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Ramdas, S.; Judd, J.; Graham, S.E.; Kanoni, S.; Wang, Y.X.; Surakka, I.; ... ; Lee, H.

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A multi-layer functional genomic analysis to understand noncoding genetic variation in lipids

Authors

Shweta Ramdas, Jonathan Judd,
Sarah E. Graham, ..., Cristen J. Willer, Xiang Zhu,
Christopher D. Brown

Correspondence

xiangzhu@psu.edu (X.Z.),
chrbro@upenn.edu (C.D.B.)

In this study, we present a multi-layer framework to combine the largest multi-ancestry GWAS to date on lipid levels with both transcriptomic and epigenomic datasets to prioritize regulatory variants, effector genes, cell types, and tissues with strong functional relevance to lipid biology.

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A multi-layer functional genomic analysis to understand noncoding genetic variation in lipids

Shweta Ramdas,^{1,4,20} Jonathan Judd,^{2,4,20} Sarah E. Graham,^{3,4,20} Stavroula Kanoni,^{4,4,20} Yuxuan Wang,^{5,4,20} Ida Surakka,³ Brandon Wenz,¹ Shoa L. Clarke,^{6,7} Alessandra Chesi,⁸ Andrew Wells,¹ Konain Fatima Bhatti,⁴ Sailaja Vedantam,^{9,10} Thomas W. Winkler,¹¹ Adam E. Locke,¹² Eirini Marouli,⁴ Greg J.M. Zajac,¹³ Kuan-Han H. Wu,¹⁴ Ioanna Ntalla,¹⁵ Qin Hui,^{16,17} Derek Klarin,^{10,18,19} Austin T. Hilliard,⁶ Zeyuan Wang,^{16,17} Chao Xue,³ Gudmar Thorleifsson,²⁰ Anna Helgadottir,²⁰ Daniel F. Gudbjartsson,^{20,21} Hilma Holm,²⁰ Isleifur Olafsson,²² Mi Yeong Hwang,²³ Sohee Han,²³ Masato Akiyama,^{24,25} Saori Sakaue,^{26,27,28} Chikashi Terao,²⁹ Masahiro Kanai,^{10,24,30} Wei Zhou,^{10,14,31} Ben M. Brumpton,^{32,33,34} Humaira Rasheed,^{32,33,35} Aki S. Havulinna,^{36,37} Yogasudha Veturi,³⁸

(Author list continued on next page)

Summary

A major challenge of genome-wide association studies (GWAS) is to translate phenotypic associations into biological insights. Here, we integrate a large GWAS on blood lipids involving 1.6 million individuals from five ancestries with a wide array of functional genomic datasets to discover regulatory mechanisms underlying lipid associations. We first prioritize lipid-associated genes with expression quantitative trait locus (eQTL) colocalizations and then add chromatin interaction data to narrow the search for functional genes. Polygenic enrichment analysis across 697 annotations from a host of tissues and cell types confirms the central role of the liver in lipid levels and highlights the selective enrichment of adipose-specific chromatin marks in high-density lipoprotein cholesterol and triglycerides. Overlapping transcription factor (TF) binding sites with lipid-associated loci identifies TFs relevant in lipid biology. In addition, we present an integrative framework to prioritize causal variants at GWAS loci, producing a comprehensive list of candidate causal genes and variants with multiple layers of functional evidence. We highlight two of the prioritized genes, *CREBRF* and *RRBP1*, which show convergent evidence across functional datasets supporting their roles in lipid biology.

Introduction

Most GWAS findings have not directly led to mechanistic interpretations, largely because approximately 90% of GWAS associations map to noncoding sequences.^{1,2} Mech-

anistic interpretations in GWAS have proven challenging because the strongest signals identified in GWAS typically contain many variants in strong linkage disequilibrium (LD)³ and functional mechanisms including genes of action are often not clear from GWAS data alone.^{4,5}

¹Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; ²Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA; ³Department of Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, MI 48109, USA; ⁴William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK; ⁵Department of Biostatistics, Boston University School of Public Health, 801 Massachusetts Avenue, Boston, MA 02118, USA; ⁶VA Palo Alto Health Care Systems, Palo Alto, CA, USA; ⁷Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA; ⁸Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA; ⁹Endocrinology, Boston Childrens Hospital, Boston, MA 02115, USA; ¹⁰Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, 75 Ames street, Cambridge, MA 02142, USA; ¹¹Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany; ¹²McDonnell Genome Institute and Department of Medicine, Washington University, St. Louis, MO 63108, USA; ¹³Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA; ¹⁴Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI, USA; ¹⁵Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, EC1M 6BQ London, UK; ¹⁶Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA; ¹⁷Atlanta VA Health Care System, Decatur, GA, USA; ¹⁸Malcolm Randall VA Medical Center, Gainesville, FL, USA; ¹⁹Division of Vascular Surgery and Endovascular Therapy, University of Florida College of Medicine, Gainesville, FL, USA; ²⁰deCODE genetics/Amgen, Inc., Sturlugata 8, Reykjavik 102, Iceland; ²¹School of Engineering and Natural Sciences, University of Iceland, Sæmundargötu 2, Reykjavik 102, Iceland; ²²Department of Clinical Biochemistry, Landspítali - National University Hospital of Iceland, Hringbraut, Reykjavik 101, Iceland; ²³Division of Genome Science, Department of Precision Medicine, National Institute of Health, Chungbuk, South Korea; ²⁴Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan; ²⁵Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; ²⁶Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan; ²⁷Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, The University of Tokyo, Tokyo, Japan; ²⁸Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; ²⁹Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan; ³⁰Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA; ³¹Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA; ³²K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway; ³³MRC Integrative Epidemiology Unit (IEU), Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, BS8 2BN Bristol, UK; ³⁴Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; ³⁵Division of Medicine and Laboratory Sciences,

(Affiliations continued on next page)



Jennifer Allen Pacheco,³⁹ Elisabeth A. Rosenthal,⁴⁰ Todd Lingren,⁴¹ QiPing Feng,⁴² Iftikhar J. Kullo,⁴³ Akira Narita,⁴⁴ Jun Takayama,⁴⁴ Hilary C. Martin,⁴⁵ Karen A. Hunt,⁴⁶ Bhavi Trivedi,⁴⁶ Jeffrey Haessler,⁴⁷ Franco Giulianini,⁴⁸ Yuki Bradford,³⁸ Jason E. Miller,³⁸ Archie Campbell,^{49,50} Kuang Lin,⁵¹ Iona Y. Millwood,^{51,52} Asif Rasheed,⁵³ George Hindy,⁵⁴ Jessica D. Faul,⁵⁵ Wei Zhao,⁵⁶ David R. Weir,⁵⁵ Constance Turman,⁵⁷ Hongyan Huang,⁵⁷ Mariaelisa Graff,⁵⁸ Ananyo Choudhury,⁵⁹ Dhriti Sengupta,⁵⁹ Anubha Mahajan,⁶⁰ Michael R. Brown,⁶¹ Weihua Zhang,^{62,63,64} Ketian Yu,¹³ Ellen M. Schmidt,¹³ Anita Pandit,¹³ Stefan Gustafsson,⁶⁵ Xianyong Yin,¹³ Jian'an Luan,⁶⁶ Jing-Hua Zhao,⁶⁷ Fumihiko Matsuda,⁶⁸ Hye-Mi Jang,²³ Kyunghoon Yoon,²³ Carolina Medina-Gomez,⁶⁹ Achilles Pitsillides,⁵ Jouke Jan Hottenga,^{70,71} Andrew R. Wood,⁷² Yingji Ji,⁷² Zishan Gao,^{73,74,75} Simon Haworth,^{33,76} Ruth E. Mitchell,^{33,77} Jin Fang Chai,⁷⁸ Mette Aadahl,^{79,80} Anne A. Bjerregaard,⁷⁹ Jie Yao,⁸¹ Ani Manichaikul,⁸² Wen-Jane Lee,⁸³ Chao Agnes Hsiung,⁸⁴ Helen R. Warren,^{4,85} Julia Ramirez,⁴ Jette Bork-Jensen,⁸⁶ Line L. Kårhus,⁷⁹ Anuj Goel,^{60,87} Maria Sabater-Lleal,^{88,89} Raymond Noordam,⁹⁰ Pala Mauro,⁹¹ Floris Matteo,^{91,92} Aaron F. McDaid,^{93,94} Pedro Marques-Vidal,⁹⁵ Matthias Wielscher,⁶² Stella Trompet,^{90,96} Naveed Sattar,⁹⁷ Line T. Møllehave,⁷⁹ Matthias Munz,⁹⁸ Lingyao Zeng,^{99,100} Jianfeng Huang,¹⁰¹ Bin Yang,¹⁰¹ Alaitz Poveda,¹⁰² Azra Kurbasic,¹⁰² Sebastian Schönherr,¹⁰³ Lukas Forer,¹⁰³ Markus Scholz,^{104,105} Tessel E. Galesloot,¹⁰⁶ Jonathan P. Bradfield,¹⁰⁷ Sanni E. Ruotsalainen,³⁶ E. Warwick Daw,¹⁰⁸ Joseph M. Zmuda,¹⁰⁹ Jonathan S. Mitchell,¹¹⁰ Christian Fuchsberger,¹¹⁰ Henry Christensen,¹¹¹ Jennifer A. Brody,¹¹² Phuong Le,^{113,114} Mary F. Feitosa,¹⁰⁸ Mary K. Wojczynski,¹⁰⁸ Daiane Hemerich,¹¹⁵ Michael Preuss,¹¹⁵ Massimo Mangino,^{116,117} Paraskevi Christofidou,¹¹⁶

(Author list continued on next page)

University of Oslo, Oslo, Norway; ³⁶Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Tukholmankatu 8, 00014 Helsinki, Finland; ³⁷Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland; ³⁸Department of Genetics, Institute for Biomedical Informatics, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA 19104, USA; ³⁹Center for Genetic Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, USA; ⁴⁰Department of Medicine (Medical Genetics), University of Washington, Seattle, WA, USA; ⁴¹Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ⁴²Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; ⁴³Department of Cardiovascular Medicine and the Gonda Vascular Center, Mayo Clinic, Rochester, MN, USA; ⁴⁴Tohoku Medical Megabank Organization, Tohoku University, Sendai 980-8573, Japan; ⁴⁵Wellcome Trust Sanger Institute, CB10 1SA Hinxton, UK; ⁴⁶Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; ⁴⁷Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, WA 98109, USA; ⁴⁸Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215, USA; ⁴⁹Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, Western General Hospital, EH4 2XU Edinburgh, UK; ⁵⁰Usher Institute, The University of Edinburgh, Nine, Edinburgh Bioquarter, 9 Little France Road, EH16 4UX Edinburgh, UK; ⁵¹Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, OX3 7LF Oxford, UK; ⁵²Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, OX3 7LF Oxford, UK; ⁵³Center for Non-Communicable Diseases, Karachi, SD, Pakistan & Faisalabad Institute of Cardiology, Faisalabad, Pakistan; ⁵⁴Department of Population Medicine, Qatar University College of Medicine, QU Health, Doha, Qatar; ⁵⁵Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48104, USA; ⁵⁶Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA; ⁵⁷Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; ⁵⁸Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; ⁵⁹Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ⁶⁰Wellcome Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK; ⁶¹Human Genetics Center, Department of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA; ⁶²Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, W2 1PG London, UK; ⁶³Department of Cardiology, Ealing Hospital, London North West University Healthcare NHS Trust, UB1 3HW Middlesex, UK; ⁶⁴Imperial College Healthcare NHS Trust, Imperial College London, W12 0HS London, UK; ⁶⁵Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden; ⁶⁶MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, CB2 0QQ Cambridge, UK; ⁶⁷Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Wort's Causeway, CB1 8RN Cambridge, UK; ⁶⁸Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan; ⁶⁹Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands; ⁷⁰Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; ⁷¹Amsterdam Public Health Research Institute, Amsterdam UMC, Amsterdam, the Netherlands; ⁷²Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, EX2 5DW Exeter, UK; ⁷³Department of Clinical Acupuncture and Moxibustion, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210029, China; ⁷⁴Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; ⁷⁵Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; ⁷⁶Bristol Dental School, University of Bristol, Lower Maudlin Street, BS1 2LY Bristol, UK; ⁷⁷Population Health Sciences, Bristol Medical School, University of Bristol, Oakfield Grove, BS8 2BN Bristol, UK; ⁷⁸Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore 117549, Singapore; ⁷⁹Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; ⁸⁰Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ⁸¹The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, Lundquist Institute for Biomedical Innovations (Formerly LABioMed) at Harbor-UCLA Medical Center, Torrance, CA 90502, USA; ⁸²Center for Public Health Genomics, University of Virginia, Charlottesville, VA 22903, USA; ⁸³Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan; No. 1650, Sec. 4, Taiwan Boulevard, Taichung City 40705, Taiwan; ⁸⁴Institute of Population Health Sciences, National Health Research Institutes, 35 Keyan Road, Zhunan Town, Miaoli County 350, Taiwan, ROC; ⁸⁵NIHR Barts Cardiovascular Biomedical Research Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, EC1M 6BQ London, UK; ⁸⁶Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ⁸⁷Division of Cardiovascular Medicine, Radcliffe Department of Medicine, John Radcliffe Hospital, University of Oxford, OX3 9DU Oxford, UK; ⁸⁸Unit of Genomics of Complex Diseases, Sant Pau

(Affiliations continued on next page)

Niek Verweij,¹¹⁸ Jan W. Benjamins,¹¹⁸ Jorgen Engmann,^{119,120} Tsao L. Noah,¹²¹ Anurag Verma,¹ Roderick C. Sliker,^{122,123} Ken Sin Lo,¹²⁴ Nuno R. Zilhao,¹²⁵ Marcus E. Kleber,^{126,127} Graciela E. Delgado,¹²⁶ Shaofeng Huo,¹²⁸ Daisuke D. Ikeda,¹²⁹ Hiroyuki Iha,¹²⁹ Jian Yang,^{130,131} Jun Liu,^{132,133} Ayşe Demirkan,^{133,134} Hampton L. Leonard,^{135,136} Jonathan Marten,¹³⁷ Carina Emmel,¹³⁸ Borge Schmidt,¹³⁸ Laura J. Smyth,¹³⁹ Marisa Cañadas-Garre,^{139,140,141,142} Chaolong Wang,^{143,144} Masahiro Nakatochi,¹⁴⁵ Andrew Wong,¹⁴⁶ Nina Hutri-Kähönen,¹⁴⁷ Xueling Sim,⁷⁸ Rui Xia,¹⁴⁸ Alicia Huerta-Chagoya,¹⁴⁹ Juan Carlos Fernandez-Lopez,¹⁵⁰ Valeriya Lyssenko,^{102,151} Suraj S. Nongmaithem,¹⁵² Alagu Sankareswaran,^{152,153} Marguerite R. Irvin,¹⁴⁶ Christopher Oldmeadow,¹⁵⁴ Han-Na Kim,^{155,156} Seungho Ryu,^{157,158} Paul R.H.J. Timmers,^{137,159} Liubov Arbeeve,¹⁶⁰ Rajkumar Dorajoo,^{144,161} Leslie A. Lange,¹⁶² Gauri Prasad,^{153,163} Laura Lorés-Motta,¹⁶⁴ Marc Pauper,¹⁶⁴ Jirong Long,¹⁶⁵ Xiaohui Li,⁸¹ Elizabeth Theusch,¹⁶⁶ Fumihiko Takeuchi,¹⁶⁷ Cassandra N. Spracklen,^{168,169} Anu Loukola,³⁶ Sailalitha Bollepalli,³⁶ Sophie C. Warner,^{170,171} Ya Xing Wang,¹⁷² Wen B. Wei,¹⁷³ Teresa Nutile,¹⁷⁴ Daniela Ruggiero,^{174,175} Yun Ju Sung,¹⁷⁶ Shufeng Chen,¹⁰¹ Fangchao Liu,¹⁰¹ Jingyun Yang,^{177,178} Katherine A. Kentistou,¹⁵⁹ Bernhard Banas,¹⁷⁹ Anna Morgan,¹⁸⁰ Karina Meidtnr,^{181,182} Lawrence F. Bielak,⁵⁶ Jennifer A. Smith,^{55,56} Prashantha Hebbar,¹⁸³ Aliko-Eleni Farmaki,^{184,185} Edith Hofer,^{186,187} Maoxuan Lin,¹⁸⁸ Maria Pina Concas,¹⁸⁰ Simona Vaccargiu,¹⁸⁹ Peter J. van der Most,¹⁹⁰ Niina Pitkänen,^{191,192} Brian E. Cade,^{193,194} Sander W. van der Laan,¹⁹⁵ Kumaraswamy Naidu Chitralla,^{196,197} Stefan Weiss,¹⁹⁸ Amy R. Bentley,¹⁹⁹ Ayo P. Doumatey,¹⁹⁹ Adebowale A. Adeyemo,¹⁹⁹ Jong Young Lee,²⁰⁰ Eva R.B. Petersen,²⁰¹ Aneta A. Nielsen,²⁰² Hyeok Sun Choi,²⁰³ Maria Nethander,^{204,205} Sandra Freitag-Wolf,²⁰⁶

(Author list continued on next page)

Biomedical Research Institute (IIB Sant Pau), Barcelona, Spain; ⁸⁹Cardiovascular Medicine Unit, Department of Medicine, Karolinska Institutet, Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden; ⁹⁰Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands; ⁹¹Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche, Rome, Italy; ⁹²Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, Sardinia, Italy; ⁹³University Center for Primary Care and Public Health, University of Lausanne, Rte de Berne 113, 1010 Lausanne, Switzerland; ⁹⁴Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland; ⁹⁵Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, 1011 Lausanne, Switzerland; ⁹⁶Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; ⁹⁷BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, UK; ⁹⁸Institute for Cardiogenetics, University of Lübeck, DZHK (German Research Centre for Cardiovascular Research), partner site Hamburg/Lübeck/Kiel, University Heart Center Lübeck, Lübeck and Charité – University Medicine Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute for Dental and Craniofacial Sciences, Department of Periodontology and Synoptic Dentistry, Berlin, Germany; ⁹⁹Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Technische Universität München, Munich, Germany; ¹⁰⁰Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) e.V., partner site Munich Heart Alliance, Munich, Germany; ¹⁰¹Key Laboratory of Cardiovascular Epidemiology & Department of Epidemiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China; ¹⁰²Lund University Diabetes Centre, Lunds University, Malmö, Sweden; ¹⁰³Institute of Genetic Epidemiology, Department of Genetics and Pharmacology, Medical University of Innsbruck, Innsbruck, Austria and German Chronic Kidney Disease Study, Austria; ¹⁰⁴Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Haertelstrasse 16-18, 04107 Leipzig, Germany; ¹⁰⁵LIFE Research Centre for Civilization Diseases, University of Leipzig, Philipp-Rosenthal-Straße 27, 04103 Leipzig, Germany; ¹⁰⁶Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands; ¹⁰⁷Quantinuum Research LLC, Wayne, PA 19087, USA; ¹⁰⁸Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, MO, USA; ¹⁰⁹Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15232, USA; ¹¹⁰Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lübeck, Via Galvani 31, 39100 Bolzano, Italy; ¹¹¹Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle, Denmark; ¹¹²Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA 98101, USA; ¹¹³Department of Anthropology, University of Toronto at Mississauga, Mississauga, ON L5L 1C6, Canada; ¹¹⁴Department of Computer Science, University of Toronto, Toronto, ON M5S 2E4, Canada; ¹¹⁵The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ¹¹⁶Department of Twin Research and Genetic Epidemiology, King's College London, SE1 7EH London, UK; ¹¹⁷NIHR Biomedical Research Centre at Guy's and St Thomas' Foundation Trust, SE1 9RT London, UK; ¹¹⁸Department of Cardiology, University of Groningen, University Medical Center Groningen, 9700RB Groningen, the Netherlands; ¹¹⁹Institute of Cardiovascular Sciences, University College London, Gower Street, WC1E 6BT London, UK; ¹²⁰Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, WC1E 6BT London, UK; ¹²¹Department of Surgery, University of Pennsylvania, Philadelphia, PA 19104, USA; ¹²²Amsterdam UMC, Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, Amsterdam 1081HV, the Netherlands; ¹²³Leiden University Medical Center, Department of Cell and Chemical Biology, Leiden 2333ZA, the Netherlands; ¹²⁴Montreal Heart Institute, Université de Montréal, 5000 Belanger street, Montreal, QC H1T1C8, Canada; ¹²⁵Icelandic Heart Association, 201 Kopavogur, Iceland; ¹²⁶Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, 68167 Mannheim, Germany; ¹²⁷SYNLAB MVZ Humangenetik Mannheim GmbH, 68163 Mannheim, Germany; ¹²⁸Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai, China; ¹²⁹Biomedical Technology Research Center, Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan; ¹³⁰School of Life Sciences, Westlake University, Hangzhou, Zhejiang 310024, China; ¹³¹Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072, Australia; ¹³²Nuffield Department of Population Health, University of Oxford, Oxford, UK; ¹³³Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands; ¹³⁴Section of Statistical Multi-omics, Department of Clinical and Experimental research, University of Surrey, Guildford, Surrey, UK; ¹³⁵Laboratory of Neurogenetics, National Institute on Aging, NIH, Bethesda, MD, USA; ¹³⁶Data Tecnica International, Glen Echo, MD, USA; ¹³⁷MRC Human Genetics Unit, Institute of Genetics and Cancer, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK; ¹³⁸Institute for Medical Informatics, Biometrie and Epidemiology, University of Duisburg-Essen, Essen, Germany; ¹³⁹Centre for Public Health, Queen's University of Belfast, Belfast, Northern Ireland; ¹⁴⁰Genomic Oncology Area, GENYO, Centre for Genomics and Oncological Research: Pfizer-University of Granada-Andalusian Regional Government, Granada, Spain; ¹⁴¹Hematology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain; ¹⁴²Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Granada, Spain; ¹⁴³Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;

(Affiliations continued on next page)

Lorraine Southam,^{45,207} Nigel W. Rayner,^{45,60,207,208} Carol A. Wang,²⁰⁹ Shih-Yi Lin,^{210,211,212} Jun-Sing Wang,^{213,214} Christian Couture,²¹⁵ Leo-Pekka Lyytikäinen,^{216,217} Kjell Nikus,^{218,219} Gabriel Cuellar-Partida,²²⁰ Henrik Vestergaard,^{86,221} Bertha Hidalgo,²²² Olga Giannakopoulou,⁴ Qiuyin Cai,¹⁶⁵ Morgan O. Obura,¹²² Jessica van Setten,²²³ Karen Y. He,²²⁴ Hua Tang,² Natalie Terzikhan,¹³³ Jae Hun Shin,²⁰³ Rebecca D. Jackson,²²⁵ Alexander P. Reiner,²²⁶ Lisa Warsinger Martin,²²⁷ Zhengming Chen,^{51,52} Liming Li,²²⁸ Takahisa Kawaguchi,⁶⁸ Joachim Thiery,^{105,229} Joshua C. Bis,¹¹² Lenore J. Launer,²³⁰ Huaixing Li,¹²⁸ Mike A. Nalls,^{135,136} Olli T. Raitakari,^{191,192,231} Sahoko Ichihara,²³² Sarah H. Wild,²³³ Christopher P. Nelson,^{170,171} Harry Campbell,¹⁵⁹ Susanne Jäger,^{181,182} Toru Nabika,²³⁴ Fahd Al-Mulla,¹⁸³ Harri Niinikoski,^{235,236} Peter S. Braund,^{170,171} Ivana Kolcic,²³⁷ Peter Kovacs,²³⁸ Tota Giardoglou,¹⁸⁴ Tomohiro Katsuya,^{239,240} Dominique de Kleijn,²⁴¹ Gert J. de Borst,²⁴¹ Eung Kweon Kim,²⁴² Hieab H.H. Adams,^{133,243} M. Arfan Ikram,¹³³ Xiaofeng Zhu,²²⁴ Folkert W. Asselbergs,²²³ Adriaan O. Kraaijeveld,²²³ Joline W.J. Beulens,^{122,244} Xiao-Ou Shu,¹⁶⁵ Loukianos S. Rallidis,²⁴⁵ Oluf Pedersen,⁸⁶ Torben Hansen,⁸⁶ Paul Mitchell,²⁴⁶ Alex W. Hewitt,^{247,248} Mika Kähönen,^{249,250} Louis Pérusse,^{215,251} Claude Bouchard,²⁵² Anke Tönjes,²³⁸ Yii-Der Ida Chen,⁸¹ Craig E. Pennell,²⁰⁹ Trevor A. Mori,²⁵³ Wolfgang Lieb,²⁵⁴ Andre Franke,²⁵⁵ Claes Ohlsson,^{204,256} Dan Mellström,^{204,257} Yoon Shin Cho,²⁰³ Hyejin Lee,²⁵⁸ Jian-Min Yuan,^{109,259} Woon-Puay Koh,^{260,261} Sang Youl Rhee,²⁶² Jeong-Taek Woo,²⁶² Iris M. Heid,¹¹ Klaus J. Stark,¹¹ Martina E. Zimmermann,¹¹ Henry Völzke,²⁶³ Georg Homuth,¹⁹⁸ Michele K. Evans,²³⁰ Alan B. Zonderman,²³⁰ Ozren Polasek,^{237,264} Gerard Pasterkamp,¹⁹⁵ Imo E. Hofer,¹⁹⁵ Susan Redline,^{193,194} Katja Pahkala,^{191,192,265} Albertine J. Oldehinkel,²⁶⁶ Harold Snieder,¹⁹⁰

(Author list continued on next page)

¹⁴⁴Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, Singapore; ¹⁴⁵Public Health Informatics Unit, Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya 461-8673, Japan; ¹⁴⁶University of Alabama at Birmingham, Epidemiology, School of Public Health, Birmingham, AL, USA; ¹⁴⁷Tampere Centre for Skills Training and Simulation, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; ¹⁴⁸Brown Foundation Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston TX 77030, USA; ¹⁴⁹CONACYT, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de Mexico, Mexico; ¹⁵⁰Departamento de Genómica Computacional, Instituto Nacional de Medicina Genómica, Ciudad de Mexico, Mexico; ¹⁵¹Center for diabetes research, University of Bergen, Bergen, Norway; ¹⁵²Genomic Research on Complex diseases (GRC Group), CSIR-Centre for Cellular and Molecular Biology, Hyderabad, Telangana, India; ¹⁵³Academy of Scientific and Innovative Research (AcSIR), CSIR-Human Resource Development Centre, New Delhi, India; ¹⁵⁴Hunter Medical Research Institute, Newcastle, NSW, Australia; ¹⁵⁵Medical Research Institute, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, Korea; ¹⁵⁶Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Seoul 06355, Korea; ¹⁵⁷Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 04514, Korea; ¹⁵⁸Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, Korea; ¹⁵⁹Centre for Global Health Research, Usher Institute, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK; ¹⁶⁰Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, USA; ¹⁶¹Health Services and Systems Research, Duke-NUS Medical School, 169857, Singapore; ¹⁶²Division of Biomedical Informatics and Personalized Medicine, Department of Medicine, Anschutz Medical Campus, University of Colorado, Denver, Aurora, CO 80045, USA; ¹⁶³Genomics and Molecular Medicine Unit, CSIR-Institute of Genomics and Integrative Biology, New Delhi 110020, India; ¹⁶⁴Departments of Ophthalmology and Human Genetics, Radboud University Nijmegen Medical Center, Philips van Leydenlaan 15, Nijmegen 6525 EX, the Netherlands; ¹⁶⁵Vanderbilt Epidemiology Center, Division of Epidemiology, Vanderbilt University Medical Center, Nashville, TN, USA; ¹⁶⁶Department of Pediatrics, University of California San Francisco, Oakland, CA 94609, USA; ¹⁶⁷National Center for Global Health and Medicine, Tokyo 1628655, Japan; ¹⁶⁸Department of Genetics, University of North Carolina, Chapel Hill, NC 27599, USA; ¹⁶⁹Department of Biostatistics and Epidemiology, University of Massachusetts-Amherst, Amherst, MA 01003, USA; ¹⁷⁰Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; ¹⁷¹NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK; ¹⁷²Beijing Institute of Ophthalmology, Beijing Key Laboratory of Ophthalmology and Visual Sciences, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, 17 Hougou Lane, Chong Wen Men, Beijing 100005, China; ¹⁷³Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, 1 Dong Jiao Min Xiang, Dong Cheng District, Beijing 100730, China; ¹⁷⁴Institute of Genetics and Biophysics “Adriano Buzzati-Traverso” - CNR, Naples, Italy; ¹⁷⁵IRCCS Neuromed, Pozzilli, Isernia, Italy; ¹⁷⁶Division of Biostatistics, Washington University School of Medicine, St. Louis, MO 63110, USA; ¹⁷⁷Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, IL, USA; ¹⁷⁸Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA; ¹⁷⁹Department of Nephrology, University Hospital Regensburg, Regensburg, Germany; ¹⁸⁰Institute for Maternal and Child Health—IRCCS, Burlo Garofolo, 34127 Trieste, Italy; ¹⁸¹Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; ¹⁸²German Center for Diabetes Research (DZD), München-Neuherberg, Germany; ¹⁸³Department of Genetics and Bioinformatics, Dasman Diabetes Institute, Kuwait City, Kuwait; ¹⁸⁴Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University of Athens, Eleftheriou Venizelou, Athens, Greece; ¹⁸⁵Department of Population Science and Experimental Medicine, University College London, London, UK; ¹⁸⁶Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria; ¹⁸⁷Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria; ¹⁸⁸Massachusetts General Hospital Cancer Center, Charlestown, MA 02129, USA; ¹⁸⁹Institute of Genetic and Biomedical Research, National Research Council of Italy, UOS of Sassari, Sassari, Italy; ¹⁹⁰Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen 9700 RB, the Netherlands; ¹⁹¹Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; ¹⁹²Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland; ¹⁹³Sleep Medicine and Circadian Disorders, Brigham and Women’s Hospital, Boston, MA 02115, USA; ¹⁹⁴Division of Sleep Medicine, Harvard Medical School, Boston, MA 02115, USA; ¹⁹⁵Central Diagnostics Laboratory, Division Laboratories, Pharmacy, and Biomedical genetics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ¹⁹⁶Laboratory of Epidemiology and Population Science National Institute on Aging Intramural Research Program, NIH 251 Bayview Blvd, NIH Biomedical Research Center, Baltimore, MD 21224, USA; ¹⁹⁷Fels Cancer Institute for Personalized Medicine, Temple University Lewis Katz School of Medicine, Philadelphia, PA, USA; ¹⁹⁸Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University of Greifswald and University Medicine Greifswald, Greifswald, Germany; ¹⁹⁹Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, 12 South Drive, Room 4047, Bethesda, MD

(Affiliations continued on next page)

Ginevra Biino,²⁶⁷ Reinhold Schmidt,¹⁸⁶ Helena Schmidt,²⁶⁸ Stefania Bandinelli,²⁶⁹ George Dedoussis,¹⁸⁴ Thangavel Alphonse Thanaraj,¹⁸³ Patricia A. Peyser,⁵⁶ Norihiro Kato,¹⁶⁷ Matthias B. Schulze,^{181,182,270} Giorgia Giroto,^{180,271} Carsten A. Böger,^{179,272,273} Bettina Jung,^{179,272,273} Peter K. Joshi,¹⁵⁹ David A. Bennett,^{177,178} Philip L. De Jager,^{10,274} Xiangfeng Lu,¹⁰¹ Vasiliki Mamakou,^{275,276} Morris Brown,^{15,85} Mark J. Caulfield,^{4,85} Patricia B. Munroe,^{4,85} Xiuqing Guo,⁸¹ Marina Ciullo,^{174,175} Jost B. Jonas,^{172,277,278,279} Nilesh J. Samani,^{170,171} Jaakko Kaprio,³⁶ Päivi Pajukanta,²⁸⁰ Teresa Tusié-Luna,^{281,282} Carlos A. Aguilar-Salinas,^{283,311} Linda S. Adair,^{284,285} Sonny Augustin Bechayda,^{286,287} H. Janaka de Silva,²⁸⁸ Ananda R. Wickremasinghe,²⁸⁹ Ronald M. Krauss,²⁹⁰ Jer-Yuarn Wu,²⁹¹ Wei Zheng,¹⁶⁵ Anneke I. den Hollander,¹⁶⁴ Dwaipayan Bharadwaj,^{153,292} Adolfo Correa,²⁹³ James G. Wilson,²⁹⁴ Lars Lind,²⁹⁵ Chew-Kiat Heng,²⁹⁶ Amanda E. Nelson,^{160,297} Yvonne M. Golightly,^{58,160,298,299} James F. Wilson,^{137,159} Brenda Penninx,^{300,301} Hyung-Lae Kim,³⁰² John Attia,^{154,209} Rodney J. Scott,^{154,209} D.C. Rao,¹⁷⁶ Donna K. Arnett,³⁰³ Mark Walker,³⁰⁴ Laura J. Scott,¹³ Heikki A. Koistinen,^{37,305,306} Giriraj R. Chandak,^{152,153,307} Josep M. Mercader,^{308,309,310} Clicerio Gonzalez Villalpando,³¹² Lorena Orozco,³¹³ Myriam Fornage,^{148,314} E. Shyong Tai,^{78,315} Rob M. van Dam,^{78,315} Terho Lehtimäki,^{216,217} Nish Chaturvedi,³¹⁶ Mitsuhiro Yokota,³¹⁷ Jianjun Liu,¹⁴⁴ Dermot F. Reilly,³¹⁸ Amy Jayne McKnight,¹³⁹ Frank Kee,¹³⁹ Karl-Heinz Jöckel,¹³⁸ Mark I. McCarthy,^{60,208} Colin N.A. Palmer,³¹⁹ Veronique Vitart,¹³⁷ Caroline Hayward,¹³⁷ Eleanor Simonsick,³²⁰ Cornelia M. van Duijn,^{132,133} Zi-Bing Jin,^{173,321} Fan Lu,³²¹ Haretsugu Hishigaki,¹²⁹ Xu Lin,¹²⁸ Winfried März,^{126,322,323} Vilmundur Gudnason,^{125,324} Jean-Claude Tardif,¹²⁴ Guillaume Lettre,¹²⁴

(Author list continued on next page)

20892, USA; ²⁰⁰Oneomics. co. ltd. 2F, Soonchunhyang Mirai Medical Center 173, Buheuyng-ro, Bucheon-si Gyeonggi-do 14585, Korea; ²⁰¹Department of Clinical Biochemistry and Immunology, Hospital of Southern Jutland, Kresten Philipsens Vej 15, 6200 Aabenraa, Denmark; ²⁰²Department of Clinical Biochemistry, Lillebaelt Hospital, Kolding, Denmark; ²⁰³Department of Biomedical Science, Hallym University, Chuncheon, Gangwon 24252, Korea; ²⁰⁴Centre for Bone and Arthritis Research, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ²⁰⁵Bioinformatics Core Facility, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ²⁰⁶Institute of Medical Informatics and Statistics, Kiel University, Kiel, Germany; ²⁰⁷Institute of Translational Genomics, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany; ²⁰⁸Oxford Centre for Diabetes, Endocrinology, and Metabolism, University of Oxford, Oxford, UK; ²⁰⁹School of Medicine and Public Health, Faculty of Medicine and Health, University of Newcastle, Newcastle, NSW 2308, Australia; ²¹⁰Center for Geriatrics and Gerontology, Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; ²¹¹School of Medicine, National Yang-Ming University, Taipei, Taiwan; ²¹²School of Medicine, National Defense Medical Center, Taipei, Taiwan; ²¹³Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; ²¹⁴Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; ²¹⁵Department of Kinesiology, Université Laval, Quebec City, QC, Canada; ²¹⁶Department of Clinical Chemistry, Fimlab Laboratories, 33520 Tampere, Finland; ²¹⁷Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, 33014 Tampere, Finland; ²¹⁸Department of Cardiology, Heart Center, Tampere University Hospital, 33521 Tampere, Finland; ²¹⁹Department of Cardiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, 33014 Tampere, Finland; ²²⁰University of Queensland Diamantina Institute, Translational Research Institute, Kent St, Woolloongabba, Brisbane, QLD 4102, Australia; ²²¹Department of Medicine, Bornholms Hospital, Rønne, Denmark; ²²²School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA; ²²³Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ²²⁴Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH 44106, USA; ²²⁵Ohio State University, Division of Endocrinology, Columbus, OH 43210, USA; ²²⁶University of Washington, Department of Epidemiology, Seattle, WA 98195, USA; ²²⁷George Washington University, School of Medicine and Health Sciences, Washington, DC 20037, USA; ²²⁸Department of Epidemiology, School of Public Health, Peking University Health Science Center, Beijing, China; ²²⁹Institute for Laboratory Medicine, University Hospital Leipzig, Paul-List-Strasse 13/15, 04103 Leipzig, Germany; ²³⁰Laboratory of Epidemiology and Population Sciences, National Institute on Aging Intramural Research Program, NIH, Baltimore, MD 20892-9205, USA; ²³¹Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland; ²³²Department of Environmental and Preventive Medicine, Jichi Medical University School of Medicine, Shimotsuke 329-0498, Japan; ²³³Centre for Population Health Sciences, Usher Institute, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK; ²³⁴Department of Functional Pathology, Shimane University School of Medicine, Izumo 6938501, Japan; ²³⁵Department of Pediatrics and Adolescent Medicine, Turku University Hospital and University of Turku, Turku, Finland; ²³⁶Department of Physiology, University of Turku, Turku, Finland; ²³⁷Faculty of Medicine, University of Split, Šoltanska 2, 21000 Split, Croatia; ²³⁸Medical Department III – Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Liebigstr. 21, 04103 Leipzig, Germany; ²³⁹Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine, Suita 5650871, Japan; ²⁴⁰Department of Geriatric and General Medicine, Osaka University Graduate School of Medicine, Suita 5650871, Japan; ²⁴¹Department of Vascular Surgery, Division of Surgical Specialties, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ²⁴²Corneal Dystrophy Research Institute, Department of Ophthalmology, Yonsei University College of Medicine, Seoul 03722, Korea; ²⁴³Department of Radiology and Nuclear Medicine, Erasmus MC - University Medical Center Rotterdam, Rotterdam, the Netherlands; ²⁴⁴Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht 3584CG, the Netherlands; ²⁴⁵Second Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; ²⁴⁶Center for Vision Research, Department of Ophthalmology and The Westmead Institute, University of Sydney, Hawkesbury Rd, Sydney, NSW 2145, Australia; ²⁴⁷Menzies Institute for Medical Research, School of Medicine, University of Tasmania, Liverpool St, Hobart, TAS 7000, Australia; ²⁴⁸Centre for Eye Research Australia, University of Melbourne, Melbourne, VIC 3002, Australia; ²⁴⁹Department of Clinical Physiology, Tampere University Hospital, 33521 Tampere, Finland; ²⁵⁰Department of Clinical Physiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, 33014 Tampere, Finland; ²⁵¹Centre Nutrition, santé et société (NUTRISS), Institute of Nutrition and Functional Foods (INAF), Quebec, QC, Canada; ²⁵²Pennington Biomedical Research Center, Baton Rouge, LA 70808, USA; ²⁵³Discipline of Internal Medicine, Medical School, The University of Western Australia, Perth, WA, Australia; ²⁵⁴Institute of Epidemiology, Kiel University, Kiel, Germany; ²⁵⁵Institute of Clinical Molecular Biology, Kiel University, Kiel, Germany; ²⁵⁶Sahlgrenska University Hospital, Department of Drug Treatment, Gothenburg, Sweden; ²⁵⁷Geriatric Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ²⁵⁸Department

(Affiliations continued on next page)

Leen M. t Hart,^{122,123,325} Petra J.M. Elders,³²⁶ Daniel J. Rader,^{327,407} Scott M. Damrauer,^{121,328} Meena Kumari,³²⁹ Mika Kivimaki,¹²⁰ Pim van der Harst,¹¹⁸ Tim D. Spector,¹¹⁶ Ruth J.F. Loos,^{86,115,330} Michael A. Province,¹⁰⁸ Esteban J. Parra,¹¹³ Miguel Cruz,³³¹ Bruce M. Psaty,^{112,226,332} Ivan Brandslund,^{111,333} Peter P. Pramstaller,¹¹⁰ Charles N. Rotimi,³³⁴ Kaare Christensen,³³⁵ Samuli Ripatti,^{36,336,337} Elisabeth Widén,³⁶ Hakon Hakonarson,^{338,339} Struan F.A. Grant,^{327,339,340} Lambertus Kiemeny,¹⁰⁶ Jacqueline de Graaf,¹⁰⁶ Markus Loeffler,^{104,105} Florian Kronenberg,¹⁰³ Dongfeng Gu,^{101,341} Jeanette Erdmann,⁹⁸ Heribert Schunkert,^{99,100} Paul W. Franks,¹⁰² Allan Linneberg,^{79,80} J. Wouter Jukema,^{96,342} Amit V. Khera,^{10,343,345,346} Minna Männikkö,³⁴⁶ Marjo-Riitta Jarvelin,^{62,347,348} Zoltan Kutalik,^{93,94} Cucca Francesco,^{349,350} Dennis O. Mook-Kanamori,^{351,352} Ko Willems van Dijk,^{353,354,355} Hugh Watkins,^{87,88} David P. Strachan,³⁵⁶ Niels Grarup,⁸⁶ Peter Sever,³⁵⁷ Neil Poulter,³⁵⁸ Wayne Huey-Herng Sheu,^{359,360} Jerome I. Rotter,⁸¹ Thomas M. Dantoft,⁷⁹ Fredrik Karpe,^{361,362} Matt J. Neville,^{361,362} Nicholas J. Timpson,^{33,77} Ching-Yu Cheng,^{363,364} Tien-Yin Wong,^{363,364} Chiea Chuen Khor,¹⁴⁴ Hengtong Li,³⁶⁵ Charumathi Sabanayagam,^{363,364} Annette Peters,^{75,100,366} Christian Gieger,^{74,75,366} Andrew T. Hattersley,³⁶⁷ Nancy L. Pedersen,³⁶⁸ Patrik K.E. Magnusson,³⁶⁸ Dorret I. Boomsma,^{70,301} Eco J.C. de Geus,^{70,301} L. Adrienne Cupples,^{5,369} Joyce B.J. van Meurs,^{69,133}

(Author list continued on next page)

of Internal Medicine, EwhaWomans University School of Medicine, Seoul, Korea; ²⁵⁹Division of Cancer Control and Population Sciences, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA 15232, USA; ²⁶⁰Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117545, Singapore; ²⁶¹Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore 117609, Singapore; ²⁶²Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul 02447, Korea; ²⁶³Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany; ²⁶⁴Algebra University College, Ilica 242, Zagreb, Croatia; ²⁶⁵Paavo Nurmi Centre, Sports and Exercise Medicine Unit, Department of Physical Activity and Health, University of Turku, Turku, Finland; ²⁶⁶Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University of Groningen, University Medical Center Groningen, Groningen 9700 RB, the Netherlands; ²⁶⁷Institute of Molecular Genetics, National Research Council of Italy, Pavia, Italy; ²⁶⁸Gottfried Schatz Research Center for Cell Signaling, Metabolism and Aging, Medical University of Graz, Graz, Austria; ²⁶⁹Local Health Unit Toscana Centro, Firenze, Italy; ²⁷⁰Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany; ²⁷¹Department of Medicine, Surgery and Health Sciences, University of Trieste, Strada di Fiume 447, 34149 Trieste, Italy; ²⁷²Department of Nephrology, Diabetology, Rheumatology, Traunstein Hospital, Traunstein, Germany; ²⁷³KfH Kidney Center Traunstein, Traunstein, Germany; ²⁷⁴Center for Translational and Systems Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, NY, USA; ²⁷⁵Medical School, National and Kapodistrian University Athens, 75 M. Assias Street, 115 27 Athens, Greece; ²⁷⁶Dromokaiteio Psychiatric Hospital, 124 61 Athens, Greece; ²⁷⁷Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Kutzerufer 1, Mannheim 68167, Germany; ²⁷⁸Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland; ²⁷⁹Privatpraxis Prof Jonas und Dr Panda-Jonas, Heidelberg, Germany; ²⁸⁰Department of Human Genetics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA, USA; ²⁸¹Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City 14080, Mexico; ²⁸²Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico; ²⁸³Departamento de Endocrinología y Metabolismo, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City 14080, Mexico; ²⁸⁴Department of Nutrition, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599, USA; ²⁸⁵Carolina Population Center, University of North Carolina, Chapel Hill, NC 27516, USA; ²⁸⁶USC–Office of Population Studies Foundation, University of San Carlos, Cebu City 6000, Philippines; ²⁸⁷Department of Anthropology, Sociology, and History, University of San Carlos, Cebu City 6000, Philippines; ²⁸⁸Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama 11010, Sri Lanka; ²⁸⁹Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama 11010, Sri Lanka; ²⁹⁰Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA; ²⁹¹Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan; ²⁹²Systems Genomics Laboratory, School of Biotechnology, Jawaharlal Nehru University, New Delhi 110067, India; ²⁹³Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA; ²⁹⁴Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS 39216, USA; ²⁹⁵Department of Medical Sciences, Uppsala University, Uppsala, Sweden; ²⁹⁶Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore; and Khoo Teck Puat - National University Children's Medical Institute, National University Health System, Singapore, Singapore; ²⁹⁷Department of Medicine, University of North Carolina, Chapel Hill, NC, USA; ²⁹⁸Injury Prevention Research Center, University of North Carolina, Chapel Hill, NC, USA; ²⁹⁹Division of Physical Therapy, University of North Carolina, Chapel Hill, NC, USA; ³⁰⁰Department of Psychiatry, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; ³⁰¹Amsterdam Public Health Research Institute, VU Medical Center Amsterdam, Amsterdam, the Netherlands; ³⁰²Department of Biochemistry, College of Medicine, Ewha Womans University, Seoul 07804, Korea; ³⁰³University of Kentucky, College of Public Health, Lexington, KY, USA; ³⁰⁴Institute of Cellular Medicine (Diabetes), The Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK; ³⁰⁵University of Helsinki and Department of Medicine, Helsinki University Hospital, P.O.Box 340, Haartmaninkatu 4, 00029 Helsinki, Finland; ³⁰⁶Minerva Foundation Institute for Medical Research, Biomedicum 2U, Tukholmankatu 8, 00290 Helsinki, Finland; ³⁰⁷JSS Academy of Higher Education and Research, Mysuru, India; ³⁰⁸Programs in Metabolism and Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA; ³⁰⁹Diabetes Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA; ³¹⁰Harvard Medical School, Boston, MA 02115, USA; ³¹¹Dirección de Nutrición and Unidad de Estudios de Enfermedades Metabólicas, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; ³¹²Instituto Nacional de Salud Pública y Centro de Estudios en Diabetes, Cuernavaca, Morelos, Mexico; ³¹³Instituto Nacional de Medicina Genómica, Mexico City, Mexico; ³¹⁴Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX 77030, USA; ³¹⁵Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore 119228, Singapore; ³¹⁶MRC Unit for Lifelong Health and Ageing at UCL, 1-19 Torrington Place, WC1E 7HB London, UK; ³¹⁷Kurume University School of Medicine, Kurume 830-0011, Japan; ³¹⁸Genetics, Merck Sharp & Dohme Corp, Kenilworth, NJ 07033, USA; ³¹⁹Division of Population Health and Genomics, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; ³²⁰Intramural Research Program, National Institute on Aging, 3001 S. Hanover St., Baltimore, MD 21225, USA; ³²¹The Eye Hospital, School of Ophthalmology & Optometry, Wenzhou Medical University, Wenzhou, Zhejiang 325027, China; ³²²Synlab Academy, SYNLAB Holding Deutschland GmbH, Mannheim and Augsburg, Germany; ³²³Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria; ³²⁴Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland; ³²⁵Leiden University Medical Center, Department of Biomedical Data Sciences, Section Molecular Epidemiology, 2333ZA Leiden, the Netherlands; ³²⁶Amsterdam UMC, Department of General Practice and

(Affiliations continued on next page)

Arfan Ikram,¹³³ Mohsen Ghanbari,^{133,370} Penny Gordon-Larsen,^{284,285} Wei Huang,³⁷¹ Young Jin Kim,²³ Yasuharu Tabara,⁶⁸ Nicholas J. Wareham,⁶⁶ Claudia Langenberg,⁶⁶ Eleftheria Zeggini,^{45,207,372} Jaakko Tuomilehto,^{37,336,373} Johanna Kuusisto,³⁷⁴ Markku Laakso,³⁷⁴ Erik Ingelsson,^{7,65,375,376} Goncalo Abecasis,^{13,377} John C. Chambers,^{62,63,64,378} Jaspal S. Kooner,^{63,64,357,379} Paul S. de Vries,⁶¹ Alanna C. Morrison,⁶¹ Scott Hazelhurst,^{59,380} Michèle Ramsay,⁵⁹ Kari E. North,⁵⁸ Martha Daviglus,³⁸¹ Peter Kraft,^{57,382} Nicholas G. Martin,³⁸³ John B. Whitfield,³⁸³ Shahid Abbas,⁵³ Danish Saleheen,^{53,384,385} Robin G. Walters,^{51,52,386} Michael V. Holmes,^{51,52,362} Corri Black,³⁸⁷ Blair H. Smith,³¹⁹ Aris Baras,³⁷⁷ Anne E. Justice,³⁸⁸ Julie E. Buring,^{48,310} Paul M. Ridker,^{48,310} Daniel I. Chasman,^{48,310} Charles Kooperberg,⁴⁷ Gen Tamiya,⁴⁴ Masayuki Yamamoto,⁴⁴ David A. van Heel,⁴⁶ Richard C. Trembath,³⁸⁹ Wei-Qi Wei,³⁹⁰ Gail P. Jarvik,³⁹¹ Bahram Namjou,³⁹² M. Geoffrey Hayes,^{39,393,394} Marylyn D. Ritchie,³⁸ Pekka Jousilahti,³⁷ Veikko Salomaa,³⁷ Kristian Hveem,^{32,395,396} Bjørn Olav Åsvold,^{32,395,397} Michiaki Kubo,³⁹⁸ Yoichiro Kamatani,^{24,399} Yukinori Okada,^{24,26,400,401} Yoshinori Murakami,⁴⁰² Bong-Jo Kim,⁴⁰³ Unnur Thorsteinsdottir,^{20,324} Kari Stefansson,^{20,324} Jifeng Zhang,³ Y. Eugene Chen,³ Yuk-Lam Ho,⁴⁰⁴ Julie A. Lynch,^{405,406} Philip S. Tsao,^{6,7,408} Kyong-Mi Chang,^{328,407} Kelly Cho,^{404,409} Christopher J. O'Donnell,^{404,409} John M. Gaziano,^{404,409} Peter Wilson,^{17,410} Karen L. Mohlke,¹⁶⁸

(Author list continued on next page)

Elderly Care, Amsterdam Public Health Research Institute, 1081HV Amsterdam, the Netherlands; ³²⁷Department of Genetics, University of Pennsylvania, Philadelphia, PA 19104, USA; ³²⁸Corporal Michael Crescenz VA Medical Center, Philadelphia, PA 19104, USA; ³²⁹Institute of Social and Economic Research, University of Essex, Wivenhoe Park CO4 3SQ, UK; ³³⁰Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ³³¹Unidad de Investigacion Medica en Bioquimica, Hospital de Especialidades, Centro Medico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico; ³³²Department of Health Services, University of Washington, Seattle, WA, USA; ³³³Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark; ³³⁴16Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, 12 South Drive, Room 4047, Bethesda, MD 20892, USA; ³³⁵Danish Aging Research Center, University of Southern Denmark, Odense C, Denmark; ³³⁶Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland; ³³⁷Broad Institute of MIT and Harvard, Cambridge, MA, USA; ³³⁸Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; ³³⁹Department of Pediatrics, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA; ³⁴⁰Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; ³⁴¹School of Medicine, Southern University of Science and Technology, Shenzhen, China; ³⁴²Netherlands Heart Institute, Utrecht, the Netherlands; ³⁴³Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ³⁴⁴Center for Genomic Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; ³⁴⁵Department of Medicine, Harvard Medical School, Boston, MA, USA; ³⁴⁶Northern Finland Birth Cohorts, Infrastructure for population studies, Faculty of Medicine, University of Oulu, Oulu, Finland; ³⁴⁷Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland; ³⁴⁸Bio-center of Oulu, University of Oulu, Oulu, Finland; ³⁴⁹Institute for Genetic and Biomedical Research, Italian National Council of Research (IRGB CNR), Cagliari, Italy; ³⁵⁰University of Sassari, Sassari, Italy; ³⁵¹Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands; ³⁵²Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands; ³⁵³Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, the Netherlands; ³⁵⁴Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands; ³⁵⁵Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands; ³⁵⁶Population Health Research Institute, St George's, University of London, SW17 0RE London, UK; ³⁵⁷National Heart and Lung Institute, Imperial College London, W2 1PG London, UK; ³⁵⁸School of Public Health, Imperial College London, W12 7RH London, UK; ³⁵⁹Tai-chung Veterans General Hospital, Taichung, Taiwan; No. 1650, Sec. 4, Taiwan Boulevard, Xitun District Taichung City 40705, Taiwan; ³⁶⁰Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; No. 201, Sec. 2, Shipai Road, Beitou District, Taipei City 112201, Taiwan; ³⁶¹OCDDEM, University of Oxford, Churchill Hospital, OX3 7LE Oxford, UK; ³⁶²NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK; ³⁶³Ocular Epidemiology, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore 168751, Singapore; ³⁶⁴Ophthalmology & Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore 169857, Singapore; ³⁶⁵Data Science, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore 168751, Singapore; ³⁶⁶German Center for Diabetes Research (DZD), Neuherberg, Germany; ³⁶⁷University of Exeter Medical School, University of Exeter, EX2 5DW Exeter, UK; ³⁶⁸Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ³⁶⁹Framingham Heart Study, National Heart, Lung, and Blood Institute, US National Institutes of Health, Bethesda, MD, USA; ³⁷⁰Department of Genetics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; ³⁷¹Department of Genetics, Shanghai-MOST Key Laboratory of Health and Disease Genomics, Chinese National Human Genome Center at Shanghai, Shanghai 201203, China; ³⁷²Technical University of Munich (TUM) and Klinikum Rechts der Isar, TUM School of Medicine, Munich, Germany; ³⁷³Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia; ³⁷⁴Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; ³⁷⁵Stanford Cardiovascular Institute, Stanford University, Stanford, CA 94305, USA; ³⁷⁶Stanford Diabetes Research Center, Stanford University, Stanford, CA 94305, USA; ³⁷⁷Regeneron Pharmaceuticals, Tarrytown, NY, USA; ³⁷⁸Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232, Singapore; ³⁷⁹MRC-PHE Centre for Environment and Health, Imperial College London, London W2 1PG, UK; ³⁸⁰School of Electrical & Information Engineering, University of the Witwatersrand, Witwatersrand, South Africa; ³⁸¹Institute for Minority Health Research, University of Illinois College of Medicine, Chicago, IL, USA; ³⁸²Department of Biostatistics, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; ³⁸³QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, QLD 4006, Australia; ³⁸⁴Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA; ³⁸⁵Department of Cardiology, Columbia University Irving Medical Center, New York, NY, USA; ³⁸⁶Big Data Institute, University of Oxford, OX3 7LF Oxford, UK; ³⁸⁷Aberdeen Centre for Health Data Science, 1:042 Polwarth Building School of Medicine, Medical Science and Nutrition University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK; ³⁸⁸Biomedical and Translational Informatics, Geisinger Health, Danville, PA 17822, USA; ³⁸⁹School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK; ³⁹⁰Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA; ³⁹¹Departments of Medicine (Medical Genetics) and Genome Sciences, University of Washington, Seattle, WA, USA; ³⁹²Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH, USA; ³⁹³Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, USA; ³⁹⁴Department of Anthropology, Northwestern University, Evanston, IL 60208, USA; ³⁹⁵HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger 7600, Norway; ³⁹⁶Department of Medicine, Levanger

(Affiliations continued on next page)

Timothy M. Frayling,⁷² Joel N. Hirschhorn,^{9,10,411} Sekar Kathiresan,^{10,344,345} Michael Boehnke,¹³ Million Veterans Program, Global Lipids Genetics Consortium, Struan Grant,^{1,340} Pradeep Natarajan,^{10,343,412,413} Yan V. Sun,^{16,17} Andrew P. Morris,⁴¹⁴ Panos Deloukas,^{4,415} Gina Peloso,⁵ Themistocles L. Assimes,^{6,7,408} Cristen J. Willer,^{3,14,416} Xiang Zhu,^{6,417,418,419,*} and Christopher D. Brown^{1,*}

Linking trait-associated variants to genome function has emerged as a promising model for mechanistic interpretation of noncoding findings in GWAS. This “variant-to-function” model is premised on recent observations that noncoding variants often affect a trait of interest through the regulation of genes and processes in trait-relevant cell types or tissues.^{2,6} Implementing this functional model in GWASs has become more feasible as large-scale functional genomic resources, such as epigenomic⁷ and transcriptomic⁸ catalogs, have been systematically generated across a wide range of human cell types and tissues. The integration of functional genomics with GWASs has identified regulatory mechanisms in variants associated with some flagship disorders such as obesity⁹ and schizophrenia,¹⁰ yielding important functional insights into the genetic architecture of human complex traits.

The history of the human genetics of lipids mirrors the successes and challenges of GWASs. Increasing sample size and genetic diversity has significantly boosted the power of discovery: the first lipid GWAS in 2008 with 8,816 European-descent individuals identified 29 lipid-associated loci;¹¹ the latest study of 1.6 million individuals across five ancestries¹² found 941. Despite the dramatic increase in the number of associations, our biological understanding of many of these genetic discoveries remains limited. The causal gene has been confidently assigned at only a small fraction of these loci,² and the regulatory mechanism connecting variant to phenotype has been conclusively characterized for only a handful of genes.⁵ Furthermore, systematic mapping of lipid-associated variants to their biological functions has been missing in the literature at the time of this study.

Here we conduct a genome-scale integrative analysis on the largest published GWAS to date of five lipid phenotypes (LDL, or low-density lipoprotein; HDL, or high-den-

sity lipoprotein; TC, or total cholesterol; nonHDL, or non-high density lipoprotein; and TG, or triglycerides)¹² involving 1.65 million individuals from five ancestries.¹² Combining the lipid GWAS with a wide array of functional genomic resources in diverse human tissues and cell types, we identify regulatory mechanisms of noncoding genetic variation in lipids with a full suite of computational approaches. Further, we develop a generalizable framework to understand how tissue-specific gene regulation can explain GWAS findings and we demonstrate its real-world value on lipid-associated loci.

Material and methods

GWAS

We used the recently published GWAS data from the Global Lipids Genetics Consortium (GLGC) for five blood lipid traits (LDL, HDL, TC, TG, and nonHDL) in 1.65 million individuals from five ancestry groups¹² (African and African-admixed, East Asian, European, Hispanic, South Asian) at 91 million variants imputed primarily from the Haplotype Reference Consortium¹³ or 1,000 Genomes Phase 3.¹⁴ GWASs of individual cohorts were based on the hg19 version of the human reference genome. MR-MEGA¹⁵ was used for meta-analysis across cohorts.

We defined “sentinel variants” as the most significant variant at independent trait-associated loci in the genome. The windows are the greater of 500 kb or 0.25 cM around the sentinel variant; genetic distances were defined using reference maps from HapMap 3.¹⁶ We performed a second round of conditional analysis, conditioning on the sentinel variants to identify and remove any significant windows that are shadow signals of (or dependent on) a neighboring locus to enforce independence of associated loci.

For each sentinel variant, we defined credible sets of potentially causal variants within ± 500 kb region around the sentinel variant representing the set of variants harboring the causal variant with

Hospital, Nord-Trøndelag Hospital Trust, Levanger 7600, Norway; ³⁹⁷Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; ³⁹⁸RIKEN Center for Integrative Medical Sciences, Yokohama, Japan; ³⁹⁹Laboratory of Complex Trait Genomics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan; ⁴⁰⁰Laboratory of Statistical Immunology, WPI Immunology Frontier Research Center, Osaka University, Osaka, Japan; ⁴⁰¹Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Osaka, Japan; ⁴⁰²Division of Molecular Pathology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan; ⁴⁰³Division of Genome Research, Center for Genome Science, National Institute of Health, Chungcheongbuk-do, South Korea; ⁴⁰⁴VA Boston Healthcare System, Boston, MA, USA; ⁴⁰⁵VA Informatics and Computing Infrastructure, VA Salt Lake City Health Care System, Salt Lake City, UT, USA; ⁴⁰⁶University of Massachusetts, Boston, MA, USA; ⁴⁰⁷Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; ⁴⁰⁸Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA, USA; ⁴⁰⁹Department of Medicine, Brigham Women's Hospital, Boston, MA, USA; ⁴¹⁰Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA; ⁴¹¹Departments of Pediatrics and Genetics, Harvard Medical School, Boston, MA, USA; ⁴¹²Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ⁴¹³Cardiovascular Research Center and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA; ⁴¹⁴Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK; ⁴¹⁵Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia; ⁴¹⁶Department of Human Genetics, University of Michigan, Ann Arbor, MI 48109, USA; ⁴¹⁷Department of Statistics, The Pennsylvania State University, University Park, PA, USA; ⁴¹⁸Huck Institutes of the Life Sciences, The Pennsylvania State University, University Park, PA, USA; ⁴¹⁹Department of Statistics, Stanford University, Stanford, CA, USA

⁴²⁰These authors contributed equally

*Correspondence: xiangzhu@psu.edu (X.Z.), chrbro@upenn.edu (C.D.B.)
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a 95% posterior probability. Full details of the credible set construction are reported in our recent GWAS publication.¹² The credible sets are freely available ([web resources](#)).

Colocalization of GWAS associations with eQTLs

We performed statistical colocalization of lipid GWASs with eQTLs obtained from GTEx v8 across 49 tissues.⁸ For each of the five lipid traits, we used the same sentinel variants defined in the previous section to represent approximately independent GWAS-associated windows (also removing shadow signals as described before). For each such window, we ran eQTL colocalization with GTEx v8 single-tissue *cis*-eQTL summary statistics.⁸ For each of 49 GTEx tissues, we first identified all genes within 1 Mb of the sentinel SNP, and then restricted analysis to those genes with significant eQTLs (i.e., eGenes as defined by GTEx) in that tissue (FDR < 0.05). We used the R package *coloc* (R v.3.4.3, *coloc* v.3.2.1)¹⁷ with default parameters to run colocalization between the GWAS signal and the eQTL signal for each of these *cis*-eGenes, using as input those SNPs in the defined window (greater than 500 kb or 0.25 cM on either side of the lead variant) that are present in both datasets. Because eQTL summary statistics were in GRCh38, we lifted over the GWAS summary statistics from hg19 to GRCh38 using *liftOver*.¹⁸ As in previous studies,¹⁹ we used a colocalization posterior probability of (PP3+PP4) > 0.8 to identify loci with enough colocalization power, and PP4/PP3 > 0.9 to define those loci that show significant colocalization, where PP4 represents posterior probability of a single shared signal, and PP3 represents posterior probability of two unique signals in the GWAS and eQTL datasets.

Overlap with promoter Capture-C data

We used four promoter-focused Capture-C (henceforth Capture-C) datasets from three human cell types ([web resources](#)) to capture physical interactions between gene promoters and their regulatory elements. The four Capture-C datasets are (1) three biological replicates of HepG2 liver carcinoma cells (HepG2.1),²⁰ (2) another HepG2 dataset described in Selvarajan et al. (HepG2.2),²¹ (3) hepatocyte-like cells (HLC) produced by differentiating three biological replicates of iPSCs (which in turn were generated from peripheral blood mononuclear cells using a previously published protocol²²), and (4) an adipose dataset obtained from Pan et al.²³ that was produced using primary human white adipocytes. Across the four datasets, the number of significant interactions on the same chromosome ranges from 67,819 (adipose) to 126,565 (HLC). The bait end has a median size of 2,141 (HepG2.1) to 6,567 (HepG2.2) bases. The interacting end has a median size of 2,100 (HepG2.1) to 3,243 base pairs (HepG2.2) for all datasets. The median distance between the bait and interacting ends for all interactions on the same chromosome ranges from 71,722 (HLC) to 285,140 base pairs (adipose).

The detailed protocol to prepare HepG2 or HLC cells for the Capture-C experiment is described in Chesi et al.²⁰ Briefly, for each dataset, 10 million cells were used for promoter Capture-C library generation. Custom capture baits were designed using an Agilent SureSelect library design targeting both ends of DpnII restriction fragments encompassing promoters (including alternative promoters) of all human coding genes, noncoding RNA, antisense RNA, snRNA, miRNA, snoRNA, and lincRNA transcripts, totalling 36,691 RNA baited fragments. Each library was then sequenced on an Illumina HiSeq 4,000 (HepG2) or Illumina NovoSeq (HLC), generating 1.6 billion read pairs per sample (50

base pair read length). We used HiCUP v0.7.2²⁴ to process the raw FASTQ files into loop calls and CHiCAGO v1.6.0²⁵ to define significant looping interactions; we defined a CHiCAGO score of 5 as significant, as specified in the default parameters.

Starting with Capture-C maps processed as described above, we re-annotated the baits to gene IDs from Gencode v.19²⁶ to ensure uniformity of gene annotations with the rest of our pipeline. For each bait, we identified any gene whose transcription start site (TSS) from any transcript in Gencode v.19 was within 175 base pair distance from the bait (to account for differing bait designs for external datasets which may not directly overlap the canonical TSS). We filtered all datasets to only include interactions in which the interacting end was not another bait. Enrichment with colocalized genes was robust to our choice of distance between bait and gene (enrichment with eQTL colocalized genes ranging from 2.94 to 2.96 for bait distances from 0 to 350 base pairs).

To identify genetic variants associated with any of the five lipid traits that physically interact with locations in the genome, we used the R package *Genomic Ranges* v.1.30.3²⁷ to find overlap between credible sets for each trait's GWAS and the previously annotated promoter Capture-C data. Given the bait end of a gene, we defined a GWAS locus as interacting with this gene if a variant in the credible set for this GWAS locus fell inside the interacting end.

Presence of gene-variant pairs in same topologically associated domains

To assess the frequency of colocalized gene-sentinel variant pairs in the same topologically associated domain (TAD), we used a list of 2,499 publicly available TADs from human liver²⁸ ([web resources](#)). We computed as a fraction the number of colocalizations with the sentinel variant and colocalized gene in the same TAD divided by all colocalizations in which the sentinel variant lies in a TAD. To test whether this fraction was statistically significant, we generated random TAD boundaries (using *bedtools shuffle*) 1,000 times and calculated the same fraction for these randomly generated TAD boundaries.

Pathway enrichment

We used *ClusterProfiler* v3.6.0²⁹ to look for pathways over-represented in each gene list: genes with eQTL colocalization and genes interacting with variants in GWAS credible sets. We used the *enrichKEGG* function to look for enriched pathways in the latest version of the KEGG database.³⁰ We first re-mapped Gencode IDs to gene symbols using the Gencode v.24 annotation and then used the *biomaRt* R package v2.34.2³¹ to convert gene symbols to Entrez IDs. We ran *enrichKEGG* to identify enriched pathways that were significant at a Benjamini-Hochberg threshold of 0.05.

Enrichment in known lipid-associated genes

We calculated enrichment odds ratio of genes identified in our analysis with four known sets of lipid-associated genes using the Fisher exact test (R function *fisher.test*). First, we identified 33 Mendelian genes from ClinVar³² with lipidemia-associated ICD10 codes (E78). Second, we used 35 genes with rare-coding variants associated with lipid levels.³³ Third, we extracted 1,115 genes associated with "cholesterol" or "lipidemia" phenotypes in mouse knockouts from the Mouse Genome Informatics (MGI) database.³⁴ Fourth, we identified 4,008 genes from a transcriptome-wide association study (TWAS) on the same GWAS and GTEx v8 summary

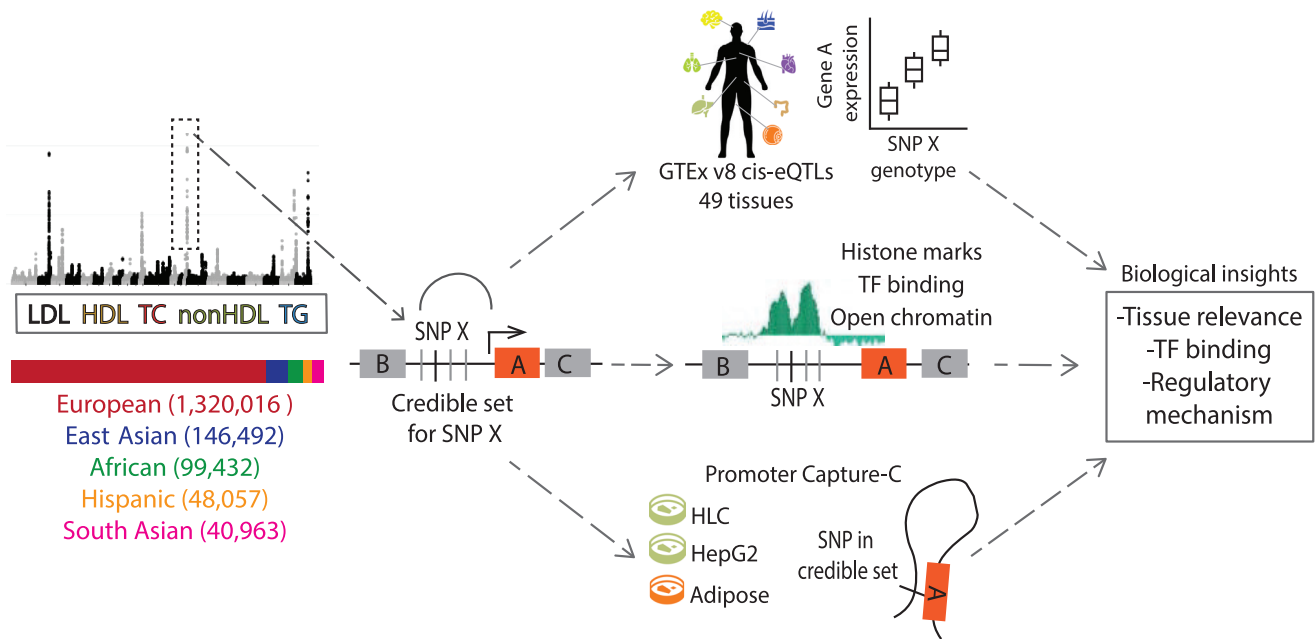


Figure 1. Schematic overview of the multi-layer functional genomic analysis

We integrate GWAS summary statistics for five lipid phenotypes with eQTL and chromatin interaction data to identify potential genes mediating the GWAS loci, and use epigenomic annotations to identify regulatory mechanisms at these loci. For a GWAS locus indexed by a lead variant X, A, B, and C represent nearby eGenes across tissues, and SNPs around SNP X represent variants in the credible set for this locus.

statistics using the S-PrediXcan software³⁵ default setup. The TWAS method accounts for allelic heterogeneity and thus complements the eQTL colocalization approach that assumes one causal variant per locus.

TF binding sites

We extracted TF binding sites from ChIP-seq data of 161 TFs in 91 cell types from the ENCODE project⁷ ([web resources](#)). We included all cell types in our primary analysis because TFs were not comprehensively assayed in most cell lines. We also performed a secondary analysis using TF binding sites from HepG2 only. All TF binding sites were aligned to the hg19 version of human reference genome (https://www.encodeproject.org/chip-seq/transcription_factor/).

Stratified LD score (S-LDSC) regression analysis

We used LDSC version 1.0.1³⁶ to estimate the enrichment of heritability explained using GWAS summary statistics in different epigenetic and transcriptomic annotations, including gene expression, chromatin marks, and TF binding sites. The gene expression and chromatin mark annotations across 205 datasets from more than 170 tissues and cell types and the corresponding LD scores were provided as Multitissuegeneexpr1000Gv3 and Multitissuechromatin1000Gv3 databases in LDSC software ([web resources](#)). The LD scores for binding sites of each TF were estimated from 1,000 Genomes Phase 3 European samples using `ldsc.py -l2`. We first converted the summary statistics for each phenotype to LDSC-formatted summary statistics using `munge_sumstats.py`. Second, we ran `ldsc.py` using the `baseline_v1.2` model on each annotation to estimate enrichment of heritability. For primary analyses, we used multi-ancestry GWAS summary statistics and LD scores estimated from 1,000 Genomes Phase 3 European samples. For secondary analyses on East Asian

(EAS) GWAS alone, we obtained EAS-specific LD scores for the same functional annotations.³⁷

Genomic regulatory elements and GWAS overlap algorithm (GREGOR) analysis

We used GREGOR³⁸ to estimate enrichment of sentinel variants for each lipid phenotype in TF binding sites for 161 TFs from ENCODE compared to a null distribution of variants matched for allele frequency. We ran GREGOR with default parameters, specifying 0.8 as the R^2 threshold, window size of 1 Mb, and 'EUR' as the population. Annotations with enrichment >2 and FDR-adjusted p value < 0.05 were considered significant.

Enrichment in single-cell expression data

We overlapped our list of colocalized genes with publicly available single-cell RNA-sequencing data of 8,444 cells from liver³⁹ and 38,408 cells from adipose ([web resources](#)) in humans. For both datasets, we downloaded normalized TPM data and existing tSNE cluster annotations for each cell. For each cluster, we defined median expression for each gene across all cells in that cluster. Then for each cluster, we quantified the overrepresentation of our gene list in ranked genes for this cluster via an enrichment p value computed by the `fgsea`⁴⁰ R package v.1.4.1 implemented in R 3.4.3.

Results

We systematically integrated lipid GWAS results¹² with multiple layers of functional genomic data from diverse tissues and cell types to understand regulatory mechanisms at lipid-associated loci ([Figure 1](#)). Specifically, we overlaid GWAS loci with eQTL and chromatin-chromatin

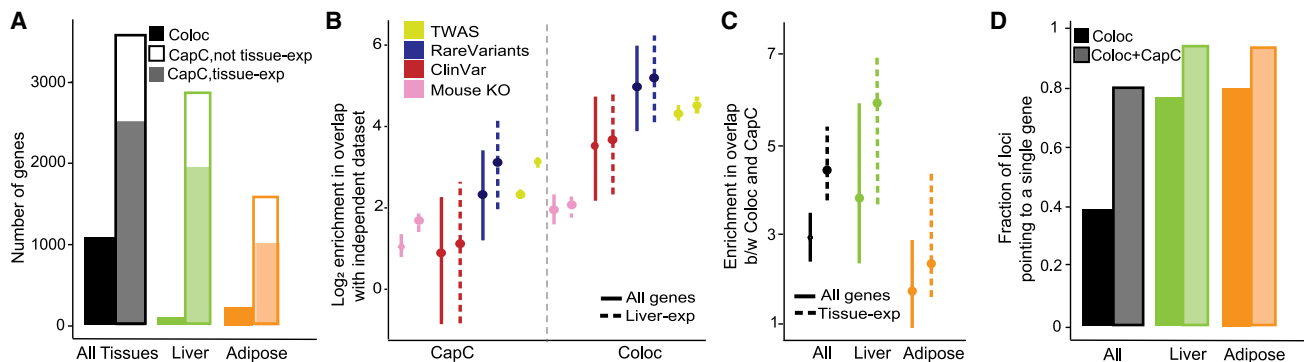


Figure 2. Overlap between eQTL colocalized genes and Capture-C prioritized genes, and their enrichments in known lipid-associated genes

(A) Numbers of genes identified by two approaches: eQTL colocalization (Coloc) and promoter Capture-C interaction (CapC). Capture-C interactions restricted to genes expressed in the tissue of interest (or in the union of adipose and liver for “all tissues”) are shaded.

(B) Overlap between two list of prioritized genes (left: Capture-C prioritized genes; right: eQTL colocalized genes) with four external sets of genes previously associated with lipid biology (MGI knockout genes, ClinVar lipidemia-associated genes, genes implicated in rare burden of lipids, and genes from a lipid TWAS). Dashed lines represent enrichments using only genes expressed in the liver.

(C) Enrichment in overlap between eQTL colocalized genes and Capture-C prioritized genes against what is expected by chance, assuming both gene sets are independent.

Dashed lines represent genes expressed in the tissue of interest (or in the union of adipose or liver for “all”). Enrichment estimates and 95% confidence intervals shown in (B) and (C) are based on the Fisher exact test.

(D) Fraction of colocalized loci that point to a single candidate gene when using eQTL data alone or using both eQTL and Capture-C data.

interactions to identify causal genes. We assessed polygenic enrichments of tissue-specific histone marks to prioritize relevant tissues and examined GWAS loci at transcription factor (TF) binding sites to detect lipid-relevant TFs. Finally, we combined all these layers to prioritize functional variants at GWAS loci, providing a holistic view of gene regulation at lipid loci in relevant tissue and cell types.

Colocalization with eQTLs identifies candidate lipid-relevant genes

First, we identified shared association signals between lipid levels and expression of nearby genes, since most GWAS signals are presumed to influence complex traits through impact on gene expression.⁴¹ To do so, we tested for colocalization of each significant lipid GWAS signal with significant *cis*-eQTL data across 49 human tissues from the GTEx consortium.⁸ The significant GWAS signals were 1,750 loci reaching genome-wide significance and corrected for shadow signals in our multi-ancestry meta-analysis for at least one of five lipid traits. Credible set sizes ranged from 1 to 417 variants at the 1,750 examined loci, with a median size of 5 variants per credible set.

Second, we restricted our analysis to loci most likely mediated through regulatory mechanisms as opposed to coding variation. Specifically, we excluded all loci with credible sets containing at least one missense variant (369 of 1,750 loci, 21% of credible sets). Of the remaining 1,381 GWAS loci, 696 significantly colocalized with eQTLs (the ratio of posterior probability of a shared signal to the posterior probability of two signals being $>0.9^{19}$) in at least one of 49 tissues for at least one lipid phenotype. This resulted in 1,076 colocalized eGenes ranging from 1 to 16

genes per locus (Figure 2A and Table S1). Since with eQTL data alone it is difficult to disentangle a single functional gene from multiple functional (and likely coregulated) genes at a locus,⁴² we performed all downstream analyses with all 1,076 colocalized genes, to further prioritize functional genes at loci with multiple eGenes.

Since lipid-associated genetic variants are often enriched in the liver and adipose,^{43,44} we repeated the colocalization analysis on eQTLs only from liver or adipose. Compared to the 1,076 colocalized eGenes identified from all 49 tissues, the liver- and adipose-only analysis identified 119 and 225, respectively (Figure 2A). The reduced discovery of colocalized eGenes in the liver- and adipose-only analysis is likely due to the small sample sizes of liver ($n = 208$) and adipose ($n = 581$) in GTEx v8 (Figure S1). Leveraging the large degree of tissue sharing in eQTLs,^{19,45} our cross-tissue colocalization analysis enhanced the discovery power through the collectively large sample size across all 49 tissues ($n = 15,201$). For example, several well-documented lipid-relevant genes such as *PPARA*⁴⁶ and *LPL*⁴⁷ were not identified in the liver- or adipose-only analysis but were identified as significant in our cross-tissue analysis.

To acquire additional functional insights into the 1,076 colocalized genes, we assessed their enrichments across existing biological and clinical gene sets (Figure 2B, Tables S2 and S3). Colocalized genes showed enrichments in (1) 20 KEGG pathways³⁰ at FDR 5%, including known lipid-related processes such as cholesterol metabolism, PPAR signaling, and bile secretion; (2) 33 Mendelian genes from ClinVar³² associated with lipid-related ICD10 codes (11.61-fold enrichment, $p = 2.08 \times 10^{-6}$, including *APOB*, *LPL*, and *APOE*), suggesting the shared genetic basis of Mendelian and complex lipid phenotypes;⁴⁸ (3) 35

genes with rare-variant burden for lipid phenotypes in a recent multi-ancestry analysis³³ (30.82-fold enrichment, $p = 1.77 \times 10^{-16}$, including *APOB*, *LPL*, *LIPG*, and *ANGPTL4*), confirming shared mechanisms of rare and common variation underlying lipid traits;⁴⁹ (4) genes implicated by cholesterol or lipidemia phenotypes in mouse knockouts (3.92-fold enrichment, $p = 2.18e-20$), suggesting the shared genetic basis of lipid traits between human and mouse.⁵⁰ Colocalized genes also showed enrichment with genes implicated in TWAS (Table S4) run on the same GWAS and eQTL summary statistics (20.14-fold enrichment, $p < 2.22e-308$). These enrichment results demonstrate the biological relevance of candidate functional genes prioritized by our approach.

Chromatin-chromatin interactions shortlist eQTL-based colocalization

Our eQTL-based colocalization analysis uses a linear sequence of DNA and ignores physical interaction between non-adjacent DNA segments, another regulatory layer underlying complex human traits.⁵¹ To add this layer to our analysis, we generated Capture-C data from HepG2 liver carcinoma cells (HepG2.1) and hepatocyte-like cells (HLC) derived from differentiating iPSCs,²² as well as publicly available Capture-C datasets from HepG2²¹ (HepG2.2) and white adipocytes.²³ Based on the Capture-C data, we defined an interaction between a GWAS locus and a gene as a significant interaction between the bait end (promoter) for this gene and the interacting end that contains a variant in the credible set for this GWAS locus. In total, 1,079 of 1,750 GWAS loci had at least one variant in the credible set with a physical interaction with a gene promoter and 3,543 of 26,621 genes with promoter-interactions had promoters physically interacting with at least one GWAS credible set variant (Figure 2A and Table S5).

Unlike eQTL-colocalized genes, genes interacting with GWAS credible sets were not significantly enriched in lipid-relevant KEGG pathways (Table S2) and lipid-related genes from ClinVar (Figure 2B and Table S3). These genes were significantly enriched in genes with rare-variant lipid associations (5.36-fold enrichment, $p = 2.8 \times 10^{-5}$), genes with lipid-related mouse knockouts (1.43-fold enrichment, $p = 2.8 \times 10^{-4}$), and TWAS-prioritized genes (5.05-fold enrichment, $p = 2.5 \times 10^{-288}$), but their enrichments were consistently lower than enrichments of eQTL-colocalized genes nonetheless (Figure 2B and Table S3).

Since genes expressed in the liver are most likely to harbor genuine lipid-relevant variant-gene interactions, we repeated the enrichment analyses above restricting both eQTL colocalization and Capture-C interactions to genes expressed in the liver (>0.1 TPM and ≥ 6 reads in at least 20% of GTEx liver samples). Reassuringly, we observed higher enrichments for each combination of two methods (eQTL, Capture-C) and four databases (ClinVar, Rare Variant, Mouse Knockout, TWAS) when we restricted our analyses to genes expressed in the liver (Figure 2B and Table S3). For the same database, we observed higher en-

richments in eQTL colocalized genes than Capture-C prioritized genes, consistent with the results based on all genes.

Genes physically interacting with GWAS loci significantly overlapped with eQTL colocalized genes despite their reduced enrichments in lipid-related gene sets. Of 1,079 credible sets with promoter interactions, 224 also colocalized with eQTLs for the same gene. Across 49 eQTL tissues and four Capture-C cell lines, 233 genes were implicated in both eQTL colocalizations and Capture-C interactions (Table S6), representing an enrichment of 3-fold compared to random chance (Figure 2C, $p = 3.11 \times 10^{-38}$). Because our Capture-C data came from liver and adipose only, we observed a stronger enrichment in overlap when restricting genes expressed in the liver or adipose (4.5-fold enrichment, $p = 2.89 \times 10^{-65}$). We observed similar enrichment patterns when analyzing liver and adipose Capture-C data separately (Figure 2C). Together, the enrichments in overlap suggest that, despite a large number of genes identified by Capture-C (Figure 2A), many of them are likely to harbor functional interactions with GWAS loci.

Chromatin-chromatin interactions helped shortlist functional genes from eQTL colocalization. Among 224 loci with concordant eQTL colocalizations and Capture-C interactions across all tissues, only 39% (88) mapped to a single gene using eQTL data alone, whereas adding Capture-C information increased this fraction to 80% (180). We observed the same trend in the adipose-only and liver-only analysis: 80% (12/15) and 79% (26/33) of loci mapped to a single gene using adipose and liver eQTLs alone, compared to 93% (14/15) and 97% (32/33) after the integration of adipose-only and liver-only Capture-C data, respectively (Figure 2D). These results showcase the potential value of combining eQTLs with physical chromatin interactions to prioritize functional genes at GWAS loci.

Since eQTLs are likely to reside in the same topologically associated domain (TAD) as the genes they regulate,⁵² we examined TADs from an independent human liver dataset²⁸ at lipid GWAS loci with eQTL colocalizations to confirm GWAS variant-target gene colocalization within the same TAD. Of eQTL-GWAS colocalizations in which the sentinel variant resided within a TAD, 84.8% (1,040 out of 1,235) had the colocalized gene residing in the same TAD ($p < 0.001$ with 1,000 permutations). When we restricted to all colocalizations concordant with Capture-C data in any cell type, 96.9% (252 out of 260) of gene-variant pairs fell in the same TAD. This fraction further increased to 100% (33 out of 33) when we repeated the analysis using liver eQTLs and liver Capture-C interactions only. These results add to the existing evidence for TAD boundaries being regulatory insulators in the cell⁵³ and confirm our integration of chromatin interactions with eQTL colocalizations as an effective strategy to hone in on functional genes.

Tissue-specific enrichment of GWAS signals differentiates lipid traits

Regulatory variants often affect complex traits in a tissue-specific manner,⁶ as shown in our eQTL colocalization

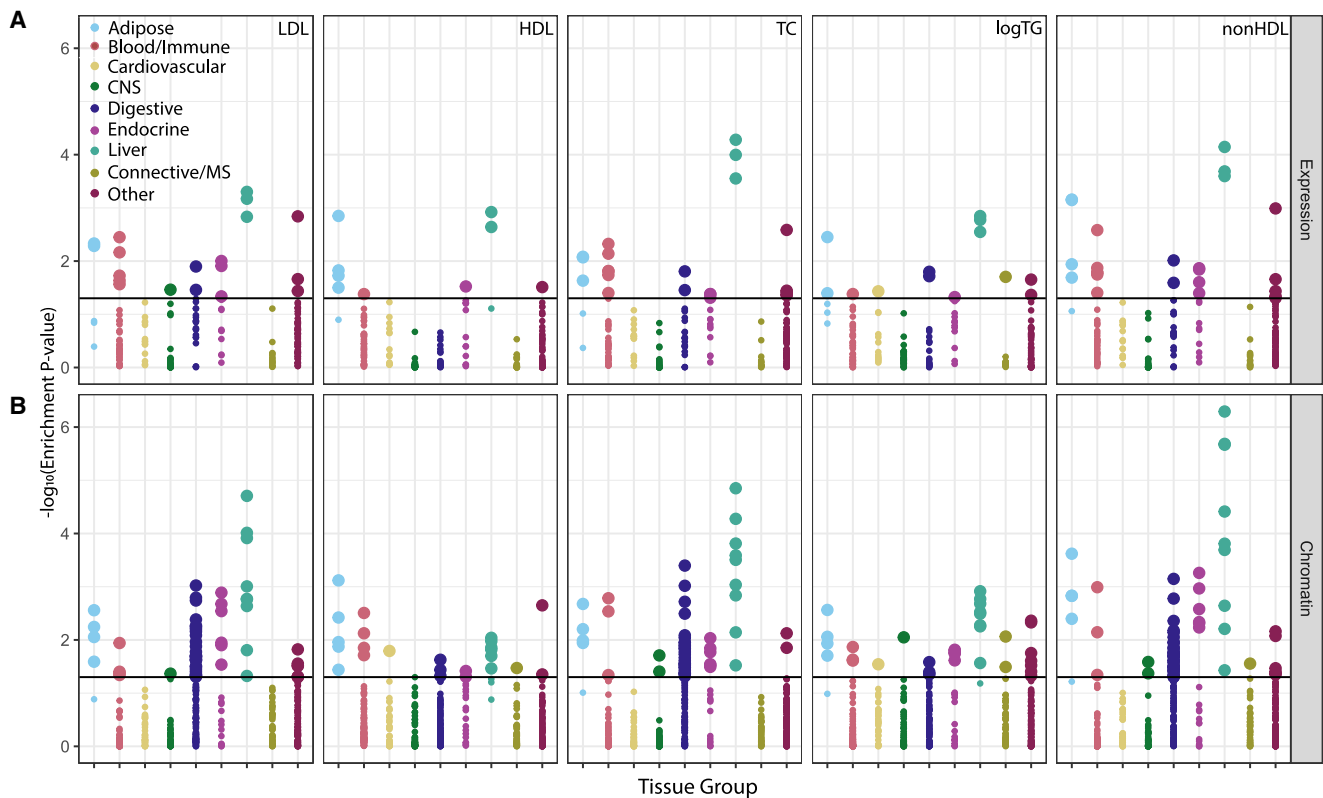


Figure 3. Tissue relevance of lipid-associated loci

Partitioning heritability of lipid GWAS summary statistics on gene expression (A) and active chromatin marks (B) across tissues. Each plotted point represents a tested dataset for enrichment of heritability, with larger dots representing datasets with enrichment p value < 0.05 . Each color represents a tissue group (Table S7), and the y-axis represents $-\log_{10}$ p value for enrichment of heritability.

analysis. Specifically, by computing the ratio of the number of colocalizations in a tissue to eQTL sample size in that tissue, we found that the liver was universally enriched for colocalized eGenes with respect to sample size across all lipid traits whereas adipose was selectively enriched in HDL and TG only (Figure S1). Motivated by these findings, we leveraged systematic approaches and additional data to identify relevant tissues and cell types for each lipid trait.

We implemented stratified LD score regression (S-LDSC),³⁶ a polygenic approach not restricted to genome-wide significant variants, on tissue-specific transcriptomic and epigenomic annotations across 205 datasets from more than 170 tissues and cell types, to identify relevant tissues for each lipid trait. Consistent with previous studies^{43,44} and our eQTL-based analysis, liver-related tissues (Tables S7 and S8) showed strong enrichments across all lipid traits (S-LDSC enrichment p values ranging from 0.001 in TG to 0.0001 in TC), for both expression (Figure 3A) and chromatin annotations (Figure 3B). This result was confirmed by analysis using two other approaches: DEPICT⁵⁴ (Figure S2 and Table S9) and RSS-NET⁵⁵ (Table S10). To assess the robustness of our S-LDSC results based on multi-ancestry GWASs, we applied S-LDSC to population-specific GWASs in European and East Asian ancestry participants together with popula-

tion-specific LD scores and obtained similar results (Table S11, Figures S3 and S4).

The S-LDSC results also highlighted tissues selectively enriched in certain lipid traits as shown in the eQTL-based analysis. The most enriched category for HDL using chromatin annotation is adipose H3K4me3 ($p = 7.6 \times 10^{-4}$); for TG, enrichment in liver-related tissues ($p = 1.2 \times 10^{-3}$) is similar to enrichment in adipose ($p = 2.7 \times 10^{-3}$). For LDL, TC, and nonHDL, enrichment p values for the liver were much more significant than for all other tissues including adipose (Figure 3B). We observed the same pattern in S-LDSC results based on gene expression (Figure 3A). This finding is consistent with the known influence of adipose on plasma HDL levels,⁵⁶ and the role of adipose as TG deposits.⁵⁷ These results were corroborated by eQTL colocalizations stratified by phenotype (Figure S1) and DEPICT analysis on gene expression⁵⁴ (Figure S2 and Table S9). Together, these results confirm the liver as a tissue of action for all five lipid traits and highlight the additional role of adipose primarily in HDL and TG.

Given the importance of the liver and adipose in modulating lipid levels, we further identified the relevant cell types within these tissues. Using existing single-cell data from adipose and liver,³⁹ we performed gene set enrichment analysis⁵⁸ to identify cell-type clusters enriched for genes with eQTL colocalizations for any lipid trait. Out

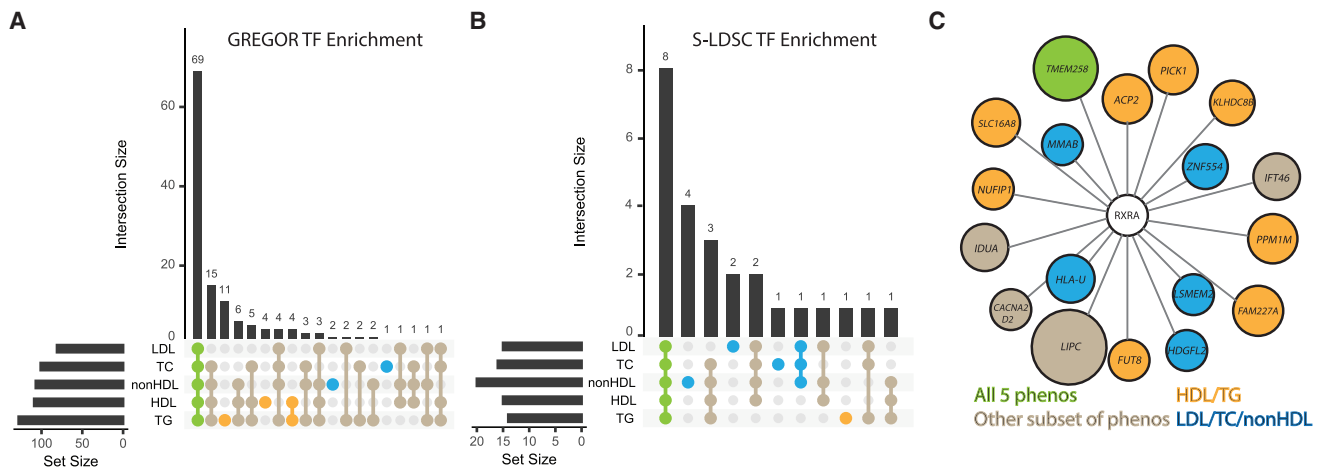


Figure 4. TF enrichment identified by GREGOR and S-LDSC

(A) Number of TFs enriched in the GREGOR analysis on GWAS loci for each of the five lipid traits.

(B) Number of TFs enriched in S-LDSC analysis on each of the five lipid traits.

(C) TF RXRA binds to the promoters of 26 colocalized genes (18 protein-coding). Colors represent the subsets of lipid phenotypes with colocalization. Larger node sizes represent smaller GWAS p values of colocalized loci.

of 11 identified cell types in 20 clusters in the liver, only hepatocytes were enriched at FDR-adjusted $p < 0.05$ (Figure S5 and Table S12), consistent with previous results.²¹ In adipose, only adipocyte clusters and macrophage-monocyte clusters showed suggestive enrichment (nominal $p < 0.05$) in colocalized genes (Figure S6 and Table S12). Of note, the enrichment in adipocytes was significant when we restricted this analysis to genes that were colocalized with HDL and TG (FDR-corrected $p < 0.05$), consistent with the selective enrichments of adipose in HDL and TG (but not the other lipid traits) from our S-LDSC analysis. Evaluations at cellular resolution are required to understand the cell-type-specific mechanisms underlying lipid GWAS loci, but our results could form a useful basis for future studies.

Overlapping GWAS signals with binding sites highlights lipid-relevant TFs

TFs have been implicated as a key mediator of linking genetic variation to complex traits.⁵⁹ To understand lipid GWASs in the context of TF activity, we assessed enrichment of genome-wide significant variants at TF binding sites using GREGOR³⁸ and performed polygenic enrichment analysis of TF binding sites using S-LDSC. Because TFs were not comprehensively assayed in most cell lines (Figure S7), we used all cell types in our primary analysis presented below.

Using ChIP-seq data from 161 TFs across 91 cell types from the ENCODE project,⁷ 70.7% of lipid credible sets overlapped with at least one TF binding site. Using GREGOR,³⁸ we identified 137 TFs whose binding sites were significantly enriched in GWAS lead SNPs for at least one lipid phenotype (enrichment >2 ; FDR adjusted p value < 0.05 ; Figure 4A and Table S13). We obtained similar results when repeating the GREGOR analysis on TF binding sites derived from HepG2 only (Table S14). To

assess the impact of GWAS power on TF enrichments, we repeated the GREGOR analysis on the same TF binding sites using a previous version of lipid GWAS, and we identified 54 enriched TFs (Table S15). Between the two versions of lipid GWASs, the total sample size and number of GWAS loci increased 8.7-fold (from 188,577 to 1,650,000) and 11-fold (from 156 to 1,750), respectively, but the number of enriched TFs only increased 2.5-fold (from 54 to 137), suggesting that the large number of enriched TFs is unlikely driven by the GWAS power alone.

Among these 137 enriched TFs, 69 of them (50%) showed significant enrichments across all five lipid phenotypes, suggesting a potential core regulatory circuit shared by all lipid traits (Figure 4A and Table S13). The TF with the strongest enrichment in all phenotypes was ESRRRA (estrogen-related receptor alpha), a nuclear receptor active in metabolic tissues;⁶⁰ ESRRRA has been implicated in adipogenesis and lipid metabolism, and ESRRRA-null mice display an increase in fat mass and obesity.⁶⁰

The GREGOR analysis also highlighted 68 TFs significantly enriched in specific subsets of (but not all five) lipid phenotypes (Figure 4A and Table S13). For example, we found 4 TFs (FOXO1, PBX3, ZKSCAN1, ZEB1) enriched in HDL and TG only, 4 TFs (EZH2, NFE2, NFATC1, KDM5A) enriched in HDL only, and 11 TFs (FOSL1, IRF3, JUN, MEF2C, NANOG, PRDM1, RUNX3, SIRT6, SMC3, STAT3, ZNF217) enriched in TG only. Of these TFs, the central role of ZEB1 in adiposity⁶¹ and fat cell differentiation has been demonstrated.⁶² These TF-centric findings corroborate the selective enrichments of adipose in HDL and TG (but not the other lipid traits) identified in our previous tissue prioritization analyses.

We also performed polygenic enrichment analysis of TF binding sites using S-LDSC (Figure 4B and Table S16), which differed from GREGOR analysis by looking at not only the genome-wide significant associations but also

the polygenic signal without GWAS p value cutoff. On the same 161 ENCODE TFs, this polygenic analysis identified 25 TFs whose binding sites were significantly enriched in heritability explained (nominal $p < 0.05$) for at least one lipid phenotype; reassuringly, 24 of 25 TFs were also significant in the GREGOR analysis. As a sensitivity check, we repeated the S-LDSC analysis on TF binding sites derived from HepG2 only, and we obtained similar results (Table S17).

Among 24 enriched TFs identified by both GREGOR and S-LDSC, eight were significantly enriched in all five lipid traits (CEBPB, CEBPD, FOXA2, HDAC2, HNF4G, NFYA, RXRA, SP1). RXRA (retinoid X receptor alpha) is encoded by a colocalized gene (*RXRA*) near a GWAS hit (chr9:137,268,682). RXRA is a ligand-activated transcription factor that forms heterodimers with other receptors (including PPARG) and is involved in lipid metabolism.⁶³ Moreover, 145 lipid GWAS loci overlap RXRA binding peaks, and RXRA binds to the promoters of 26 colocalized genes (18 of which are protein-coding) (Figure 4C and Table S18), suggesting that the GWAS variants might affect lipids (partially) through affecting the binding activity of RXRA. While *RXRA* has been previously implicated,⁶⁴ our study demonstrates its role in lipid biology through its regulatory influence on other lipid-associated genes.

Multi-layer functional integration reveals regulatory mechanisms at GWAS loci

Motivated by our finding that integrating chromatin interaction shortlisted eQTL colocalizations, we further brought together multiple lines of functional evidence at each GWAS locus for mechanistic inference. We started with the list of genes with evidence for both eQTL colocalization and Capture-C interactions in the liver or adipose. We next annotated each variant in the 95% credible set with various indicators of regulatory function, including its open chromatin status in liver²⁰ or adipose-related cell types,⁶⁵ its proximity to a promoter or an enhancer,⁶⁶ and its RegulomeDB regulation probability;⁶⁷ see Table S19 for the complete list of annotations used. To account for complexities of regulatory mechanisms and limitations of functional datasets, we combined evidence across these datasets to prioritize variants at GWAS loci (Figure 5A). Specifically, we prioritized variants with at least three independent lines of functional evidence (chromatin openness, physically interaction with target genes, and promoter/enhancer status) in the liver or adipose, with at least two being in the same tissue with colocalization with the target gene, and with a RegulomeDB score >0.5 . Applying this simple procedure to lipid GWASs we prioritized 28 candidate loci with the strongest multi-layer evidence, 13 of which point to a single functional variant (Table 1). We have also made the full results of variant prioritization freely available ([web resources](#)). Below we describe two examples to highlight key features of this multi-layer integration framework.

RRBP1 (ribosomal binding protein 1) could be identified from eQTL colocalization alone, but our multi-layer integration approach strengthened the conclusion via convergent evidence from various sources (Figure 5B). The *RRBP1* eQTL signals in the liver colocalize with LDL, TC, and nonHDL GWAS signals. The credible set at this locus contains a single lead variant (chr20:17,844,684). The “T” allele of this lead variant decreases *RRBP1* expression levels and increases LDL, TC, and nonHDL levels. This lead variant is in open chromatin in HLC and adipose and physically interacts with the *RRBP1* promoter (250 kb away) in adipose. All these data consistently point to *RRBP1* as the functional gene underlying this locus. *RRBP1* specifically tethers the endoplasmic reticulum to the mitochondria in the liver (an interaction that is enriched in hepatocytes) and regulates very low-density lipoprotein levels.⁶⁸ Rare variants in *RRBP1* are associated with LDL in humans⁶⁹ and silencing *RRBP1* in liver affects lipid homeostasis in mice.⁶⁸

CREBRF (CREB3 regulatory factor) further demonstrates the power of our multi-layer integration framework in prioritizing functional variants (Figure 5C). The eQTL signals of *CREBRF* colocalized with a GWAS locus for HDL with 30 candidate variants. In contrast, our multi-layer approach identified a single candidate variant (chr5:172,566,698) at this locus that physically interacts with the *CREBRF* promoter in adipose and is predicted to be a regulatory element (RegulomeDB score = 0.91). Consistent with the index variant (chr5:172,591,337), the allele “A” at this functional variant increased HDL levels and increased *CREBRF* expression in adipose. Missense variants in *CREBRF* have been linked to body mass index, and the gene has been linked to obesity risk in Samoans.⁷⁰

Finally, to compare the power of functional fine-mapping with multi-ancestry fine-mapping, we applied our prioritization rule to credible sets derived from European-only meta-analysis. The 111 variants prioritized by our rule described above (including multiple variants in the same credible set) were all found in the multi-ancestry credible sets, representing a 3.7-fold enrichment ($p < 1 \times 10^{-4}$ based on 10,000 permutations randomly sampling variants from the European-only credible sets). This convergence of complementary approaches to the same smaller set of fine-mapped variants highlights the power of multi-ancestry datasets as an approach to narrow in on functional variants.

Discussion

Here we integrate the largest multi-ancestry lipid GWAS to date with a wide array of functional genomic resources to understand how noncoding genetic variation affects lipids through gene regulation. Specifically, we identify 1,076 genes whose eQTL signals colocalize with lipid GWAS signals and demonstrate how physical chromatin interaction can improve standard eQTL-based colocalization. We

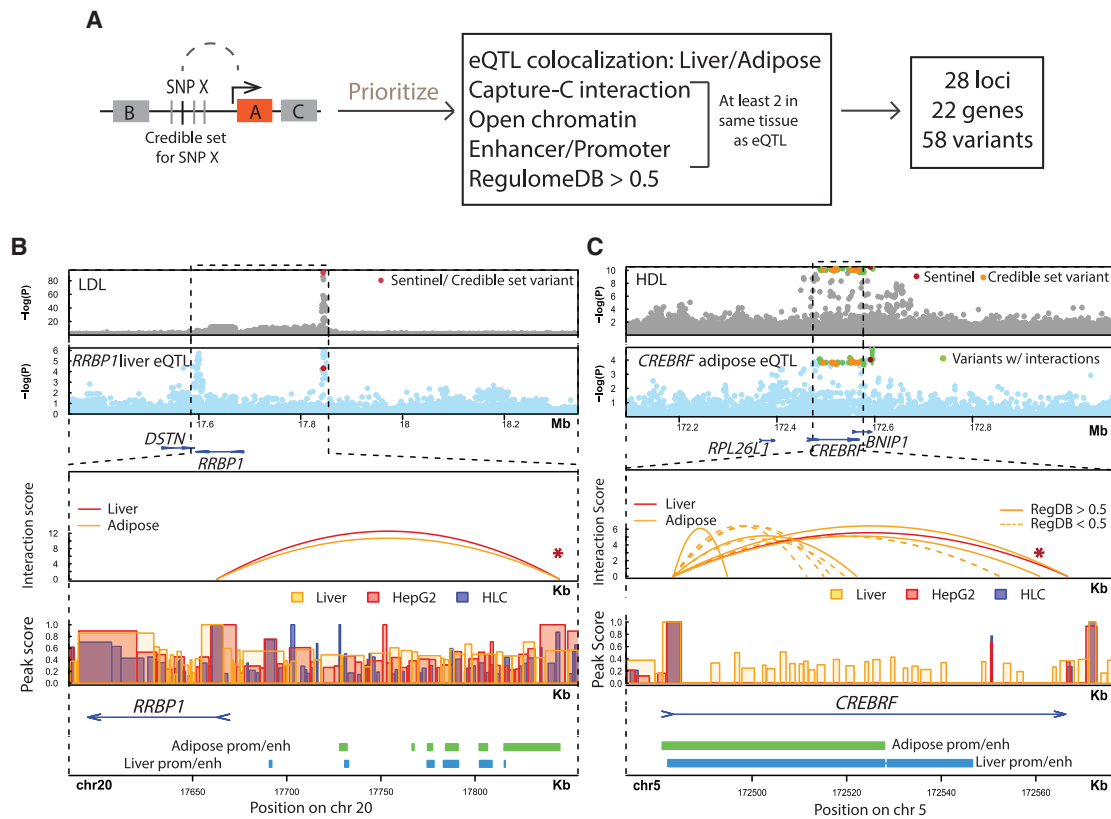


Figure 5. Multi-layer functional integration to prioritize variants at GWAS loci

(A) Variant annotation and prioritization scheme at each GWAS credible set.

(B) Evidence for *RRBP1* from functional genomics data. The LDL GWAS locus at this region (first row) is an eQTL for *RRBP1* in the liver (second row). Variants in the credible set of this locus interact with the gene promoter in both adipose and HepG2 Capture-C data (third row). The interacting variant is also in an open chromatin peak in three liver-related cell types (fourth row).

(C) Multiple sources of functional genomics data support *CREBRF* as a gene contributing to HDL levels. The HDL GWAS locus at this region (first row) is an eQTL for *CREBRF* in adipose (second row). Variants in the credible set at this locus interact with the *CREBRF* promoter in adipose (third row). The interacting variant is also in open chromatin in liver-related cell types (fourth row).

assess tissue-specific enrichments of lipid GWAS signals and demonstrate the selective importance of adipose in HDL and triglyceride biology. We examine binding site enrichments of 161 TFs in lipid GWASs and expand our understanding of lipid GWAS loci (e.g., *RXRRA*) in the context of TF activity. Finally, we build a simple and interpretable prioritization framework that automatically combines multiple lines of evidence from orthogonal datasets, pinpointing a single functional variant at each of 13 lipid-associated loci (e.g., *RRBP1* and *CREBRF*). While there are studies that interpret lipid GWAS associations,^{21,71,72} the size of our multi-ancestry GWAS and multi-layer functional integration represent a comprehensive effort and an important step forward in this direction.

Our multi-layer analysis has two key strengths. First, despite a large array of functional genomic resources being embedded, our analysis produces results with high consistency. For example, the selective enrichment of adipose in HDL and TG identified by S-LDSC is confirmed by our eQTL-based colocalization and TF binding site overlap. Another example of consistency is the multi-layer prioritization of *RRBP1*, which can be identified from eQTL-based

colocalization alone and it is further validated by chromatin accessibility and interaction. Such convergent evidence from various sources improves the confidence of our findings. Second, our analysis highlights that combining multiple layers of regulatory information can improve sensitivity to prioritize functional genes and variants. For example, we refined eQTL colocalized genes (1,076) to a smaller set of functional genes (233) through integration with promoter Capture-C data. Another example of sensitivity is *CREBRF*, where eQTL-based colocalization implicates 30 candidate variants and adding other regulatory layers points to a single functional variant. Moving forward, we expect these two features will serve as useful guidelines for future integrative genomic analyses of other traits.

Our results rely on the breadth and accuracy of functional genomic datasets used in our analyses. First, unlike our lipid GWASs, current functional datasets⁷³ are limited both in sample size and ancestral diversity, which can affect discovery and replication of regulatory mechanisms in diverse populations. Second, some functional datasets are generated at limited resolution. For example, our colocalizations

Table 1. Thirteen prioritized loci with highest confidence of a single functional variant in the credible set

Gene Name	Tissue	Sentinel	Prioritized Var	Open	CapC	Enhancer	Prom-oter	RegDB
<i>CEP68</i>	adipose	2:65284231	65279414	liver	liver	none	ad	0.5896
<i>TIPARP</i>	adipose	3:156797941	156795408	both	both	ad	liver	0.705
<i>CREBRF</i>	adipose	5:172591337	172566698	liver	ad	none	both	0.9124
<i>PALM2</i>	adipose	9:112556911	112556911	both	ad	both	none	0.6091
<i>MEGF9</i>	adipose	9:123481206	123421556	liver	ad	none	liver	0.9933
<i>GBF1</i>	liver	10:104142294	104107191	ad	ad	none	both	0.705
<i>MICAL2</i>	liver	11:12071855	12221016	liver	liver	none	liver	0.6018
<i>ACP2</i>	liver	11:47278917	47276350	ad	liver	liver	ad	0.6091
<i>PTPRJ</i>	adipose	11:48021778	48011180	liver	ad	liver	ad	0.8797
<i>NFATC2IP</i>	adipose	16:28899411	28883327	liver	liver	none	both	0.6091
<i>HELZ</i>	liver	17:65109591	65156919	liver	liver	none	both	0.60906
<i>FAM210A</i>	liver	18:13725674	13725674	liver	liver	none	both	0.7571
<i>RRBP1</i>	liver	20:17844684	17844684	both	ad	both	none	0.6091

The “sentinel” column represents the lead variant at the locus. The “prioritized var” column represents the prioritized variant in the credible set. Columns 5–8 represent overlap of the functional variant with open chromatin (“open”), capture-C (“CapC”) interactions with the candidate gene, enhancer and promoter marks from Roadmap in liver (“liver”), adipose (“ad”), both, or none of these tissues. The “RegDB” column represents the RegulomeDB score of the prioritized variant.

are based on eQTLs from bulk tissue RNA-seq,^{8,74} which may miss detailed cell types and biological processes in which lipid-associated SNPs regulate gene expression. Third, some functional datasets are not available across the full spectrum of human tissues and cell types. One example is that our chromatin-chromatin interaction analysis examines only a few cell types in two known lipid-related tissues (liver and adipose), producing results that may be biased toward known lipid biology. Another example is that ENCODE TF ChIP-seq data are not available in adipose-related cell lines. Fourth, our results are validated computationally but not experimentally. That said, our results provide a high-confidence list of regulatory mechanisms at lipid GWAS loci, forming a useful basis for future experiments. As more comprehensive and accurate functional genomic resources are becoming publicly available in diverse cellular contexts and ancestry groups, the resolution and power of integrative analyses like ours will be markedly increased.

Other limitations of this study stem from computational methods embedded in our framework. First, the colocalization approach coloc assumes one causal variant per locus, whereas recent studies suggest extensive allelic heterogeneity⁷⁵ consistent with a model of a milieu of related transcription factors binding within a single locus. Accounting for allelic heterogeneity in summary statistics-based colocalization typically requires modeling multiple correlated SNPs through LD matrix,⁷⁶ which is computationally intensive in large-scale analyses derived from many cohorts with diverse ancestries, like the multi-ancestry GWASs examined here. Second, due to restricted access to individual genotypes of 201 cohorts, we cannot produce multi-ancestry LD scores within GLGC but have to use European-based LD scores in all S-LDSC analyses. This

approach, though less rigorous in principle, provides robust results in practice (as confirmed by our ancestry-specific analysis), largely because 79% of cohorts in GLGC are of European descent.¹² That said, we caution that the same approach might fall short in ancestrally diverse studies with few European individuals.⁷⁷ Third, our multi-layer variant prioritization framework is built on a series of simple rules that are easy to implement on large datasets. This approach could possibly be formalized as statistical models (e.g., priors in Bayesian methods⁵⁵), but our approach simplifies computation and allows for scalability of the underlying framework. Despite the technical limitations, our approach here can serve as a useful benchmark for future development of methods with improved statistical rigor and computation efficiency.

In summary, mapping noncoding genetic variation of complex traits to biological functions can benefit greatly from thorough integration of multiple layers of functional genomics, as demonstrated in the present study. Although tested on lipids only, our integrative framework is straightforward to implement more broadly on many other phenotypes, yielding functional insights of heritable traits and diseases in humans.

Data and code availability

The accession number for the HLC Capture-C data reported in this paper is <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE189026>.

Supplemental information

Supplemental information can be found online at <https://doi.org/10.1016/j.ajhg.2022.06.012>

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Declaration of interests

G.C.-P. is currently an employee of 23andMe Inc. M.J.C. is the Chief Scientist for Genomics England, a UK Government company. B.M. Psaty serves on the steering committee of the Yale Open Data Access Project funded by Johnson & Johnson. G. Thorleifsson, A.H., D.F.G., H. Holm, U.T., and K.S. are employees of deCODE/Amgen Inc. V.S. has received honoraria for consultations from Novo Nordisk and Sanofi and has an ongoing research collaboration with Bayer Ltd. M. McCarthy has served on advisory panels for Pfizer, NovoNordisk, and Zoe Global and has received honoraria from Merck, Pfizer, Novo Nordisk, and Eli Lilly and research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. M. McCarthy and A. Mahajan are employees of Genentech and holders of Roche stock. M.S. receives funding from Pfizer Inc. for a project unrelated to this work. M.E.K. is employed by SYNLAB MVZ Mannheim GmbH. W.M. has received grants from Siemens Healthineers, grants and personal fees from Aegerion Pharmaceuticals, grants and personal fees from AMGEN, grants from Astrazeneca, grants and personal fees from Sanofi, grants and personal fees from Alexion Pharmaceuticals, grants and personal fees from BASF, grants and personal fees from Abbott Diagnostics, grants and personal fees from Numares AG, grants and personal fees from Berlin-Chemie, grants and personal fees from Akzea Therapeutics, grants from Bayer Vital GmbH, grants from bestbion dx GmbH, grants from Boehringer Ingelheim Pharma GmbH Co KG, grants from Immundiagnostik GmbH, grants from Merck Chemicals GmbH, grants from MSD Sharp and Dohme GmbH, grants from Novartis Pharma GmbH, grants from Olink Proteomics, and other from Synlab Holding Deutschland GmbH, all outside the submitted work. A.V.K. has served as a consultant to Sanofi, Medicines Company, Maze Pharmaceuticals, Navitor Pharmaceuticals, Verve Therapeutics, Amgen, and Color Genomics; received speaking fees from Illumina and the Novartis Institute for Biomedical Research; received sponsored research agreements from the Novartis Institute for Biomedical Research and IBM Research, and reports a patent related to a genetic risk predictor (20190017119). S. Kathiresan is an employee of Verve Therapeutics and holds equity in Verve Therapeutics, Maze Therapeutics, Catabasis, and San Therapeutics. He is a member of the scientific advisory boards for Regeneron Genetics Center and Corvidia Therapeutics; he has served as a consultant for Acceleron, Eli Lilly, Novartis, Merck, Novo Nordisk, Novo Ventures, Ionis, Alnylam, Aegerion, Haug Partners, Noble Insights,

Leerink Partners, Bayer Healthcare, Illumina, Color Genomics, MedGenome, Quest, and Medscape; and he reports patents related to a method of identifying and treating a person having a predisposition to or afflicted with cardiometabolic disease (20180010185) and a genetics risk predictor (20190017119). D.K. accepts consulting fees from Regeneron Pharmaceuticals. D.O.M.-K. is a part-time clinical research consultant for Metabolon, Inc. D. Saleheen has received support from the British Heart Foundation, Pfizer, Regeneron, Genentech, and Eli Lilly pharmaceuticals. P.N. reports investigator-initiated grants from Amgen, Apple, AstraZeneca, Boston Scientific, and Novartis, personal fees from Apple, AstraZeneca, Blackstone Life Sciences, Foresite Labs, Novartis, Roche / Genentech, is a co-founder of TenSixteen Bio, is a scientific advisory board member of Esperion Therapeutics, geneXwell, and TenSixteen Bio, and spousal employment at Vertex, all unrelated to the present work. The spouse of C.J.W. is employed by Regeneron.

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Web resources

Adipose single-cell data, https://singlecell.broadinstitute.org/single_cell/study/SCP133/human-adipose-svf-single-cell
bedtools, <https://bedtools.readthedocs.io/en/latest/>
biomaRt, <https://bioconductor.org/packages/release/bioc/html/biomaRt.html>
Browser of noncoding variant prioritization, http://csg.sph.umich.edu/willer/public/glgc-lipids2021/variant_prioritization.html
CHiCAGO, <https://www.bioconductor.org/packages/release/bioc/html/Chicago.html>
ClinVar, <https://www.ncbi.nlm.nih.gov/clinvar/>
ClusterProfiler, <https://guangchuangyu.github.io/clusterProfiler>
coloc, <https://cran.r-project.org/web/packages/coloc>
DEPICT, <https://data.broadinstitute.org/mpg/depict>
East Asian LD scores and related annotations, <http://jenger.riken.jp/en/data>
ENCODE ChIP-Seq data, <https://hgdownload.cse.ucsc.edu/goldenpath/hg19/encodeDCC/wgEncodeRegTfbsClustered/wgEncodeRegTfbsClusteredWithCellsV3.bed.gz>
European LD scores and related annotations, <https://data.broadinstitute.org/alkesgroup/LDSCORE/>
fgsea, <http://bioconductor.org/packages/release/bioc/html/fgsea.html>
GenomicRanges, <https://bioconductor.org/packages/release/bioc/html/GenomicRanges.html>
GLGC GWAS summary statistics and credible sets, <http://csg.sph.umich.edu/willer/public/glgc-lipids2021/>
GREGOR, <https://genome.sph.umich.edu/wiki/GREGOR>
GTEx v8 summary statistics, <https://www.gtexportal.org/home/datasets>
HepG2 Capture-C data (Chesi et al.²⁰), <https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-7144/>
HepG2 Capture-C data (Selvarajan et al.²¹), <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE157306>
HiCUP, <https://www.bioinformatics.babraham.ac.uk/projects/hicup/>
Human liver Hi-C data, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58752>

Human white adipocyte Capture-C data, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110619>
 LDSC software, <https://github.com/bulik/ldsc>
 liftOver, <https://genome.ucsc.edu/cgi-bin/hgLiftOver>
 Liver single-cell data, <http://shiny.baderlab.org/HumanLiverAtlas/MGI/> <http://www.informatics.jax.org/downloads/reports/index.html#pheno>
 Open chromatin data from HepG2, <https://www.omicsdi.org/dataset/arrayexpress-repository/E-MTAB-7543>
 Open chromatin data from adipose, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110734>
 Roadmap epigenomic data (promoters and enhancer annotation), <https://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/>
 RegulomeDB, <https://regulomedb.org/regulome-search/>
 RSS-NET, <https://github.com/SUwonglab/rss-net>
 S-PrediXcan, <https://github.com/hakyimlab/MetaXcan>

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