

*Genes within +/− 500 kb of the lead SNP

**Positions according to Build 36 and allele coding based on the positive strand

***Effect sizes in kg/m2 obtained from Stage 2 cohorts only

[Q]Association and eQTL data converge to affect gene expression

[B]Biological candidate

[M]BMI-associated variant is in strong LD (r2 ≥ 0.75) with a missense variant in the indicated gene

[C]CNV