

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

3 Shweta Ramdas^{1*}, Jonathan Judd^{2*}, Sarah E Graham^{3*}, Stavroula Kanoni^{4*}, Yuxuan Wang^{5*}, Ida
4 Surakka³, Brandon Wenz¹, Shoa L Clarke^{6,7}, Alessandra Chesi⁸, Andrew Wells¹, Konain Fatima
5 Bhatti⁴, Sailaja Vedantam^{9,10}, Thomas W Winkler¹¹, Adam E Locke¹², Eirini Marouli⁴, Greg JM
6 Zajac¹³, Kuan-Han H Wu¹⁴, Ioanna Ntalla¹⁵, Qin Hui^{16,17}, Derek Klarin^{18,19,20}, Austin T Hilliard⁶,
7 Zeyuan Wang^{16,17}, Chao Xue³, Gudmar Thorleifsson²¹, Anna Helgadottir²¹, Daniel F
8 Gudbjartsson^{21,22}, Hilma Holm²¹, Isleifur Olafsson²³, Mi Yeong Hwang²⁴, Sohee Han²⁴, Masato
9 Akiyama^{25,26}, Saori Sakaue^{27,28,29}, Chikashi Terao³⁰, Masahiro Kanai^{25,31,32}, Wei Zhou^{33,14,20}, Ben M
10 Brumpton^{34,35,36}, Humaira Rasheed^{34,35,37}, Aki S Havulinna^{38,39}, Yogasudha Veturi⁴⁰, Jennifer Allen
11 Pacheco⁴¹, Elisabeth A Rosenthal⁴², Todd Lingren⁴³, QiPing Feng⁴⁴, Iftikhar J. Kullo⁴⁵, Akira
12 Narita⁴⁶, Jun Takayama⁴⁶, Hilary C Martin⁴⁷, Karen A Hunt⁴⁸, Bhavi Trivedi⁴⁸, Jeffrey Haessler⁴⁹,
13 Franco Giulianini⁵⁰, Yuki Bradford⁴⁰, Jason E Miller⁴⁰, Archie Campbell^{51,52}, Kuang Lin⁵³, Iona Y
14 Millwood^{53,54}, Asif Rasheed⁵⁵, George Hindy⁵⁶, Jessica D Faul⁵⁷, Wei Zhao⁵⁸, David R Weir⁵⁷,
15 Constance Turman⁵⁹, Hongyan Huang⁵⁹, Mariaelisa Graff⁶⁰, Ananyo Choudhury⁶¹, Dhriti
16 Sengupta⁶¹, Anubha Mahajan⁶², Michael R Brown⁶³, Weihua Zhang^{64,65,66}, Ketian Yu¹³, Ellen M
17 Schmidt¹³, Anita Pandit¹³, Stefan Gustafsson⁶⁷, Xianyong Yin¹³, Jian'an Luan⁶⁸, Jing-Hua Zhao⁶⁹,
18 Fumihiko Matsuda⁷⁰, Hye-Mi Jang²⁴, Kyunghoon Yoon²⁴, Carolina Medina-Gomez⁷¹, Achilles
19 Pitsillides⁵, Jouke Jan Hottenga^{72,73}, Andrew R Wood⁷⁴, Yingji Ji⁷⁴, Zishan Gao^{75,76,77}, Simon
20 Haworth^{35,78}, Ruth E Mitchell^{35,79}, Jin Fang Chai⁸⁰, Mette Aadahl^{81,82}, Anne A Bjerregaard⁸¹, Jie
21 Yao⁸³, Ani Manichaikul⁸⁴, PhD Wen-Jane⁸⁵, PhD Chao A⁸⁶, Helen R Warren^{87,88}, Julia Ramirez⁸⁷,
22 Jette Bork-Jensen⁸⁹, Line L Kårhus⁸¹, Anuj Goel^{90,91}, Maria Sabater-Lleal^{92,93}, Raymond
23 Noordam⁹⁴, Pala Mauro⁹⁵, Floris Matteo^{96,95}, Aaron F McDaid^{97,98}, Pedro Marques-Vidal⁹⁹,
24 Matthias Wielscher¹⁰⁰, Stella Trompet^{101,102}, Naveed Sattar¹⁰³, Line T Møllehave⁸¹, Matthias
25 Munz¹⁰⁴, Lingyao Zeng^{105,106}, Jianfeng Huang¹⁰⁷, Bin Yang¹⁰⁷, Alaitz Poveda¹⁰⁸, Azra Kurbasic¹⁰⁸,

26 Sebastian Schönherr¹⁰⁹, Lukas Forer¹⁰⁹, Markus Scholz^{110,111}, Tessel E. Galesloot¹¹², Jonathan P.
27 Bradfield¹¹³, Sanni E Ruotsalainen³⁸, E Warwick Daw¹¹⁴, Joseph M Zmuda¹¹⁵, Jonathan S
28 Mitchell¹¹⁶, Christian Fuchsberger¹¹⁶, Henry Christensen¹¹⁷, Jennifer A Brody¹¹⁸, Phuong Le^{119,120},
29 Mary F Feitosa¹¹⁴, Mary K Wojczynski¹¹⁴, Daiane Hemerich¹²¹, Michael Preuss¹²¹, Massimo
30 Mangino^{122,123}, Paraskevi Christofidou¹²², Niek Verweij¹²⁴, Jan W Benjamins¹²⁴, Jorgen
31 Engmann^{125,126}, Tsao L. Noah¹²⁷, Anurag Verma¹, Roderick C Sliker^{128,129}, Ken Sin Lo¹³⁰, Nuno R
32 Zilhao¹³¹, Marcus E Kleber^{132,133}, Graciela E Delgado¹³², Shaofeng Huo¹³⁴, Daisuke D Ikeda¹³⁵,
33 Hiroyuki Iha¹³⁵, Jian Yang^{136,137,138}, Jun Liu^{139,140}, Ayşe Demirkan^{141,142}, Hampton L Leonard^{143,144},
34 Jonathan Marten¹⁴⁵, Carina Emmel¹⁴⁶, Børge Schmidt¹⁴⁶, Laura J Smyth¹⁴⁷, Marisa Cañadas-
35 Garre^{147,148,149,150}, Chaolong Wang^{151,152}, Masahiro Nakatochi¹⁵³, Andrew Wong¹⁵⁴, Nina Hutri-
36 Kähönen¹⁵⁵, Xueling Sim⁸⁰, Rui Xia¹⁵⁶, Alicia Huerta-Chagoya¹⁵⁷, Juan Carlos Fernandez-
37 Lopez¹⁵⁸, Valeriya Lyssenko^{159,160}, Suraj S Nongmaithem¹⁶¹, Alagu Sankareswaran^{161,162},
38 Marguerite R Irvin¹⁵⁴, Christopher Oldmeadow¹⁶³, Han-Na Kim^{164,165}, Seungho Ryu^{166,167}, Paul RHJ
39 Timmers^{168,145}, Liubov Arbeeveva¹⁶⁹, Rajkumar Dorajoo^{152,170}, Leslie A Lange¹⁷¹, Gauri Prasad^{172,173},
40 Laura Lorés-Motta¹⁷⁴, Marc Pauper¹⁷⁴, Jirong Long¹⁷⁵, Xiaohui Li⁸³, Elizabeth Theusch¹⁷⁶,
41 Fumihiko Takeuchi¹⁷⁷, Cassandra N Spracklen^{178,179}, Anu Loukola³⁸, Sailalitha Bollepalli³⁸,
42 Sophie C Warner^{180,181}, Ya Xing Wang¹⁸², Wen B. Wei¹⁸³, Teresa Nutile¹⁸⁴, Daniela Ruggiero^{184,185},
43 Yun Ju Sung¹⁸⁶, Shufeng Chen¹⁰⁷, Fangchao Liu¹⁰⁷, Jingyun Yang^{187,188}, Katherine A Kentistou¹⁶⁸,
44 Bernhard Banas¹⁸⁹, Anna Morgan¹⁹⁰, Karina Meidtnr^{191,192}, Lawrence F Bielak⁵⁸, Jennifer A
45 Smith^{58,57}, Prashantha Hebbar¹⁹³, Aliko-Eleni Farmaki^{194,195}, Edith Hofer^{196,197}, Maoxuan Lin¹⁹⁸, Maria
46 Pina Concas¹⁹⁹, Simona Vaccargiu²⁰⁰, Peter J van der Most²⁰¹, Niina Pitkänen^{202,203}, Brian E
47 Cade^{204,205}, Sander W. van der Laan²⁰⁶, Kumaraswamy Naidu Chitralla^{207,208}, Stefan Weiss²⁰⁹, Amy
48 R Bentley²¹⁰, Ayo P Doumatey²¹⁰, Adebawale A Adeyemo²¹⁰, Jong Young Lee²¹¹, Eva RB
49 Petersen²¹², Aneta A Nielsen²¹³, Hyeok Sun Choi²¹⁴, Maria Nethander^{215,216}, Sandra Freitag-Wolf¹⁷,
50 Lorraine Southam^{218,47}, Nigel W Rayner^{219,220,47,218}, Carol A Wang²²¹, Shih-Yi Lin^{222,223,224}, Jun-Sing

51 Wang^{225,226}, Christian Couture²²⁷, Leo-Pekka Lyytikäinen^{228,229}, Kjell Nikus^{230,231}, Gabriel Cuellar-
52 Partida²³², Henrik Vestergaard^{89,233}, Bertha Hidalgo²³⁴, Olga Giannakopoulou⁴, Qiuyin Cai¹⁷⁵,
53 Morgan O Obura¹²⁸, Jessica van Setten²³⁵, Karen Y. He²³⁶, Hua Tang²³⁷, Natalie Terzikhan²³⁸, Jae
54 Hun Shin²¹⁴, Rebecca D Jackson²³⁹, Alexander P Reiner²⁴⁰, Lisa Warsinger Martin²⁴¹, Zhengming
55 Chen^{53,54}, Liming Li²⁴², Takahisa Kawaguchi⁷⁰, Joachim Thiery^{243,111}, Joshua C Bis¹¹⁸, Lenore J
56 Launer²⁴⁴, Huaixing Li²⁴⁵, Mike A Nalls^{143,144}, Olli T Raitakari^{246,247,248}, Sahoko Ichihara²⁴⁹, Sarah H
57 Wild²⁵⁰, Christopher P Nelson^{180,181}, Harry Campbell¹⁶⁸, Susanne Jäger^{191,192}, Toru Nabika²⁵¹, Fahd
58 Al-Mulla¹⁹³, Harri Niinikoski^{252,253}, Peter S Braund^{180,181}, Ivana Kolcic²⁵⁴, Peter Kovacs²⁵⁵, Tota
59 Giardoglou²⁵⁶, Tomohiro Katsuya^{257,258}, Dominique de Kleijn²⁵⁹, Gert J. de Borst²⁵⁹, Eung Kweon
60 Kim²⁶⁰, Hieab H.H. Adams^{238,261}, M. Arfan Ikram²³⁸, Xiaofeng Zhu²³⁶, Folkert W Asselbergs²³⁵,
61 Adriaan O Kraaijeveld²³⁵, Joline WJ Beulens^{128,262}, Xiao-Ou Shu¹⁷⁵, Loukianos S Rallidis²⁶³, Oluf
62 Pedersen⁸⁹, Torben Hansen⁸⁹, Paul Mitchell²⁶⁴, Alex W Hewitt^{265,266}, Mika Kähönen^{267,268}, Louis
63 Pérusse^{227,269}, Claude Bouchard²⁷⁰, Anke Tönjes²⁷¹, Yii-Der Ida Chen⁸³, Craig E Pennell²²¹, Trevor
64 A Mori²⁷², Wolfgang Lieb²⁷³, Andre Franke²⁷⁴, Claes Ohlsson^{215,275}, Dan Mellström^{215,276}, Yoon Shin
65 Cho²¹⁴, Hyejin Lee²⁷⁷, Jian-Min Yuan^{278,279}, Woon-Puay Koh^{280,281}, Sang Youl Rhee²⁸², Jeong-Taek
66 Woo²⁸², Iris M Heid¹¹, Klaus J Stark¹¹, Martina E Zimmermann¹¹, Henry Völzke²⁸³, Georg
67 Homuth²⁰⁹, Michele K Evans²⁸⁴, Alan B Zonderman²⁸⁴, Ozren Polasek^{254,285}, Gerard Pasterkamp²⁰⁶,
68 Imo E Hofer²⁰⁶, Susan Redline^{204,205}, Katja Pahkala^{202,203,286}, Albertine J Oldehinkel²⁸⁷, Harold
69 Snieder²⁰¹, Ginevra Biino²⁸⁸, Reinhold Schmidt¹⁹⁶, Helena Schmidt²⁸⁹, Stefania Bandinelli²⁹⁰,
70 George Dedoussis¹⁹⁴, Thangavel Alphonse Thanaraj¹⁹³, Patricia A Peyser⁵⁸, Norihiro Kato¹⁷⁷,
71 Matthias B Schulze^{191,192,291}, Giorgia Grotto^{292,199}, Carsten A Böger^{189,293,294}, Bettina Jung^{189,293,294}, Peter
72 K Joshi¹⁶⁸, David A Bennett^{187,188}, Philip L De Jager^{295,296}, Xiangfeng Lu¹⁰⁷, Vasiliki Mamakou^{297,298},
73 Morris Brown^{299,88}, Mark J Caulfield^{87,88}, Patricia B Munroe^{87,88}, Xiuqing Guo⁸³, Marina Ciullo^{184,185},
74 Jost B. Jonas^{300,182,301,302}, Nilesh J Samani^{180,181}, Jaakko Kaprio³⁸, Päivi Pajukanta³⁰³, Teresa Tusié-
75 Luna^{304,305}, Carlos A Aguilar-Salinas³⁰⁶, Linda S Adair^{307,308}, Sonny Augustin Bechayda^{309,310}, H.

76 Janaka de Silva³¹¹, Ananda R Wickremasinghe³¹², Ronald M Krauss³¹³, Jer-Yuarn Wu³¹⁴, Wei
77 Zheng¹⁷⁵, Anneke I den Hollander¹⁷⁴, Dwaipayana Bharadwaj^{173,315}, Adolfo Correa³¹⁶, James G
78 Wilson³¹⁷, Lars Lind³¹⁸, Chew-Kiat Heng³¹⁹, Amanda E Nelson^{169,320}, Yvonne M Golightly^{169,321,322,323},
79 James F Wilson^{168,145}, Brenda Penninx^{324,325}, Hyung-Lae Kim³²⁶, John Attia^{327,163}, Rodney J Scott^{327,163},
80 D C Rao³²⁸, Donna K Arnett³²⁹, Mark Walker³³⁰, Laura J Scott¹³, Heikki A Koistinen^{39,331,332}, Giriraj
81 R Chandak^{161,162,333}, Josep M Mercader^{334,335,336}, Teresa Tusie-Luna³³⁷, Carlos Aguilar-Salinas³³⁸,
82 Clicerio Gonzalez Villalpando³³⁹, Lorena Orozco³⁴⁰, Myriam Fornage^{156,341}, E Shyong Tai^{342,80}, Rob
83 M van Dam^{80,342}, Terho Lehtimäki^{228,229}, Nish Chaturvedi³⁴³, Mitsuhiro Yokota³⁴⁴, Jianjun Liu¹⁵²,
84 Dermot F Reilly³⁴⁵, Amy Jayne McKnight¹⁴⁷, Frank Kee¹⁴⁷, Karl-Heinz Jöckel¹⁴⁶, Mark I
85 McCarthy^{62,346}, Colin NA Palmer³⁴⁷, Veronique Vitart¹⁴⁵, Caroline Hayward¹⁴⁵, Eleanor
86 Simonsick³⁴⁸, Cornelia M van Duijn^{139,140}, Zi-Bing Jin^{349,350}, Fan Lu³⁵⁰, Haretsugu Hishigaki¹³⁵, Xu
87 Lin¹³⁴, Winfried März^{351,352,132}, Vilmundur Gudnason^{131,353}, Jean-Claude Tardif¹³⁰, Guillaume
88 Lettre¹³⁰, Leen M t Hart^{354,355,356}, Petra JM Elders³⁵⁷, Daniel J Rader³⁵⁸, Scott M Damrauer^{359,360},
89 Meena Kumari³⁶¹, Mika Kivimäki¹²⁶, Pim van der Harst³⁶², Tim D Spector¹²², Ruth J.F. Loos^{121,363,89},
90 Michael A Province¹¹⁴, Esteban J Parra¹¹⁹, Miguel Cruz³⁶⁴, Bruce M Psaty^{118,365,366}, Ivan
91 Brandslund^{117,367}, Peter P Pramstaller¹¹⁶, Charles N Rotimi³⁶⁸, Kaare Christensen³⁶⁹, Samuli
92 Ripatti^{38,370,371}, Elisabeth Widén³⁸, Hakon Hakonarson^{372,373}, Struan F.A. Grant^{373,374,375}, Lambertus
93 ALM Kiemeny³⁷⁶, Jacqueline de Graaf³⁷⁶, Markus Loeffler^{110,111}, Florian Kronenberg¹⁰⁹,
94 Dongfeng Gu^{107,377}, Jeanette Erdmann³⁷⁸, Heribert Schunkert^{105,106}, Paul W Franks¹⁰⁸, Allan
95 Linneberg^{81,82}, J. Wouter Jukema^{101,379}, Amit V Khera^{380,381,382,383}, Minna Männikkö³⁸⁴, Marjo-Riitta
96 Jarvelin^{100,385,386}, Zoltan Kutalik^{97,98}, Cucca Francesco^{387,388}, Dennis O Mook-Kanamori^{389,390}, Ko
97 Willems van Dijk^{391,392,393}, Hugh Watkins^{90,91}, David P Strachan³⁹⁴, Niels Grarup⁹⁹, Peter Sever³⁹⁵,
98 Neil Poulter³⁹⁶, Wayne Huey-Herng Sheu^{397,398}, Jerome I Rotter⁸³, Thomas M Dantoft⁸¹, Fredrik
99 Karpe^{399,400}, Matt J Neville^{399,400}, Nicholas J Timpson^{35,79}, Ching-Yu Cheng^{401,402}, Tien-Yin Wong^{401,402},
100 Chiea Chuen Khor¹⁵², Hengtong Li⁴⁰³, Charumathi Sabanayagam^{401,402}, Annette Peters^{77,404,405},

101 Christian Gieger^{76,77,405}, Andrew T Hattersley⁴⁰⁶, Nancy L Pedersen⁴⁰⁷, Patrik KE Magnusson⁴⁰⁷,
102 Dorret I Boomsma^{72,408}, Eco JC de Geus^{72,408}, L Adrienne Cupples^{5,409}, Joyce B.J. van Meurs^{71,140},
103 Arfan Ikram¹⁴⁰, Mohsen Ghanbari^{140,410}, Penny Gordon-Larsen^{307,308}, Wei Huang⁴¹¹, Young Jin
104 Kim²⁴, Yasuharu Tabara⁷⁰, Nicholas J Wareham⁶⁸, Claudia Langenberg⁶⁸, Eleftheria
105 Zeggini^{218,47,412}, Jaakko Tuomilehto^{39,413,414}, Johanna Kuusisto⁴¹⁵, Markku Laakso⁴¹⁵, Erik
106 Ingelsson^{7,416,417,418}, Goncalo Abecasis^{13,419}, John C Chambers^{420,64,65,421}, Jaspal S Kooner^{65,66,422,423}, Paul S
107 de Vries⁶³, Alanna C Morrison⁶³, Scott Hazelhurst^{61,424}, Michèle Ramsay⁶¹, Kari E. North⁴²⁵,
108 Martha Daviglus⁴²⁶, Peter Kraft^{59,427}, Nicholas G Martin⁴²⁸, John B Whitfield⁴²⁸, Shahid Abbas⁴²⁹,
109 Danish Saleheen^{55,430,431}, Robin G Walters^{53,54,432}, Michael V Holmes^{53,54,433}, Corri Black⁴³⁴, Blair H
110 Smith⁴³⁵, Aris Baras⁴¹⁹, Anne E Justice⁴³⁶, Julie E Buring^{50,437}, Paul M Ridker^{50,437}, Daniel I
111 Chasman^{50,437}, Charles Kooperberg⁴⁹, Gen Tamiya⁴⁶, Masayuki Yamamoto⁴⁶, David A van Heel⁴⁸,
112 Richard C Trembath⁴³⁸, Wei-Qi Wei⁴³⁹, Gail P Jarvik⁴⁴⁰, Bahram Namjou⁴⁴¹, M. Geoffrey
113 Hayes^{442,443,444}, Marylyn D Ritchie⁴⁰, Pekka Jousilahti³⁹, Veikko Salomaa³⁹, Kristian Hveem^{34,445,446},
114 Bjørn Olav Åsvold^{34,445,447}, Michiaki Kubo⁴⁴⁸, Yoichiro Kamatani^{25,449}, Yukinori Okada^{27,25,450,451},
115 Yoshinori Murakami⁴⁵², Bong-Jo Kim⁴⁵³, Unnur Thorsteinsdottir^{21,454}, Kari Stefansson^{21,454}, Jifeng
116 Zhang³, Y Eugene Chen³, Yuk-Lam Ho⁴⁵⁵, Julie A Lynch^{456,457}, Daniel Rader⁴⁵⁸, Philip S Tsao^{6,7,459},
117 Kyong-Mi Chang^{460,458}, Kelly Cho^{455,461}, Christopher J O'Donnell^{455,461}, John M Gaziano^{455,461}, Peter
118 Wilson^{17,462}, Karen L Mohlke¹⁷⁸, Timothy M Frayling⁷⁴, Joel N Hirschhorn^{463,10,464}, Sekar
119 Kathiresan^{465,381,383}, Michael Boehnke¹³, Million Veterans Program, Global Lipids Genetics
120 Consortium, Struan Grant^{1,374}, Pradeep Natarajan^{466,467,20,468}, Yan V Sun^{16,17}, Andrew P Morris⁴⁶⁹,
121 Panos Deloukas^{4,470}, Gina Peloso⁴⁷¹, Themistocles L Assimes^{6,7,459}, Cristen J Willer^{3,472,148}, Xiang
122 Zhu^{473,474,475,476}, Christopher D Brown¹

123

124 ¹Department of Genetics, Perelman School of Medicine, University of Pennsylvania,
125 Philadelphia, PA 19104, USA, ²Department of Genetics, Stanford University School of
126 Medicine, Stanford, CA, USA, ³Department of Internal Medicine, Division of Cardiology,
127 University of Michigan, Ann Arbor, MI, 48109, USA, ⁴William Harvey Research Institute,
128 Barts and the London School of Medicine and Dentistry, Queen Mary University of London,
129 Charterhouse square, EC1M 6BQ, UK, ⁵Department of Biostatistics, Boston University
130 School of Public Health, 801 Massachusetts Ave, Boston, MA 02118, USA, ⁶VA Palo Alto
131 Health Care Systems, Palo Alto, California, USA, ⁷Department of Medicine, Division of
132 Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA 94305,
133 USA, ⁸Department of Pathology and Laboratory Medicine, University of Pennsylvania,
134 Philadelphia, PA, USA, ⁹Endocrinology, Boston Childrens Hospital, Boston 02115 MA, USA,
135 ¹⁰Medical and Population Genetics, Broad Institute, 75 Ames street, Cambridge, MA
136 02142, USA, ¹¹Department of Genetic Epidemiology, University of Regensburg, Regensburg,
137 Germany, ¹²McDonnell Genome Institute and Department of Medicine, Washington
138 University, St. Louis, MO, 63108, USA, ¹³Department of Biostatistics, Center for Statistical
139 Genetics, University of Michigan, Ann Arbor, MI, USA, ¹⁴Department of Computational
140 Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI, USA, ¹⁵Clinical
141 Pharmacology, William Harvey Research Institute, Barts and The London School of
142 Medicine and Dentistry, Queen Mary University of London, London, EC1M 6BQ UK,
143 ¹⁶Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta,
144 Georgia, USA, ¹⁷Atlanta VA Health Care System, Decatur, GA, USA, ¹⁸Malcolm Randall VA
145 Medical Center, Gainesville, FL, USA, ¹⁹Division of Vascular Surgery and Endovascular
146 Therapy, University of Florida College of Medicine, Gainesville, FL, USA, ²⁰Program in
147 Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA,
148 USA, ²¹deCODE genetics/Amgen, Inc. Sturlugata 8, Reykjavik, 102, Iceland, ²²School of

149 Engineering and Natural Sciences, University of Iceland, Sæmundargötu 2, Reykjavik, 102,
150 Iceland, ²³Department of Clinical Biochemistry, Landspítali - National University Hospital of
151 Iceland, Hringbraut, Reykjavik, 101, Iceland, ²⁴Division of Genome Science, Department of
152 Precision Medicine, National Institute of Health, Chungcheongbuk-do, South Korea,
153 ²⁵Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences,
154 Yokohama, Japan, ²⁶Department of Ophthalmology, Graduate School of Medical Sciences,
155 Kyushu University, Fukuoka, Japan, ²⁷Department of Statistical Genetics, Osaka University
156 Graduate School of Medicine, Osaka, Japan, ²⁸Laboratory for Statistical Analysis, RIKEN
157 Center for Integrative Medical Sciences, ²⁹Department of Allergy and Rheumatology,
158 Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, ³⁰Laboratory for
159 Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences,
160 Yokohama, Japan, ³¹Program in Medical and Population Genetics, Broad Institute of MIT and
161 Harvard, Cambridge, MA, USA., ³²Department of Biomedical Informatics, Harvard Medical
162 School, Boston, MA, USA, ³³Analytic and Translational Genetics Unit, Massachusetts
163 General Hospital, Boston, Massachusetts, USA, ³⁴K.G. Jebsen Center for Genetic
164 Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of
165 Science and Technology, Trondheim, Norway, ³⁵MRC Integrative Epidemiology Unit (IEU),
166 Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8
167 2BN, UK, ³⁶Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital,
168 Trondheim, Norway, ³⁷Division of Medicine and Laboratory Sciences, University of
169 Oslo, Norway, ³⁸Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of
170 Helsinki, Tukholmankatu 8, 00014 Helsinki, Finland, ³⁹Department of Public Health and
171 Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland, ⁴⁰Department of
172 Genetics, Institute for Biomedical Informatics, University of Pennsylvania, Perelman School
173 of Medicine, Philadelphia, PA 19104, USA, ⁴¹Center for Genetic Medicine, Northwestern

174 University, Feinberg School of Medicine, Chicago, IL 60611, USA, ⁴²Department of
175 Medicine (Medical Genetics), University of Washington, WA, USA, ⁴³Division of Biomedical
176 Informatics, Cincinnati Children's Hospital Medical Center, OH, USA, ⁴⁴Division of Clinical
177 Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville,
178 TN, USA, ⁴⁵Department of Cardiovascular Medicine and the Gonda Vascular Center, Mayo
179 Clinic, Rochester, MN, USA, ⁴⁶Tohoku Medical Megabank Organization, Tohoku University,
180 Sendai 980-8573, Japan, ⁴⁷Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, UK,
181 ⁴⁸Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary
182 University of London, London, UK, ⁴⁹Fred Hutchinson Cancer Research Center, Division of
183 Public Health Sciences, Seattle WA 9810, USA, ⁵⁰Division of Preventive Medicine, Brigham
184 and Women's Hospital, Boston, MA 02215, USA, ⁵¹Centre for Genomic and Experimental
185 Medicine, Institute of Genetics and Cancer, University of Edinburgh, Western General
186 Hospital, Edinburgh EH4 2XU, United Kingdom, ⁵²Usher Institute, The University of
187 Edinburgh, Nine, Edinburgh Bioquarter, 9 Little France Road, Edinburgh, EH16 4UX, UK,
188 ⁵³Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of
189 Population Health, University of Oxford, Oxford OX3 7LF, UK, ⁵⁴Medical Research Council
190 Population Health Research Unit, Nuffield Department of Population Health, University of
191 Oxford, Oxford OX3 7LF, UK, ⁵⁵Center for Non-Communicable Diseases, Karachi, Sindh,
192 Pakistan, ⁵⁶Department of Population Medicine, Qatar University College of Medicine, QU
193 Health, Doha, Qatar, ⁵⁷Survey Research Center, Institute for Social Research, University of
194 Michigan, Ann Arbor, MI, 48104, USA, ⁵⁸Department of Epidemiology, School of Public
195 Health, University of Michigan, Ann Arbor, MI, 48109, USA, ⁵⁹Program in Genetic
196 Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard T.H. Chan
197 School of Public Health, 677 Huntington Avenue, Boston, MA, 02115, USA, ⁶⁰Department of
198 Epidemiology, Gillings School of Global Public Health, University of North Carolina at

199 Chapel Hill, NC USA, ⁶¹Sydney Brenner Institute for Molecular Bioscience, Faculty of Health
200 Sciences, University of the Witwatersrand, Johannesburg, South Africa, ⁶²Wellcome Centre
201 for Human Genetics, University of Oxford, UK, ⁶³Human Genetics Center, Department of
202 Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, The
203 University of Texas Health Science Center at Houston, Houston, Texas, 77030, USA,
204 ⁶⁴Department of Epidemiology and Biostatistics, Imperial College London, London W2 1PG,
205 UK, ⁶⁵Department of Cardiology, Ealing Hospital, London North West University Healthcare
206 NHS Trust, Middlesex UB1 3HW, UK, ⁶⁶Imperial College Healthcare NHS Trust, London
207 W12 0HS, UK, ⁶⁷Department of Medical Sciences, Molecular Epidemiology and Science for
208 Life Laboratory, Uppsala University, Uppsala, Sweden, ⁶⁸MRC Epidemiology Unit,
209 University of Cambridge School of Clinical Medicine, Cambridge, CB2 0QQ, UK,
210 ⁶⁹Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care,
211 University of Cambridge, Strangeways Research Laboratory, Wort's Causeway, Cambridge
212 CB1 8RN, UK, ⁷⁰Center for Genomic Medicine, Kyoto University Graduate School of
213 Medicine, Kyoto, Japan, ⁷¹Department of Internal Medicine, Erasmus MC, University Medical
214 Center Rotterdam, the Netherlands, ⁷²Department of Biological Psychology, Vrije Universiteit
215 Amsterdam, The Netherlands, ⁷³Amsterdam Public Health Research Institute, Amsterdam
216 UMC, the Netherlands, ⁷⁴Genetics of Complex Traits, University of Exeter Medical School,
217 University of Exeter, Exeter, EX2 5DW, UK, ⁷⁵Department of Clinical Acupuncture and
218 Moxibustion, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210029, China,
219 ⁷⁶Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research
220 Center for Environmental Health, Neuherberg, Germany, ⁷⁷Institute of Epidemiology,
221 Helmholtz Zentrum München, German Research Center for Environmental Health,
222 Neuherberg, Germany, ⁷⁸Bristol Dental School, University of Bristol, Lower Maudlin Street,
223 Bristol BS1 2LY, United Kingdom, ⁷⁹Population Health Sciences, Bristol Medical School,

224 University of Bristol, Oakfield Grove, Bristol, BS8 2BN, United Kingdom, ⁸⁰Saw Swee Hock
225 School of Public Health, National University of Singapore and National University Health
226 System, 117549, Singapore, ⁸¹Center for Clinical Research and Prevention, Bispebjerg and
227 Frederiksberg Hospital, Copenhagen, Denmark, ⁸²Department of Clinical Medicine, Faculty of
228 Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, ⁸³The
229 Institute for Translational Genomics and Population Sciences, Department of Pediatrics,
230 Lundquist Institute for Biomedical Innovations (Formerly LABioMed) at Harbor-UCLA
231 Medical Center, Torrance, CA 90502, USA, ⁸⁴Center for Public Health Genomics, University
232 of Virginia, Charlottesville, VA 22903 USA, ⁸⁵Department of Medical Research, Taichung
233 Veterans General Hospital, Taichung, Taiwan; No. 1650, Sec. 4, Taiwan Boulevard,
234 Taichung City 40705, Taiwan, ⁸⁶Institute of Population Health Sciences, National Health
235 Research Institutes, 35 Keyan Road, Zhunan Town, Miaoli County 350, Taiwan, ROC,
236 ⁸⁷William Harvey Research Institute, Barts and The London School of Medicine and
237 Dentistry, Queen Mary University of London, John Vane Science Centre, Charterhouse
238 Square, London, EC1M 6BQ, UK, ⁸⁸NIHR Barts Cardiovascular Biomedical Research Centre,
239 Barts and The London School of Medicine and Dentistry, Queen Mary University of London,
240 London, EC1M 6BQ, UK, ⁸⁹Novo Nordisk Foundation Center for Basic Metabolic Research,
241 Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark,
242 ⁹⁰Division of Cardiovascular Medicine, Radcliffe Department of Medicine, John Radcliffe
243 Hospital, University of Oxford, Oxford. UK. OX3 9DU, ⁹¹Wellcome Centre for Human
244 Genetics, University of Oxford, Oxford. UK. OX3 7BN, ⁹²Unit of Genomics of Complex
245 Diseases. Sant Pau Biomedical Research Institute (IIB Sant Pau), Barcelona, Spain,
246 ⁹³Cardiovascular Medicine Unit, Department of Medicine, Karolinska Institutet, Center for
247 Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden, ⁹⁴Department of
248 Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center,

249 Leiden, the Netherlands, ⁹⁵Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle
250 Ricerche, Italy, ⁹⁶Dipartimento di Scienze Biomediche, Università degli Studi di Sassari,
251 Sardinia, Italy, ⁹⁷University Center for Primary Care and Public Health, University of
252 Lausanne, Rte de Berne 113, Lausanne, 1010, Switzerland, ⁹⁸Swiss Institute of
253 Bioinformatics, Lausanne, 1015, Switzerland, ⁹⁹Department of Medicine, Internal Medicine,
254 Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, Lausanne,
255 1011, Switzerland, ¹⁰⁰Department of Epidemiology and Biostatistics, MRC-PHE Centre for
256 Environment and Health, School of Public Health, Imperial College London, London, UK,
257 ¹⁰¹Dept of Cardiology, Leiden University Medical Center, Leiden, the Netherlands, ¹⁰²Dept of
258 Internal Medicine, Section of Gerontology and Geriatrics, Leiden university Medical Center,
259 Leiden, the Netherlands, ¹⁰³BHF Glasgow Cardiovascular Research Centre, Faculty of
260 Medicine, Glasgow, United Kingdom, ¹⁰⁴Institute for Cardiogenetics, University of Lübeck,
261 DZHK (German Research Centre for Cardiovascular Research), partner site
262 Hamburg/Lübeck/Kiel, University Heart Center Lübeck, Lübeck and Charité – University
263 Medicine Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu
264 Berlin, and Berlin Institute of Health, Institute for Dental and Craniofacial Sciences,
265 Department of Periodontology and Synoptic Dentistry, Berlin, Germany, ¹⁰⁵Deutsches
266 Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Technische Universität
267 München, Munich, Germany., ¹⁰⁶Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK)
268 e.V., partner site Munich Heart Alliance, Munich, Germany., ¹⁰⁷Key Laboratory of
269 Cardiovascular Epidemiology & Department of Epidemiology, State Key Laboratory of
270 Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases,
271 Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037,
272 China, ¹⁰⁸Lund University Diabetes Centre, Malmö, Sweden, ¹⁰⁹Institute of Genetic
273 Epidemiology, Department of Genetics and Pharmacology, Medical University of Innsbruck,

274 Innsbruck, Austria and German Chronic Kidney Disease Study, Austria, ¹¹⁰Institute for
275 Medical Informatics, Statistics and Epidemiology, University of Leipzig, Haertelstrasse 16-
276 18, 04107 Leipzig, Germany, ¹¹¹LIFE Research Centre for Civilization Diseases, University of
277 Leipzig, Philipp-Rosenthal-Straße 27, 04103 Leipzig, Germany, ¹¹²Radboud university
278 medical center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands,
279 ¹¹³Quantinum Research LLC, Wayne, PA, 19087 USA, ¹¹⁴Division of Statistical Genomics,
280 Department of Genetics; Washington University School of Medicine; St. Louis, MO, USA,
281 ¹¹⁵Department of Epidemiology; University of Pittsburgh; Pittsburgh, PA, USA, ¹¹⁶Institute for
282 Biomedicine, Eurac Research, Affiliated Institute of the University of Lübeck, Via Galvani
283 31, 39100, Bolzano, Italy, ¹¹⁷Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle,
284 Denmark, ¹¹⁸Cardiovascular Health Research Unit, Department of Medicine, University of
285 Washington, Seattle, 98101, USA, ¹¹⁹Department of Anthropology, University of Toronto at
286 Mississauga, Mississauga, ON L5L 1C6, Canada, ¹²⁰Department of Computer Science,
287 University of Toronto, Toronto, ON M5S 2E4, Canada, ¹²¹The Charles Bronfman Institute for
288 Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA,
289 ¹²²Department of Twin Research and Genetic Epidemiology, King's College London, London
290 SE1 7EH, UK, ¹²³NIHR Biomedical Research Centre at Guy's and St Thomas' Foundation
291 Trust, London SE1 9RT, UK, ¹²⁴Department of Cardiology, University of Groningen,
292 University Medical Center Groningen, 9700RB Groningen, the Netherlands, ¹²⁵Institute of
293 Cardiovascular Sciences, University College London, Gower Street, WC1E 6BT London,
294 UK, ¹²⁶Department of Epidemiology and Public Health, University College London, 1-19
295 Torrington Place, WC1E 6BT London, United Kingdom, ¹²⁷Department of Surgery, University
296 of Pennsylvania, Philadelphia, PA, ¹²⁸Amsterdam UMC, Department of Epidemiology and
297 Data Science, Amsterdam Public Health Research Institute, Amsterdam, 1081HV, the
298 Netherlands, ¹²⁹Leiden University Medical Center, Department of Cell and Chemical Biology,

299 Leiden, 2333ZA, the Netherlands, ¹³⁰Montreal Heart Institute, Université de Montréal, 5000
300 Belanger street, Montreal, PQ, Canada H1T1C8, ¹³¹Icelandic Heart Association, 201
301 Kopavogur, Iceland, ¹³²Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg
302 University, 68167 Mannheim, Germany, ¹³³SYNLAB MVZ Humangenetik Mannheim GmbH,
303 68163 Mannheim, Germany, ¹³⁴Shanghai Institute of Nutrition and Health, University of
304 Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai, China, ¹³⁵Biomedical
305 Technology Research Center, Tokushima Research Institute, Otsuka Pharmaceutical Co.,
306 Ltd., Tokushima, Japan, ¹³⁶School of Life Sciences, Westlake University, Hangzhou, Zhejiang
307 310024, China, ¹³⁷Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou,
308 Zhejiang 310024, China, ¹³⁸Institute for Molecular Bioscience, The University of Queensland,
309 Brisbane, Queensland 4072, Australia, ¹³⁹Nuffield Department of Population Health,
310 University of Oxford, Oxford, United Kingdom, ¹⁴⁰Department of Epidemiology, Erasmus
311 MC, University Medical Center Rotterdam, the Netherlands, ¹⁴¹Department of Epidemiology,
312 Erasmus MC, University Medical Center, Rotterdam, the Netherlands, ¹⁴²Section of Statistical
313 Multi-omics, Department of Clinical and Experimental research, University of Surrey,
314 Guildford, Surrey, UK, ¹⁴³Laboratory of Neurogenetics, National Institute on Aging, NIH,
315 Bethesda MD, USA, ¹⁴⁴Data Tecnica International, Glen Echo MD, USA, ¹⁴⁵MRC Human
316 Genetics Unit, Institute of Genetics and Cancer, University of Edinburgh, Western General
317 Hospital, Crewe Road, Edinburgh, EH4 2XU, Scotland, ¹⁴⁶Institute for Medical Informatics,
318 Biometrie and Epidemiology, University of Duisburg-Essen, Essen, Germany, ¹⁴⁷Centre for
319 Public Health, Queen's University of Belfast, Northern Ireland, ¹⁴⁸Genomic Oncology Area,
320 GENYO, Centre for Genomics and Oncological Research: Pfizer-University of Granada-
321 Andalusian Regional Government, Granada, Spain, ¹⁴⁹Hematology Department, Hospital
322 Universitario Virgen de las Nieves, Granada, Spain, ¹⁵⁰Instituto de Investigación Biosanitaria
323 de Granada (ibs.GRANADA), Granada, Spain, ¹⁵¹Department of Epidemiology and

324 Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of
325 Science and Technology, Wuhan, China, ¹⁵²Genome Institute of Singapore, Agency for
326 Science, Technology and Research, Singapore, ¹⁵³Public Health Informatics Unit, Department
327 of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya,
328 461-8673, Japan, ¹⁵⁴University of Alabama at Birmingham, Epidemiology, School of Public
329 Health, AL, USA, ¹⁵⁵Tampere Centre for Skills Training and Simulation, Faculty of Medicine
330 and Health Technology, Tampere University, Tampere, Finland, ¹⁵⁶Brown Foundation
331 Institute of Molecular Medicine, McGovern Medical School, University of Texas Health
332 Science Center at Houston, Houston TX 77030, USA, ¹⁵⁷CONACYT, Instituto Nacional de
333 Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de Mexico, Mexico, ¹⁵⁸Departamento
334 de Genómica Computacional, Instituto Nacional de Medicina Genómica, Ciudad de Mexico,
335 Mexico, ¹⁵⁹Center for diabetes research, University of Bergen, Bergen, Norway, ¹⁶⁰Lund
336 University Diabetes Center, Lunds University, Malmö, Sweden, ¹⁶¹Genomic Research on
337 Complex diseases (GRC Group), CSIR-Centre for Cellular and Molecular Biology,
338 Hyderabad, Telangana, India, ¹⁶²Academy of Scientific and Innovative Research (AcSIR),
339 New Delhi, India, ¹⁶³Hunter Medical Research Institute, Newcastle, Australia, ¹⁶⁴Medical
340 Research Institute, Kangbuk Samsung Hospital, Sungkyunkwan University School of
341 Medicine, Seoul, 03181, Korea, ¹⁶⁵Department of Clinical Research Design & Evaluation,
342 SAIHST, Sungkyunkwan University, Seoul, 06355, Korea, ¹⁶⁶Center for Cohort Studies, Total
343 Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of
344 Medicine, Seoul, 04514, Korea, ¹⁶⁷Department of Occupational and Environmental Medicine,
345 Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, 03181,
346 Korea, ¹⁶⁸Centre for Global Health Research, Usher Institute, University of Edinburgh, Teviot
347 Place, Edinburgh, EH8 9AG, Scotland, ¹⁶⁹Thurston Arthritis Research Center, University of
348 North Carolina, Chapel Hill, North Carolina, USA, ¹⁷⁰Health Services and Systems Research,

349 Duke-NUS Medical School, 169857, Singapore, ¹⁷¹Division of Biomedical Informatics and
350 Personalized Medicine, Department of Medicine, Anschutz Medical Campus, University of
351 Colorado, Denver, Aurora, CO 80045, USA, ¹⁷²Genomics and Molecular Medicine Unit,
352 CSIR-Institute of Genomics and Integrative Biology, New Delhi - 110020, India, ¹⁷³Academy
353 of Scientific and Innovative Research, CSIR-Human Resource Development Centre,
354 Ghaziabad, Uttar Pradesh, India, ¹⁷⁴Departments of Ophthalmology and Human Genetics,
355 Radboud University Nijmegen Medical Center, Philips van Leydenlaan 15, Nijmegen, 6525
356 EX, the Netherlands, ¹⁷⁵Vanderbilt Epidemiology Center, Division of Epidemiology,
357 Vanderbilt University Medical Center, USA, ¹⁷⁶Department of Pediatrics, University of
358 California San Francisco, Oakland, CA 94609 USA, ¹⁷⁷National Center for Global Health and
359 Medicine, Tokyo, 1628655, Japan, ¹⁷⁸Department of Genetics, University of North Carolina,
360 Chapel Hill, NC 27599 USA, ¹⁷⁹Department of Biostatistics and Epidemiology, University of
361 Massachusetts-Amherst, Amherst, MA 01003 USA, ¹⁸⁰Department of Cardiovascular
362 Sciences, University of Leicester, Leicester, UK, ¹⁸¹NIHR Leicester Biomedical Research
363 Centre, Glenfield Hospital, Leicester, UK, ¹⁸²Beijing Institute of Ophthalmology, Beijing Key
364 Laboratory of Ophthalmology and Visual Sciences, Beijing Tongren Eye Center, Beijing
365 Tongren Hospital, Capital Medical University, 17 Hougou Lane, Chong Wen Men, Beijing,
366 100005, China, ¹⁸³Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical
367 University, 1 Dong Jiao Min Xiang, Dong Cheng District, Beijing, 100730, China, ¹⁸⁴Institute
368 of Genetics and Biophysics "Adriano Buzzati-Traverso" - CNR, Naples, Italy, ¹⁸⁵IRCCS
369 Neuromed, Pozzilli, Isernia, Italy, ¹⁸⁶Division of Biostatistics, Washington University, St.
370 Louis, MO 63110, USA, ¹⁸⁷Rush Alzheimer's Disease Center, Rush University Medical
371 Center, IL, USA, ¹⁸⁸Department of Neurological Sciences, Rush University Medical Center,
372 IL, USA, ¹⁸⁹Dept of Nephrology, University Hospital Regensburg, Regensburg, Germany,
373 ¹⁹⁰Institute for Maternal and Child Health—IRCCS, Burlo Garofolo, 34127 Trieste, Italy,

374 ¹⁹¹Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-
375 Rehbruecke, Nuthetal, Germany, ¹⁹²German Center for Diabetes Research (DZD), München-
376 Neuherberg, Germany, ¹⁹³Department of Genetics and Bioinformatics, Dasman Diabetes
377 Institute, Kuwait, ¹⁹⁴Department of Nutrition and Dietetics, School of Health Science and
378 Education, Harokopio University of Athens, Athens, Greece, ¹⁹⁵Department of Population
379 Science and Experimental Medicine, University College London, London, UK, ¹⁹⁶Clinical
380 Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz,
381 Austria, ¹⁹⁷Institute for Medical Informatics, Statistics and Documentation, Medical University
382 of Graz, Graz, Austria, ¹⁹⁸Massachusetts General Hospital Cancer Center, Charlestown, MA
383 02129, USA, ¹⁹⁹Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy,
384 ²⁰⁰Institute of Genetic and Biomedical Research, National Research Council of Italy, UOS of
385 Sassari, Sassari, Italy, ²⁰¹Department of Epidemiology, University of Groningen, University
386 Medical Center Groningen, Groningen, 9700 RB, the Netherlands, ²⁰²Research Centre of
387 Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland,
388 ²⁰³Centre for Population Health Research, University of Turku and Turku University Hospital,
389 Turku, Finland, ²⁰⁴Sleep Medicine and Circadian Disorders, Brigham and Women's Hospital,
390 Boston, Massachusetts 02115, USA, ²⁰⁵Division of Sleep Medicine, Harvard Medical School,
391 Boston, Massachusetts 02115, USA, ²⁰⁶Central Diagnostics Laboratory, Division Laboratories,
392 Pharmacy, and Biomedical genetics, University Medical Center Utrecht, Utrecht University,
393 Utrecht, the Netherlands, ²⁰⁷Laboratory of Epidemiology and Population Science National
394 Institute on Aging Intramural Research Program, NIH, USA, ²⁰⁸Fels Cancer Institute for
395 Personalized Medicine, Temple University Lewis Katz School of Medicine, Philadelphia,
396 PA, USA, ²⁰⁹Interfaculty Institute for Genetics and Functional Genomics, Department of
397 Functional Genomics, University of Greifswald and University Medicine Greifswald,
398 Greifswald, Germany, ²¹⁰Center for Research on Genomics and Global Health, National

399 Human Genome Research Institute, National Institutes of Health, 12 South Drive, Room
400 4047, Bethesda, MD, 20892, USA, ²¹¹Oneomics. co. ltd. 2F, Soonchunhyang Mirai Medical
401 Center 173, Buheuyng-ro, Bucheon-si Gyeonggi-do, 14585, Korea, ²¹²Department of Clinical
402 Biochemistry and Immunology, Hospital of Southern Jutland, Kresten Philipsens Vej 15,
403 6200 Aabenraa, Denmark, ²¹³Department of Clinical Biochemistry, Lillebaelt Hospital,
404 Kolding, Denmark, ²¹⁴Department of Biomedical Science, Hallym University, Chuncheon,
405 Gangwon-do 24252, Korea, ²¹⁵Centre for Bone and Arthritis Research, Department of Internal
406 Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of
407 Gothenburg, Gothenburg, Sweden, ²¹⁶Bioinformatics Core Facility, Sahlgrenska Academy,
408 University of Gothenburg, Gothenburg, Sweden, ²¹⁷Institute of Medical Informatics and
409 Statistics, Kiel University, Kiel, Germany, ²¹⁸Institute of Translational Genomics, Helmholtz
410 Zentrum München – German Research Center for Environmental Health, Neuherberg,
411 Germany, ²¹⁹Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK,
412 ²²⁰Oxford Centre for Diabetes Endocrinology and Metabolism, Oxford, UK, ²²¹School of
413 Medicine and Public Health, Faculty of Medicine and Health, University of Newcastle,
414 Newcastle, New South Wales, 2308, Australia, ²²²Center for Geriatrics and Gerontology,
415 Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung
416 Veterans General Hospital, Taichung, Taiwan, ²²³School of Medicine, National Yang-Ming
417 University, Taipei, Taiwan, ²²⁴School of Medicine, National Defense Medical Center, Taipei,
418 Taiwan, ²²⁵Division of Endocrinology and Metabolism, Department of Internal Medicine,
419 Taichung Veterans General Hospital, Taichung, Taiwan, ²²⁶Department of Medicine, School
420 of Medicine, National Yang-Ming University, Taipei, Taiwan, ²²⁷Department of Kinesiology,
421 Université Laval, Québec, Canada, ²²⁸Department of Clinical Chemistry, Fimlab Laboratories,
422 Tampere 33520, Finland, ²²⁹Department of Clinical Chemistry, Finnish Cardiovascular
423 Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere

424 University, Tampere 33014, Finland, ²³⁰Department of Cardiology, Heart Center, Tampere
425 University Hospital, Tampere 33521, Finland, ²³¹Department of Cardiology, Finnish
426 Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology,
427 Tampere University, Tampere 33014, Finland, ²³²University of Queensland Diamantina
428 Institute, Translational Research Institute, Kent St, Woolloongabba, Brisbane, QLD, 4102,
429 Australia, ²³³Department of Medicine, Bornholms Hospital, Rønne, Denmark, ²³⁴School of
430 Public Health, University of Alabama at Birmingham, AL, USA, ²³⁵Cardiology, Division
431 Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the
432 Netherlands, ²³⁶Department of Population and Quantitative Health Sciences, Case Western
433 Reserve University, Cleveland, OH, 44106, USA, ²³⁷Department of Genetics, Stanford
434 University School of Medicine Stanford, CA 94305, USA, ²³⁸Department of Epidemiology -
435 Erasmus MC - University Medical Center Rotterdam, Rotterdam, the Netherlands, ²³⁹Ohio
436 State University, Division of Endocrinology, Columbus OH 43210, USA, ²⁴⁰University of
437 Washington, Department of Epidemiology, Seattle WA 98195, USA, ²⁴¹George Washington
438 University, School of Medicine and Health Sciences, Washington DC 20037, USA,
439 ²⁴²Department of Epidemiology, School of Public Health, Peking University Health Science
440 Center, Beijing, China, ²⁴³Institute for Laboratory Medicine, University Hospital Leipzig,
441 Paul-List-Strasse 13/15, 04103 Leipzig, Germany, ²⁴⁴Laboratory of Epidemiology and
442 Population Sciences, National Institute on Aging, NIH, Baltimore, MD, 20892-9205, USA,
443 ²⁴⁵Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences,
444 Chinese Academy of Sciences, Shanghai, China, ²⁴⁶Centre for Population Health Research,
445 University of Turku and Turku University Hospital, Finland, ²⁴⁷Research Centre of Applied
446 and Preventive Cardiovascular Medicine, University of Turku, Finland, ²⁴⁸Department of
447 Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland,
448 ²⁴⁹Department of Environmental and Preventive Medicine, Jichi Medical University School of

449 Medicine, Shimotsuke, 329-0498, Japan, ²⁵⁰Centre for Population Health Sciences, Usher
450 Institute, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland,
451 ²⁵¹Department of Functional Pathology, Shimane University School of Medicine, Izumo,
452 6938501, Japan, ²⁵²Department of Pediatrics and Adolescent Medicine, Turku University
453 Hospital and University of Turku, Turku, Finland, ²⁵³Department of Physiology, University of
454 Turku, Turku, Finland, ²⁵⁴Faculty of Medicine, University of Split, Šoltanska 2, HR-21000,
455 Split, Croatia, ²⁵⁵Medical Department III – Endocrinology, Nephrology, Rheumatology,
456 University of Leipzig Medical Center, Liebigstr. 21, 04103 Leipzig, Germany, ²⁵⁶Department
457 of Nutrition-Dietetics, Harokopio University, Eleftheriou Venizelou, Athens, 17676, Greece,
458 ²⁵⁷Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine,
459 Suita, 5650871, Japan, ²⁵⁸Department of Geriatric and General Medicine, Osaka University
460 Graduate School of Medicine, Suita, 5650871, Japan, ²⁵⁹Department of Vascular Surgery,
461 Division of Surgical Specialties, University Medical Center Utrecht, Utrecht University,
462 Utrecht, the Netherlands, ²⁶⁰Corneal Dystrophy Research Institute, Department of
463 Ophthalmology, Yonsei University College of Medicine, Seoul 03722, Korea, ²⁶¹Dept of
464 Radiology and Nuclear Medicine, Erasmus MC - University Medical Center Rotterdam,
465 Rotterdam, the Netherlands, ²⁶²Julius Centre for Health Sciences and Primary Care, University
466 Medical Centre Utrecht, 3584CG, the Netherlands, ²⁶³Second Department of Cardiology,
467 Medical School, National and Kapodistrian University of Athens, Attikon University
468 Hospital, Athens, Greece, ²⁶⁴Center for Vision Research, Department of Ophthalmology and
469 The Westmead Institute, University of Sydney, Hawkesbury Rd, Sydney, New South Wales,
470 2145, Australia, ²⁶⁵Menzies Institute for Medical Research, School of Medicine, University of
471 Tasmania, Liverpool St, Hobart, Tasmania, 7000, Australia, ²⁶⁶Centre for Eye Research
472 Australia, University of Melbourne, Melbourne, Victoria, 3002, Australia, ²⁶⁷Department of
473 Clinical Physiology, Tampere University Hospital, Tampere 33521, Finland, ²⁶⁸Department of

474 Clinical Physiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine
475 and Health Technology, Tampere University, Tampere 33014, Finland, ²⁶⁹Centre Nutrition,
476 santé et société (NUTRISS), Institute of Nutrition and Functional Foods (INAF), Québec,
477 Canada, ²⁷⁰Pennington Biomedical Research Center, Baton Rouge, LA 70808, USA, ²⁷¹Medical
478 Department III – Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical
479 Center, Liebigstr. 18, 04103 Leipzig, Germany, ²⁷²Discipline of Internal Medicine, Medical
480 School, The University of Western Australia, Perth, WA, Australia, ²⁷³Institute of
481 Epidemiology, Kiel University, Kiel, Germany, ²⁷⁴Institute of Clinical Molecular Biology,
482 Kiel University, Kiel, Germany, ²⁷⁵Sahlgrenska University Hospital, Department of Drug
483 Treatment, Gothenburg, Sweden, ²⁷⁶Geriatric Medicine, Institute of Medicine, Sahlgrenska
484 Academy, University of Gothenburg, Gothenburg, Sweden, ²⁷⁷Department of Internal
485 Medicine, EwhaWomans University School of Medicine, Seoul, Korea, ²⁷⁸Division of Cancer
486 Control and Population Sciences, UPMC Hillman Cancer Center, University of Pittsburgh,
487 Pittsburgh, PA 15232, USA, ²⁷⁹Department of Epidemiology, Graduate School of Public
488 Health, University of Pittsburgh, Pittsburgh, PA 15232, USA, ²⁸⁰Healthy Longevity
489 Translational Research Programme, Yong Loo Lin School of Medicine, National University
490 of Singapore, Singapore 117545, Singapore, ²⁸¹Singapore Institute for Clinical Sciences,
491 Agency for Science Technology and Research (A*STAR), Singapore 117609, Singapore,
492 ²⁸²Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine,
493 Seoul 02447, Korea, ²⁸³Institute for Community Medicine, University Medicine Greifswald,
494 Germany, ²⁸⁴Laboratory of Epidemiology and Population Science National Institute on Aging
495 Intramural Research Program, NIH 251 Bayview Blvd, NIH Biomedical Research Center,
496 Baltimore, MD 21224, USA, ²⁸⁵Algebra University College, Ilica 242, Zagreb, Croatia,
497 ²⁸⁶Paavo Nurmi Centre, Sports and Exercise Medicine Unit, Department of Physical Activity
498 and Health, University of Turku, Turku, Finland, ²⁸⁷Interdisciplinary Center Psychopathology

499 and Emotion Regulation (ICPE), University of Groningen, University Medical Center
500 Groningen, Groningen, 9700 RB, the Netherlands, ²⁸⁸Institute of Molecular Genetics, National
501 Research Council of Italy, Pavia, Italy, ²⁸⁹Gottfried Schatz Research Center for Cell Signaling,
502 Metabolism and Aging, Medical University of Graz, Graz, Austria, ²⁹⁰Local Health Unit
503 Toscana Centro, Firenze, Italy, ²⁹¹Institute of Nutritional Science, University of Potsdam,
504 Nuthetal, Germany, ²⁹²Department of Medicine, Surgery and Health Sciences, University of
505 Trieste, Strada di Fiume 447, 34149, Trieste, Italy, ²⁹³Dept of Nephrology, Diabetology,
506 Rheumatology; Traunstein Hospital, Traunstein, Germany, ²⁹⁴KfH Kidney Center Traunstein,
507 Traunstein, Germany, ²⁹⁵Center for Translational and Systems Neuroimmunology, Department
508 of Neurology, Columbia University Medical Center, New York, NY, USA, ²⁹⁶Program in
509 Medical and Population Genetics, Broad Institute, Cambridge, MA, USA, ²⁹⁷Medical School,
510 National and Kapodistrian University Athens, 75 M. Assias Street, 115 27 Athens, Greece,
511 ²⁹⁸Dromokaiteio Psychiatric Hospital, 124 61 Athens, Greece, ²⁹⁹Clinical Pharmacology,
512 William Harvey Research Institute, Queen Mary University of London, London, EC1M
513 6BQ, UK, ³⁰⁰Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg
514 University, Kutzerufer 1, Mannheim, 68167, Germany, ³⁰¹Institute of Molecular and Clinical
515 Ophthalmology Basel, Switzerland, ³⁰²Privatpraxis Prof Jonas und Dr Panda-Jonas,
516 Heidelberg, Germany, ³⁰³Department of Human Genetics, David Geffen School of Medicine at
517 UCLA, University of California, Los Angeles, CA, USA, ³⁰⁴Unidad de Biología Molecular y
518 Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán,
519 Mexico 14080, Mexico, ³⁰⁵Instituto de Investigaciones Biomédicas, UNAM, Mexico,
520 ³⁰⁶Departamento de Endocrinología y Metabolismo, Instituto Nacional de Ciencias Médicas y
521 Nutrición Salvador Zubirán, Mexico 14080, Mexico, ³⁰⁷Department of Nutrition, Gillings
522 School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina,
523 27599 USA, ³⁰⁸Carolina Population Center, University of North Carolina, Chapel Hill, North

524 Carolina, 27516 USA, ³⁰⁹USC–Office of Population Studies Foundation, University of San
525 Carlos, Cebu City, 6000, Philippines, ³¹⁰Department of Anthropology, Sociology, and History,
526 University of San Carlos, Cebu City, 6000 Philippines, ³¹¹Department of Medicine, Faculty of
527 Medicine, University of Kelaniya, Ragama, 11010, Sri Lanka, ³¹²Department of Public Health,
528 Faculty of Medicine, University of Kelaniya, Ragama, 11010, Sri Lanka, ³¹³Children's
529 Hospital Oakland Research Institute, Oakland, CA 94609 USA, ³¹⁴Institute of Biomedical
530 Sciences, Academia Sinica, Taiwan, ³¹⁵Systems Genomics Laboratory, School of
531 Biotechnology, Jawaharlal Nehru University, New Delhi - 110067, India, ³¹⁶Department of
532 Medicine, University of Mississippi Medical Center, Jackson, MS, 39216, USA,
533 ³¹⁷Department of Physiology and Biophysics, University of Mississippi Medical Center,
534 Jackson, MS, 39216, USA, ³¹⁸Department of Medical Sciences, Uppsala University, Sweden,
535 ³¹⁹Department of Paediatrics, Yong Loo Lin School of Medicine, National University of
536 Singapore; and Khoo Teck Puat - National University Children's Medical Institute, National
537 University Health System, Singapore, ³²⁰Department of Medicine, University of North
538 Carolina, Chapel Hill, NC, USA, ³²¹Department of Epidemiology, Gillings School of Global
539 Public Health, University of North Carolina, Chapel Hill, North Carolina, USA, ³²²Injury
540 Prevention Research Center, University of North Carolina, Chapel Hill, North Carolina,
541 USA, ³²³Division of Physical Therapy, University of North Carolina, Chapel Hill, North
542 Carolina, USA, ³²⁴Department of Psychiatry, Amsterdam UMC, Vrije Universiteit
543 Amsterdam, the Netherlands, ³²⁵Amsterdam Public Health research institute, VU medical
544 center Amsterdam, the Netherlands, ³²⁶Department of Biochemistry, College of Medicine,
545 Ewha Womans University, Seoul 07804, Korea, ³²⁷Faculty of Health and Medicine, University
546 of Newcastle, Australia, ³²⁸Washington University School of Medicine, Division of
547 Biostatistics, MO, USA, ³²⁹University of Kentucky, College of Public Health, KY, USA,
548 ³³⁰Institute of Cellular Medicine (Diabetes), The Medical School, Newcastle University,

549 Framlington Place, Newcastle upon Tyne, NE2 4HH, UK, ³³¹University of Helsinki and
550 Department of Medicine, Helsinki University Hospital, P.O.Box 340, Haartmaninkatu 4,
551 Helsinki, FI-00029, Finland, ³³²Minerva Foundation Institute for Medical Research,
552 Biomedicum 2U, Tukholmankatu 8, Helsinki, FI-00290, Finland, ³³³JSS Academy of Higher
553 Education and Research, Mysuru, India, ³³⁴Programs in Metabolism and Medical and
554 Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA, ³³⁵Diabetes
555 Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA,
556 USA10, ³³⁶Harvard Medical School, Boston, Massachusetts, USA, ³³⁷Unidad de Biología
557 Molecular y Medicina Genómica, Instituto de Investigaciones Bimédicas UNAM/ Instituto
558 Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico,
559 ³³⁸Dirección de Nutrición and Unidad de Estudios de Enfermedades Metabólicas, Instituto
560 Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico,
561 ³³⁹Instituto Nacional de Salud Pública y Centro de Estudios en Diabetes, Mexico, ³⁴⁰Instituto
562 Nacional de Medicina Genómica, Mexico, ³⁴¹Human Genetics Center, School of Public
563 Health, University of Texas Health Science Center at Houston, Houston TX 77030, USA,
564 ³⁴²Yong Loo Lin School of Medicine, National University of Singapore and National
565 University Health System, 119228, Singapore, ³⁴³MRC Unit for Lifelong Health and Ageing at
566 UCL, 1-19 Torrington Place, London, WC1E 7HB, United Kingdom, ³⁴⁴Kurume University
567 School of Medicine, Kurume, 830-0011, Japan, ³⁴⁵Genetics, Merck Sharp & Dohme Corp.,
568 Kenilworth, NJ, 07033, USA, ³⁴⁶Oxford Centre for Diabetes, Endocrinology & Metabolism,
569 University of Oxford, UK, ³⁴⁷Population Health and Genomics, University of Dundee,
570 Ninwells Hospital and Medical School, Dundee, DD1 9SY, UK, ³⁴⁸Intramural Research
571 Program, National Institute on Aging, 3001 S. Hanover St., Baltimore, MD 21225, ³⁴⁹Beijing
572 Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital
573 Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, 100730

574 Beijing, China, ³⁵⁰The Eye Hospital, School of Ophthalmology & Optometry, Wenzhou
575 Medical University, Wenzhou, Zhejiang 325027, China, ³⁵¹Synlab Academy, SYNLAB
576 Holding Deutschland GmbH, Mannheim and Augsburg, Germany, ³⁵²Clinical Institute of
577 Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria,
578 ³⁵³Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland, ³⁵⁴Leiden University
579 Medical Center, Department of Cell and Chemical Biology, Leiden, 2333ZA, The
580 Netherlands, ³⁵⁵Leiden University Medical Center, Department of Biomedical Data Sciences,
581 Section Molecular Epidemiology, Leiden, 2333ZA, The Netherlands, ³⁵⁶Amsterdam UMC,
582 Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute,
583 Amsterdam, 1081HV, the Netherlands., ³⁵⁷Amsterdam UMC, Department of General Practice
584 and Elderly Care, Amsterdam Public Health Research Institute, Amsterdam, 1081HV, The
585 Netherlands, ³⁵⁸Department of Genetics, University of Pennsylvania, Philadelphia, PA, 19104,
586 USA, ³⁵⁹Department of Surgery, University of Pennsylvania, Philadelphia, PA, 19104, USA,
587 ³⁶⁰Corporal Michael Crescenz VA Medical Center, Philadelphia, Pennsylvania, PA, 19104,
588 USA, ³⁶¹Institute of Social and Economic Research, University of Essex, Wivenhoe Park, CO4
589 3SQ, United Kingdom, ³⁶²Department of Cardiology, University of Groningen, University
590 Medical Center Groningen, 9700RB Groningen, The Netherlands, ³⁶³Department of
591 Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New
592 York, NY, USA, ³⁶⁴Unidad de Investigacion Medica en Bioquimica, Hospital de
593 Especialidades, Centro Medico Nacional Siglo XXI, Instituto Mexicano del Seguro Social,
594 Mexico City, Mexico., ³⁶⁵Department of Epidemiology, University of Washington, Seattle,
595 WA, USA, ³⁶⁶Department of Health Services, University of Washington, Seattle, WA, USA,
596 ³⁶⁷Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark,
597 ³⁶⁸16Center for Research on Genomics and Global Health, National Human Genome Research
598 Institute, National Institutes of Health, 12 South Drive, Room 4047, Bethesda, MD, 20892,

599 USA,, ³⁶⁹Danish Aging Research Center, University of Southern Denmark; Odense C,
600 Denmark, ³⁷⁰Public Health, Faculty of Medicine, University of Helsinki, Finland, ³⁷¹Broad
601 Institute of MIT and Harvard, Cambridge, MA, ³⁷²Center for Applied Genomics, Children's
602 Hospital of Philadelphia, Philadelphia, PA, 19104 USA, ³⁷³Department of Pediatrics, The
603 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104 USA,
604 ³⁷⁴Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, 19104
605 USA, ³⁷⁵Department of Genetics, University of Pennsylvania, Philadelphia, PA, 19104 USA,
606 ³⁷⁶Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, The
607 Netherlands, ³⁷⁷School of Medicine, Southern University of Science and Technology,
608 Shenzhen, China, ³⁷⁸Institute for Cardiogenetics, University of Lübeck, DZHK (German
609 Research Centre for Cardiovascular Research), partner site Hamburg/Lübeck/Kiel, and
610 University Heart Center Lübeck, Lübeck, Germany, ³⁷⁹Netherlands Heart Institute, Utrecht,
611 the Netherlands, ³⁸⁰Division of Cardiology, Department of Medicine, Massachusetts General
612 Hospital, Boston, Massachusetts, USA, ³⁸¹Program of Medical and Population Genetics, Broad
613 Institute, Cambridge, Massachusetts, USA, ³⁸²Center for Genomic Medicine, Massachusetts
614 General Hospital, Boston, Massachusetts, USA, ³⁸³Department of Medicine, Harvard Medical
615 School, Boston, Massachusetts, USA, ³⁸⁴Northern Finland Birth Cohorts, Infrastructure for
616 population studies, Faculty of Medicine, University of Oulu, Oulu, Finland, ³⁸⁵Center for Life
617 Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland, ³⁸⁶Biocenter
618 of Oulu, University of Oulu, Oulu, Finland, ³⁸⁷Institute for Genetic and Biomedical Research,
619 Italian National Council of Research (IRGB CNR), Cagliari, Italy, ³⁸⁸University of Sassari,
620 Sassari, Italy, ³⁸⁹Department of Clinical Epidemiology, Leiden University Medical Center,
621 Leiden, the Netherlands, ³⁹⁰Department of Public Health and Primary Care, Leiden University
622 Medical Center, Leiden, the Netherlands, ³⁹¹Department of Internal Medicine, Division of
623 Endocrinology, Leiden University Medical Center, Leiden, the Netherlands, ³⁹²Eindhoven

624 Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden,
625 the Netherlands, ³⁹³Department of Human Genetics, Leiden University Medical Center,
626 Leiden, the Netherlands, ³⁹⁴Population Health Research Institute, St George's, University of
627 London, London SW17 0RE, UK, ³⁹⁵National Heart and Lung Institute, Imperial College
628 London, London, W2 1PG, UK, ³⁹⁶School of Public Health, Imperial College London,
629 London, W12 7RH, UK, ³⁹⁷Taichung Veterans General Hospital, Taichung, Taiwan; No. 1650,
630 Sec. 4, Taiwan Boulevard, Xitun District Taichung City 40705, Taiwan, ³⁹⁸Division of
631 Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital,
632 Taipei, Taiwan; No. 201, Sec. 2, Shipai Road, Beitou District, Taipei City, 112201, Taiwan,
633 ³⁹⁹OCDEM, University of Oxford, Churchill Hospital, Oxford OX3 7LE, UK, ⁴⁰⁰NIHR Oxford
634 Biomedical Research Centre, Churchill Hospital, Oxford, UK, ⁴⁰¹Ocular Epidemiology,
635 Singapore Eye Research Institute, Singapore National Eye Centre, 168751, Singapore,
636 ⁴⁰²Ophthalmology & Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS
637 Medical School, 169857, Singapore, ⁴⁰³Data Science, Singapore Eye Research Institute,
638 Singapore National Eye Centre, 168751, Singapore, ⁴⁰⁴DZHK (German Centre for
639 Cardiovascular Research), Munich Heart Alliance partner site, Munich, Germany, ⁴⁰⁵German
640 Center for Diabetes Research (DZD), Neuherberg, Germany, ⁴⁰⁶University of Exeter Medical
641 School, University of Exeter, Exeter, EX2 5DW, UK, ⁴⁰⁷Department of Medical Epidemiology
642 and Biostatistics, Karolinska Institutet, Stockholm, Sweden, ⁴⁰⁸Amsterdam Public Health
643 research institute, Amsterdam UMC, the Netherlands, ⁴⁰⁹Framingham Heart Study, National
644 Heart, Lung, and Blood Institute, US National Institutes of Health, Bethesda, MD, USA.,
645 ⁴¹⁰Department of Genetics, School of Medicine, Mashhad University of Medical Sciences,
646 Mashhad, Iran, ⁴¹¹Department of Genetics, Shanghai-MOST Key Laboratory of Health and
647 Disease Genomics, Chinese National Human Genome Center at Shanghai, Shanghai, 201203
648 China, ⁴¹²Technical University of Munich (TUM) and Klinikum Rechts der Isar, TUM School

649 of Medicine, Munich, Germany, ⁴¹³Department of Public Health, University of Helsinki,
650 Helsinki, Finland, ⁴¹⁴Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi
651 Arabia, ⁴¹⁵Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland and
652 Kuopio University Hospital, Finland, ⁴¹⁶Stanford Cardiovascular Institute, Stanford
653 University, Stanford, CA 94305, USA, ⁴¹⁷Stanford Diabetes Research Center, Stanford
654 University, Stanford, CA 94305, USA, ⁴¹⁸Department of Medical Sciences, Molecular
655 Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.,
656 ⁴¹⁹Regeneron Pharmaceuticals, Tarrytown, NY, USA, ⁴²⁰Lee Kong Chian School of Medicine,
657 Nanyang Technological University, Singapore 308232, Singapore, ⁴²¹Imperial College
658 Healthcare NHS Trust, Imperial College London, London W12 0HS, UK, ⁴²²MRC-PHE
659 Centre for Environment and Health, Imperial College London, London W2 1PG, UK,
660 ⁴²³National Heart and Lung Institute, Imperial College London, London W12 0NN, UK,
661 ⁴²⁴School of Electrical & Information Engineering, University of the Witwatersrand, South
662 Africa, ⁴²⁵Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA,
663 ⁴²⁶Institute for Minority Health Research, University of Illinois College of Medicine, Chicago,
664 Illinois, USA, ⁴²⁷Department of Biostatistics, Harvard T.H. Chan School of Public Health, 677
665 Huntington Avenue, Boston, MA, 02115, USA, ⁴²⁸QIMR Berghofer Medical Research
666 Institute, 300 Herston Road, Brisbane, Queensland 4006, Australia, ⁴²⁹Center for Non-
667 Communicable Diseases, Karachi, Sindh, Pakistan & Faisalabad Institute of Cardiology,
668 Faisalabad, Pakistan, ⁴³⁰Department of Medicine, Columbia University Irving Medical Center,
669 New York, NY, USA, ⁴³¹Department of Cardiology, Columbia University Irving Medical
670 Center, New York, NY, USA, ⁴³²Big Data Institute, University of Oxford, Oxford OX3 7LF,
671 UK, ⁴³³National Institute for Health Research Oxford Biomedical Research Centre, Oxford
672 University Hospitals, Oxford, UK, ⁴³⁴Aberdeen Centre for Health Data Science, 1:042
673 Polwarth Building School of Medicine, Medical Science and Nutrition University of

674 Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK, ⁴³⁵Division of Population Health and
675 Genomics, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1
676 9SY, United Kingdom, ⁴³⁶Biomedical and Translational Informatics, Geisinger Health,
677 Danville, PA 17822, USA, ⁴³⁷Harvard Medical School, Boston, MA 02115, USA, ⁴³⁸School of
678 Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College
679 London, London, UK, ⁴³⁹Department of Biomedical Informatics, Vanderbilt University
680 Medical Center, Nashville, TN, USA, ⁴⁴⁰Departments of Medicine (Medical Genetics) and
681 Genome Sciences, University of Washington, USA, ⁴⁴¹Center for Autoimmune Genomics and
682 Etiology, Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, OH, USA.,
683 ⁴⁴²Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine,
684 Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, USA,
685 ⁴⁴³Department of Anthropology, Northwestern University, Evanston, IL 60208, USA, ⁴⁴⁴Center
686 for Genetic Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL
687 60611, USA, ⁴⁴⁵HUNT Research Centre, Department of Public Health and Nursing, NTNU,
688 Norwegian University of Science and Technology, Levanger, 7600 Norway, ⁴⁴⁶Department of
689 Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, 7600 Norway,
690 ⁴⁴⁷Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital,
691 Trondheim, Norway, ⁴⁴⁸RIKEN Center for Integrative Medical Sciences, Yokohama, Japan,
692 ⁴⁴⁹Laboratory of Complex Trait Genomics, Department of Computational Biology and
693 Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo,
694 Japan, ⁴⁵⁰Laboratory of Statistical Immunology, WPI Immunology Frontier Research Center,
695 Osaka University, Osaka, Japan, ⁴⁵¹Integrated Frontier Research for Medical Science Division,
696 Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Osaka,
697 Japan, ⁴⁵²Division of Molecular Pathology, Institute of Medical Science, The University of
698 Tokyo, Tokyo, Japan, ⁴⁵³Division of Genome Research, Center for Genome Science, National

699 Institute of Health, Chungcheongbuk-do, South Korea, ⁴⁵⁴Faculty of Medicine, University of
700 Iceland, Sæmundargötu 2, Reykjavik, 102, Iceland, ⁴⁵⁵VA Boston Healthcare System, Boston,
701 MA, USA, ⁴⁵⁶VA Informatics and Computing Infrastructure, VA Salt Lake City Health Care
702 System, Salt Lake City, UT, USA, ⁴⁵⁷University of Massachusetts, Boston, MA, USA,
703 ⁴⁵⁸Department of Medicine, University of Pennsylvania Perelman School of Medicine,
704 Philadelphia, PA, USA, ⁴⁵⁹Cardiovascular Institute, Stanford University School of Medicine,
705 Stanford, California, USA, ⁴⁶⁰Corporal Michael J. Crescenz VA Medical Center, Philadelphia,
706 PA, USA, ⁴⁶¹Department of Medicine, Brigham Women's Hospital, Boston, MA, USA,
707 ⁴⁶²Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA,
708 ⁴⁶³Endocrinology, Boston Childrens Hospital, Boston 02115 MA, USA, ⁴⁶⁴Departments of
709 Pediatrics and Genetics, Harvard Medical School, Boston, MA, USA, ⁴⁶⁵Center for Genomic
710 Medicine, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts,
711 USA, ⁴⁶⁶Cardiology Division, Massachusetts General Hospital, Harvard Medical School,
712 Boston, MA, USA, ⁴⁶⁷Department of Medicine, Massachusetts General Hospital, Harvard
713 Medical School, Boston, MA, USA, ⁴⁶⁸Cardiovascular Research Center and Center for
714 Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA, ⁴⁶⁹Centre for
715 Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Division of
716 Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester,
717 UK, ⁴⁷⁰Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary
718 Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia, ⁴⁷¹Department of
719 Biostatistics, Boston University School of Public Health, Boston, MA, USA, ⁴⁷²Department of
720 Human Genetics, University of Michigan, Ann Arbor, MI, 48109, USA, ⁴⁷³Department of
721 Statistics, The Pennsylvania State University, University Park, PA, USA, ⁴⁷⁴Huck Institutes of
722 the Life Sciences, The Pennsylvania State University, University Park, PA, USA, ⁴⁷⁵VA Palo

723 Alto Health Care System, Palo Alto, CA, USA, ⁴⁷⁶Department of Statistics, Stanford

724 University, Stanford, CA, USA

725 Corresponding Authors:

726 Xiang Zhu, PhD

727 Department of Statistics

728 Huck Institutes of the Life Sciences

729 The Pennsylvania State University

730 University Park, PA 16802

731 xiangzhu@psu.edu

732

733 Christopher D Brown, PhD

734 Department of Genetics

735 Perelman School of Medicine

736 University of Pennsylvania

737 Philadelphia PA 19104

738 chrbro@upenn.edu

739

740 **Abstract**

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

756

757

758 **Introduction**

759

760 Most GWAS findings have not directly led to mechanistic interpretations, largely because
761 90% of GWAS associations map to non-coding sequences^{1,2}. Mechanistic interpretations in
762 GWAS have proven challenging because the strongest signals identified in GWAS typically
763 contain many variants in strong linkage disequilibrium (LD)³ and functional mechanisms
764 including genes of action are often not clear from GWAS data alone^{4,5}.

765

766 Linking trait-associated variants to genome function has emerged as a promising model for
767 mechanistic interpretation of non-coding findings in GWAS. This 'variant-to-function' model
768 is premised on recent observations that non-coding variants often affect a trait of interest
769 through the regulation of genes and processes in trait-relevant cell types or tissues^{2,6}.

770 Implementing this functional model in GWAS has become more feasible as large-scale
771 functional genomic resources, such as epigenomic⁷ and transcriptomic⁸ catalogues, have
772 been systematically generated across a wide range of human cell types and tissues. The
773 integration of functional genomics with GWAS has identified regulatory mechanisms in
774 variants associated with some flagship disorders such as obesity⁹ and schizophrenia¹⁰,
775 yielding important functional insights into the genetic architecture of human complex traits.

776

777 The history of the human genetics of lipids mirrors the successes and challenges of GWAS.
778 Increasing sample size and genetic diversity has significantly boosted the power of discovery:
779 the first lipid GWAS in 2008 with 8,816 European-descent individuals identified 29 lipid-
780 associated loci¹¹; the latest study of 1.6 million individuals across five ancestries¹² found
781 941. Despite the dramatic increase in the number of associations, our biological
782 understanding of many of these genetic discoveries remains limited. The causal gene has

783 been confidently assigned at only a small fraction of these loci ², and the regulatory
784 mechanism connecting variant to phenotype has been conclusively characterized only for a
785 handful of genes ⁵. Furthermore, systematic mapping of lipid-associated variants to their
786 biological functions has been missing in the literature at the time of this study.

787

788 Here we conduct a genome-scale integrative analysis on the largest GWAS to-date of five
789 lipid phenotypes (LDL, or low density lipoprotein; HDL, or high density lipoprotein; TC, or
790 total cholesterol; nonHDL, or non-high density lipoprotein; and TG, or triglycerides)
791 involving 1.65 million individuals from five ancestries ¹². Combining the lipid GWAS with a
792 wide array of functional genomic resources in diverse human tissues and cell types, we
793 identify regulatory mechanisms of noncoding genetic variation in lipids with a full suite of
794 computational approaches. Further, we develop a generalizable framework to understand how
795 tissue-specific gene regulation can explain GWAS findings, and demonstrate its real-world
796 value on lipid-associated loci.

797

798 **Material and Methods**

799 *GWAS*

800

801 We performed GWAS for five blood lipid traits (LDL, HDL, TC, TG, and nonHDL) in 1.65
802 million individuals from five ancestry groups ¹²(African and African-admixed, East Asian,
803 European, Hispanic, South Asian) at 91 million variants imputed primarily from the
804 Haplotype Reference Consortium ¹³ or 1000 Genomes Phase 3 ¹⁴. The individual GWAS and
805 meta-analyses were performed using the hg19 version of the human reference genome. We
806 used MR-MEGA ¹⁵ for meta-analysis across cohorts.

807

808 We defined 'sentinel variants' as lead variants representing independent trait-associated loci in
809 the genome. These windows are the greater of 500kb or 0.25cM around the sentinel variant;
810 genetic distances were defined using reference maps from HapMap 3¹⁶. We performed a
811 second round of conditional analysis, conditioning on the sentinel variants to identify and
812 remove any significant windows that are shadow signals (or dependent on) of a neighboring
813 locus to enforce independence of associated loci.

814

815 *Colocalization with eQTLs*

816

817 We performed statistical colocalization of lipid GWAS with eQTLs obtained from GTEx v8
818 across 49 tissues⁸. For each of the five lipid traits, we used the same sentinel variants defined
819 in the previous section to represent approximately independent GWAS-associated windows
820 (also removing shadow signals as described before).

821

822 For each such window, we ran eQTL colocalization with GTEx v8 single-tissue cis-eQTL
823 summary statistics⁸. For each of 49 GTEx tissues, we first identified all genes within 1Mb of
824 the sentinel SNP, and then restricted analysis to those genes with significant eQTLs (i.e.,
825 'eGenes' as defined by GTEx) in that tissue (FDR < 0.05). We used the R package 'coloc' (run
826 on R version 3.4.3, coloc version 3.2.1)¹⁷ with default parameters to run colocalization
827 between the GWAS signal and the eQTL signal for each of these cis-eGenes, using as input
828 those SNPs in the defined window (greater than 500kb or 0.25cM on either side of the lead
829 variant), i.e. all SNPs present in both datasets. eQTL summary statistics were in GRCh38, so
830 we first lifted over the GWAS summary statistics (in hg19) to GRCh38 using liftOver¹⁸. As
831 in previous studies¹⁹, we used a colocalization posterior probability of (PP3+PP4) > 0.8 to
832 identify loci with enough colocalization power, and PP4/PP3 > 0.9 to define those loci that

833 show significant colocalization, where PP4 represents posterior probability of a single shared
834 signal, and PP3 represents posterior probability of two unique signals in the GWAS and
835 eQTL datasets.

836

837 *Overlap with promoter Capture-C data*

838

839 We used four promoter-focused Capture-C (henceforth Capture-C) datasets from three human
840 cell/tissue types to capture physical interactions between gene promoters and their regulatory
841 elements. We used three biological replicates of HepG2 liver carcinoma cells²⁰, another
842 HepG2 dataset described in Selvarajan et al²¹, hepatocyte-like cells (HLC) produced by
843 differentiating three biological replicates of iPSCs (which in turn were generated from
844 peripheral blood mononuclear cells using a previously published protocol²²), and an adipose
845 dataset obtained from Pan et al²³ that was produced using primary human white adipocytes.

846

847 The detailed protocol to prepare HepG2 or HLC cells for the Capture-C experiment is
848 described in Chesi et al²⁰. Briefly, for each dataset, 10 million cells were used for promoter
849 Capture-C library generation. Custom capture baits were designed using an Agilent
850 SureSelect library design targeting both ends of DpnII restriction fragments encompassing
851 promoters (including alternative promoters) of all human coding genes, noncoding RNA,
852 antisense RNA, snRNA, miRNA, snoRNA, and lincRNA transcripts, totaling 36,691 RNA
853 baited fragments. Each library was then sequenced on an Illumina HiSeq 4000 (HepG2) or
854 Illumina NovoSeq (HLC), generating 1.6 billion read pairs per sample (50 base pair read
855 length.) We used HiCUP v0.7.2²⁴ to process the raw FastQ files into loop calls and
856 CHiCAGO v1.6.0^{24,25} to define significant looping interactions; we defined a CHiCAGO
857 score of 5 as significant, as specified in the default parameters.

858

859 Starting with Capture-C maps processed as described above, we re-annotated the baits to
860 gene IDs from Gencode v19²⁶ to ensure uniformity of gene annotations with the rest of our
861 pipeline. For each bait, we identified any gene whose transcription start site (TSS) from any
862 transcript in Gencode v19 was within 175 base pair distance from the bait (to account for
863 differing bait designs for external datasets which may not directly overlap the canonical
864 TSS). We filtered all datasets to only include interactions in which the interacting end was
865 not another bait. Enrichment with colocalized genes was robust to our choice of distance
866 between bait and gene (enrichment with eQTL colocalized genes ranging from 2.94-2.96 for
867 bait distances from 0-350 base pairs).

868

869 To identify genetic variants associated with any of the five lipid traits that physically interact
870 with locations in the genome, we used the R package 'Genomic Ranges' version 1.30.3²⁷ to
871 find overlap between credible sets for each trait's GWAS and the previously annotated
872 promoter Capture-C data; we refer to these as Capture-C/GWAS interactions. Each credible
873 set was defined as the set of variants with a 95% posterior probability of being the causal
874 variant. For all individual variants within all GWAS-associated loci for the five lipid traits,
875 we identified which variants overlapped any interacting end of the four previously annotated
876 promoter Capture-C data.

877

878 *Presence of gene-variant pairs in same topologically associated domains*

879

880 To estimate the frequency of colocalized gene-sentinel pairs in the same topologically
881 associated domain (TAD), we used publicly-available TADs from human liver²⁸. We
882 compared the number of colocalizations with the sentinel variant and colocalized gene in the

883 same TAD divided by all colocalizations in which the sentinel variant lies in a TAD. To test
884 if this ratio was statistically significant, we generated random TAD boundaries using
885 ‘bedtools shuffle’ 1000 times, and calculated the same ratio for these randomly-generated
886 TAD boundaries.

887

888 *Pathway enrichment*

889

890 We used ClusterProfiler v3.6.0²⁹ to look for pathways over-represented in each gene list:
891 genes with eQTL colocalization and genes interacting with variants in GWAS credible sets.
892 We used the enrichKEGG function to look for pathway enrichment in KEGG pathways
893 (using the latest version of the KEGG database³⁰). We first re-mapped gencode IDs to gene
894 symbols using the Gencode v24 annotation and then used the biomaRt R package v2.34.2³¹
895 to convert gene symbols to Entrez IDs. We ran enrichKEGG to identify enriched pathways
896 significant at a Benjamini-Hochberg threshold of 0.05.

897

898 *Enrichment in known lipid-associated genes*

899

900 We calculated enrichment odds ratio of genes identified in our analysis with three known sets
901 of lipid-associated genes using the Fisher’s exact test (R function ‘fisher.test’). First, we
902 identified a list of 33 Mendelian genes from ClinVar³² with lipidemia-associated ICD10
903 codes (E78). Second, we used the set of genes identified from a transcriptome-wide
904 association study (TWAS) on the same GWAS and GTEx v8 summary statistics using the S-
905 PrediXcan software³³ default setup. Third, we used 35 genes with rare-coding variants
906 associated with lipid levels³⁴.

907

908 *Stratified LD score regression*

909

910 We used LDSC version 1.0.1³⁵ to estimate the enrichment of heritability using GWAS
911 summary statistics in different epigenetic and transcriptomic annotations, including gene
912 expression, chromatin marks and TF binding sites. The gene expression and chromatin mark
913 annotations and the corresponding LD scores were provided as
914 'Multitissuegeneexpr1000Gv3' and 'Multitissuechromatin1000Gv3' databases in LDSC
915 software. The TF binding site annotations were extracted from ChIP-seq data of 161 TFs
916 from ENCODE, and their LD scores were estimated from 1000 Genomes Phase 3 European
917 samples using 'ldsc.py --l2'. We first converted the summary statistics for each phenotype to
918 LDSC-formatted summary statistics using 'munge_sumstats.py'. Second, we ran 'ldsc.py'
919 using the baseline_v1.2 baseline model on each annotation to estimate enrichment of
920 heritability. For primary analyses, we used multi-population GWAS summary statistics and
921 LD scores estimated from 1000 Genomes Phase 3 European samples. For secondary analyses
922 on East Asian GWAS alone, we obtained EAS-specific LD scores for the same epigenomic
923 annotations³⁶.

924

925 *GREGOR analysis*

926

927 We used GREGOR³⁷ to estimate enrichment of sentinel variants for each lipid phenotype in
928 TF binding sites for 161 TFs from ENCODE compared to a null distribution of variants
929 matched for allele frequency. We ran GREGOR with default parameters, specifying 0.8 as
930 the R^2 threshold, window size of 1Mb, and 'EUR' as the population. Annotations with FDR-
931 adjusted P-value < 0.05 were considered significant.

932

933 *Enrichment in single-cell expression data*

934

935 We overlapped our list of colocalized genes with publicly available single-cell RNA-
936 sequencing data of 8,444 cells from liver³⁸ and 38,408 cells from adipose (Web resources) in
937 humans. For both datasets, we downloaded normalized TPM data and existing tSNE cluster
938 annotations for each cell. For each cluster, we defined median expression for each gene
939 across all cells in that cluster. Then for each cluster, we calculated the enrichment P-value for
940 our list of colocalized genes using the ‘fgsea’ R package v1.4.1, which looks for
941 overrepresentation of our gene list in ranked genes for each cluster³⁹, implemented in R
942 3.4.3.

943

944 **Results**

945

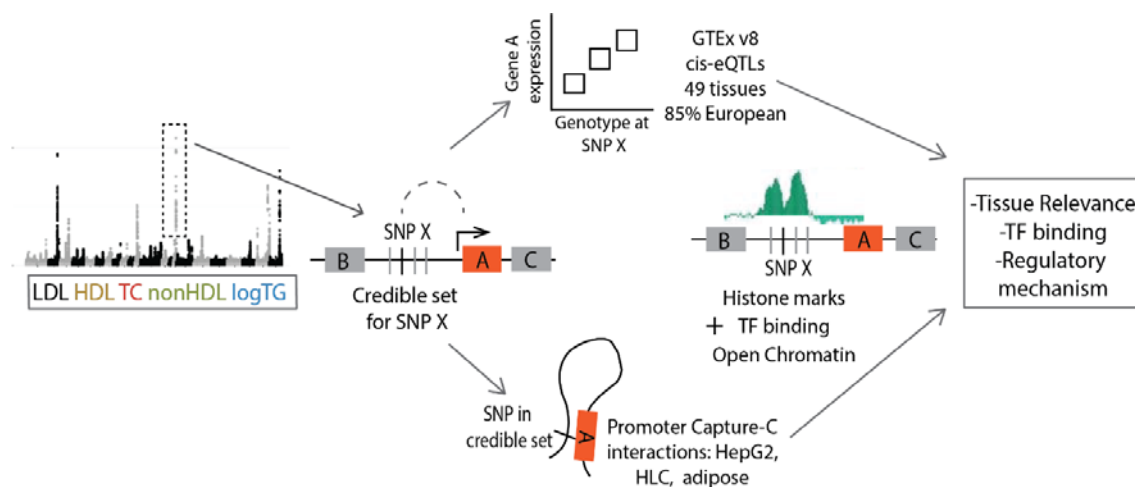
946 We systematically integrated lipid GWAS results¹² with multiple layers of functional
947 genomic data from diverse tissues and cell types to understand regulatory mechanisms at
948 lipid-associated loci (Figure 1). Specifically, we overlaid GWAS loci with eQTL and
949 chromatin-chromatin interactions to identify causal genes. We assessed polygenic
950 enrichments of tissue-specific histone marks to prioritize relevant tissues and examined
951 GWAS loci at transcription factor (TF) binding sites to detect lipid-relevant TFs. Finally, we
952 combined all these layers to prioritize functional variants at GWAS loci, providing a holistic
953 view of gene regulation at lipid loci in relevant tissue and cell types.

954

955 *Figure 1: Schematic overview of the multi-layer functional genomic analysis. We first*
956 *integrate GWAS summary statistics for five lipid phenotypes with eQTL and chromatin*
957 *interaction data to identify potential genes mediating the GWAS association, and then*

958 *incorporate epigenomic annotations to identify regulatory mechanisms at these loci. For any*
959 *lead variant 'X', A, B, and C represent nearby eGenes, and SNPs around SNP X represent*
960 *variants in the credible set.*

961



962

963 *Colocalization with eQTLs identifies candidate lipid-relevant genes*

964

965 First, we identified shared association signals between lipid levels and expression of nearby
966 genes, since most GWAS signals are presumed to influence complex traits through impact on
967 gene expression⁴⁰. To do so, we tested for colocalization of each of the 1,750 significant
968 lipid GWAS association signals across the five traits examined with significant cis-eQTL
969 data across 49 human tissues from the GTEx consortium⁸. Here, we defined significant
970 GWAS signals as 1,750 loci reaching genome-wide significance and corrected for shadow
971 signals (Methods) in our multi-population meta-analysis for at least one of five lipid traits.

972

973 Second, we restricted our analysis to those loci likely mediated through regulatory

974 mechanisms as opposed to coding variation. In particular, we excluded all loci with credible

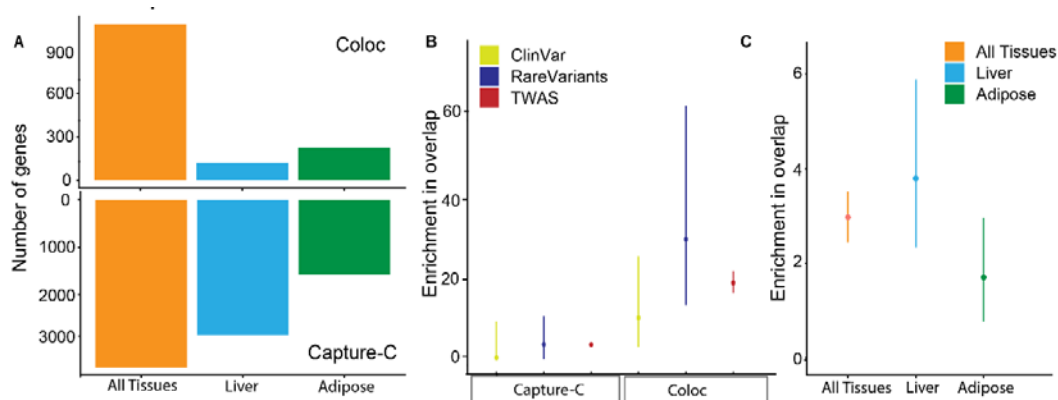
975 sets containing at least one missense variant (369 of 1,750 loci, 21% of credible sets). Of the
976 remaining 1,381 GWAS loci, 696 significantly colocalized with eQTLs (the ratio of posterior
977 probability of a shared signal to the posterior probability of two signals being > 0.9 ¹⁹;
978 Methods) in at least one of 49 tissues for at least one lipid phenotype. This resulted in 1,076
979 colocalized eGenes ranging from 1 to 16 genes per locus (Figure 2A; Table S1). Since with
980 eQTL data alone it is difficult to disentangle a single functional gene from multiple functional
981 (and likely coregulated) genes at a locus⁴¹ we performed all downstream analyses with all
982 1,076 colocalized genes, to further prioritize functional genes at loci with multiple eGenes.
983

984 To acquire additional functional insights into the 1,076 colocalized genes, we assessed their
985 enrichments across existing biological and clinical gene sets. Colocalized genes showed
986 enrichments in (a) 20 KEGG pathways³⁰ at FDR 5% (Table S2), including known lipid-
987 related processes such as cholesterol metabolism, PPAR signaling, and bile secretion; (b) 33
988 Mendelian genes from ClinVar³² associated with lipid-related ICD10 codes, (11 fold
989 enrichment at $P=2.08e-06$, including *APOB*, *LPL*, and *APOE*; Figure 2B), suggesting the
990 shared genetic basis of Mendelian and complex lipid phenotypes⁴²; (c) 35 genes with rare-
991 variant burden for lipid phenotypes in a recent multi-ancestry analysis³⁴ (30-fold enrichment,
992 $P = 1.77e-16$, including *APOB*, *LPL*, *LIPG* and *ANGPTL4*), confirming shared mechanisms
993 of rare and common variation underlying lipid traits^{42,43}. Colocalized genes also showed
994 enrichment with genes implicated in TWAS run on the same GWAS and eQTL summary
995 statistics (20-fold enrichment, $P<2.22e-308$). These enrichment results demonstrate the
996 biological relevance of candidate functional genes prioritized by our approach.

997

998 *Figure 2: Overlap between eQTL colocalized genes and capture-C prioritized genes, and*
999 *their enrichment in known lipid-associated genes. A. Numbers of genes identified by two*

1000 approaches: eQTL colocalization (upper half) and promoter capture-c interactions (lower
1001 half) B. Overlap between our list of prioritized genes (left: capture-C prioritized genes; right:
1002 eQTL colocalized genes) with three sets of genes previously associated with lipid biology
1003 (ClinVar lipidemia-associated genes, genes implicated in rare burden of lipids, and genes
1004 from a lipid TWAS). C. Enrichment in overlap between eQTL colocalized genes and capture-
1005 C prioritized genes against what is expected by chance, assuming both gene sets are
1006 independent. Enrichment estimates and confidence intervals shown in Panels B and C were
1007 obtained using Fisher's exact test.



1008

1009

1010 *Chromatin-chromatin interactions improve eQTL-based colocalization*

1011

1012 Our eQTL-based colocalization analysis uses a linear sequence of DNA, and ignores physical
1013 interaction between non-adjacent DNA segments, another regulatory layer underlying
1014 complex human traits⁴⁴. To add this layer to our analysis, we generated Capture-C data from
1015 HepG2 liver carcinoma cells (denoted as HepG2.1) and hepatocyte-like cells (HLC) derived
1016 from differentiating iPSCs (the latter is described in²²), as well as publicly-available Capture-
1017 C datasets from HepG2^{21,43} (denoted as HepG2.2) and adipose tissue²³. We defined a
1018 GWAS-relevant interaction as any Capture-C interaction between any gene and a variant in
1019 the 95% credible set for a GWAS locus⁴⁵. Credible set sizes ranged from 1 to 417 variants at

1020 the 1,750 examined loci, with a median size of 5 variants per credible set. In total, 1,079
1021 GWAS loci had at least one variant in the credible set with a physical interaction with a gene
1022 promoter and 3,543 of 26,621 genes with promoter-interactions had promoters physically
1023 interacting with at least one GWAS credible set variant (Figure 2A; Table S3). Unlike eQTL-
1024 colocalized genes, these genes interacting with their credible sets showed limited enrichment
1025 in relevant KEGG pathways (Table S2) and lipid-related genes from ClinVar (Figure 2B),
1026 though we see 5-fold enrichment (compared to greater than 10-fold enrichment for eQTL-
1027 colocalized genes) in genes with rare-variant lipid associations ($P = 2.8 \times 10^{-5}$) and TWAS
1028 genes ($P = 2.5 \times 10^{-288}$).

1029

1030 Genes physically interacting with GWAS loci helped shortlist functional genes from eQTL
1031 colocalization despite their reduced enrichments in known gene sets. Of 1,079 credible sets
1032 with promoter interactions, 224 also colocalized with eQTLs for the same gene. At the gene
1033 level, 233 genes were implicated in both eQTL colocalization and Capture-C interactions
1034 (Figure 2C), representing an enrichment of 3-fold compared to random chance ($P = 3.11 \times 10^{-38}$).
1035 Among these loci with concordant eQTL colocalizations and Capture-C interactions, only
1036 39% of them mapped to a single gene using eQTL data alone, whereas adding Capture-C
1037 information increased this fraction to 80%. These results showcase the potential value of
1038 combining eQTLs with physical chromatin interactions to prioritize functional genes at
1039 GWAS loci.

1040

1041 Since eQTLs are likely to reside in the same topologically associated domain (TADs) as the
1042 genes they regulate⁴⁶, we examined TAD structure from independent datasets at lipid GWAS
1043 loci with eQTL colocalizations. Of eQTL-GWAS colocalizations in which the sentinel
1044 variant resided within a liver TAD²⁸, the colocalized gene resided in the same liver TAD

1045 84.8% of the time ($P < 0.001$ with 1000 permutations; Methods). When we restricted
1046 colocalizations to those supported by Capture-C data in any cell type, 91.2% fall in the same
1047 TAD. These results add to the existing evidence for TAD boundaries being regulatory
1048 insulators in the cell⁴⁷ and confirm our integration of chromatin interactions with eQTL
1049 colocalizations as an effective strategy to hone in on functional genes.

1050

1051 *Tissue-specific enrichment of GWAS signals differentiates lipid traits*

1052

1053 Regulatory variants often affect complex traits in a tissue-specific manner⁶, as shown in our
1054 eQTL colocalization analysis. Specifically, by computing the ratio of the number of
1055 colocalizations in a tissue to eQTL sample size in that tissue, we found that the liver was
1056 universally enriched for colocalized eGenes with respect to sample size across all lipid traits
1057 whereas adipose was selectively enriched in HDL and TG only (Figure S1). Motivated by
1058 these findings, we leveraged systematic approaches and additional data to identify relevant
1059 tissues and cell types for each lipid trait.

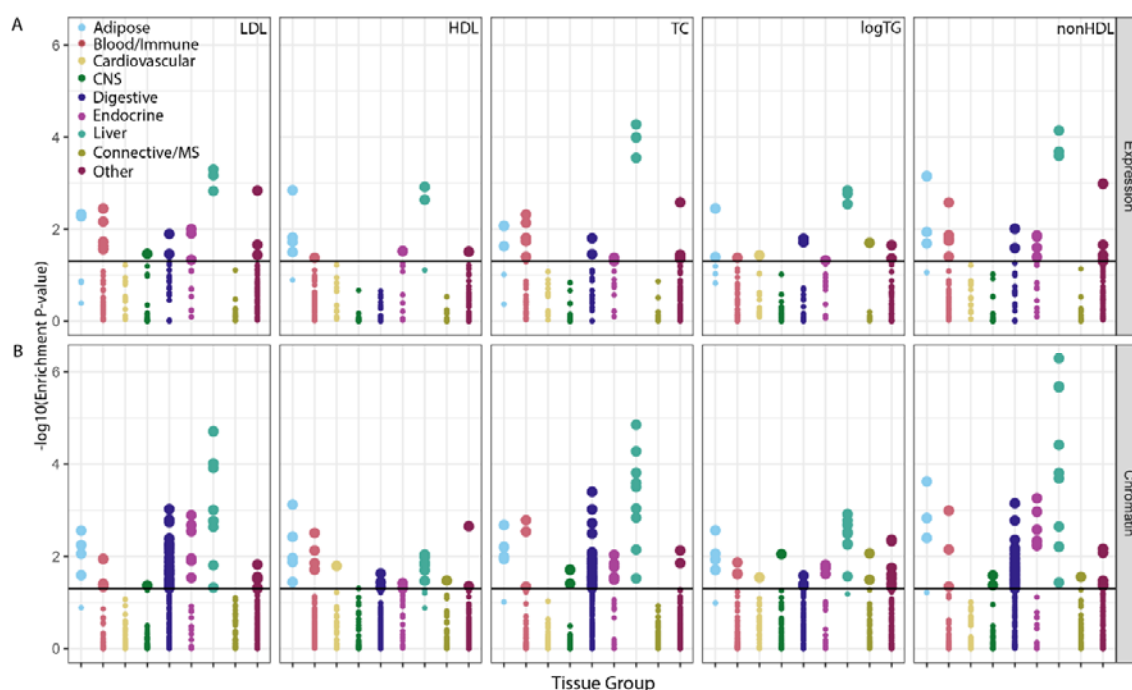
1060

1061 We implemented stratified LD score regression (S-LDSC), a polygenic approach not
1062 restricted to genome-wide significant variants, on tissue-specific transcriptomic and
1063 epigenomic annotations across 204 datasets from more than 170 tissues and cell types, to
1064 identify relevant tissues for each lipid trait (Methods). Consistent with previous studies and
1065 our eQTL-based analysis, liver-related tissues (Table S4) showed strong enrichments across
1066 all lipid traits (S-LDSC enrichment p-values ranging from .001 in TG to .0001 in TC), for
1067 both expression (Figure 3A) and chromatin annotations (Figure 3B). This result was
1068 confirmed by analysis using two other approaches: DEPICT⁴⁸ (Figure S2) and RSS-NET⁴⁹
1069 (Table S5). To assess the robustness of our S-LDSC results based on multi-population

1070 GWAS, we applied S-LDSC to population-specific GWAS in European and East Asian
1071 ancestry participants together with population-specific LD scores (Methods) and obtained
1072 similar results (Table S6).

1073

1074 *Figure 3: Tissue relevance based on lipid GWAS and functional annotations. Partitioning*
1075 *heritability of GWAS summary statistics for five lipid traits on gene expression (A) and*
1076 *chromatin mark (B) annotations across tissues. Each plotted point represents a tested dataset*
1077 *for enrichment of heritability, with larger dots representing datasets with P-value < 0.05;*
1078 *multiple annotation datasets are tested for the same tissue group. Each color represents a*
1079 *tissue group, and the y-axis represents $-\log_{10}$ P-value of enrichment of heritability.*



1080

1081

1082

1083 The S-LDSC results also highlighted tissues selectively enriched in certain lipid traits as
1084 shown in the eQTL-based analysis. The most enriched category for HDL using chromatin
1085 annotation is 'Adipose H3K4me3' (P-value 7.6e-04); for TG, enrichment in liver-related

1086 tissues (P-value 1.2e-03) is similar to enrichment in adipose (P-value 2.7e-03). For LDL, TC,
1087 and non-HDL, enrichment P-values for the liver were much more significant than for all
1088 other tissues including adipose (Figure 3B). We observed the same pattern in S-LDSC results
1089 based on gene expression (Figure 3A). This finding is consistent with the known influence of
1090 adipose on plasma HDL levels⁵⁰, and the role of adipose as TG deposits⁵¹. These results
1091 were corroborated by eQTL colocalizations stratified by phenotype (Figure S1) and DEPICT
1092 analysis on gene expression⁴⁸ (Figure S2). Together, these results confirm the liver as the
1093 tissue of action for all five lipid traits, and highlight the additional role of adipose in HDL and
1094 TG only.

1095

1096 Given the importance of the liver and adipose in modulating lipid levels, we further identified
1097 the relevant cell types within these tissues. Using existing single-cell data from adipose and
1098 liver, we performed gene-set enrichment analysis⁵² to identify cell-type clusters enriched for
1099 genes colocalized with any lipid trait. Out of 11 identified cell types in 20 clusters in the
1100 liver, only hepatocytes were enriched at FDR-adjusted $P < 0.05$ (Figure S3), consistent with
1101 previous results²¹. In adipose, only adipocyte clusters and macrophage-monocyte clusters
1102 showed suggestive enrichment (nominal $P < 0.05$) in colocalized genes (Figure S4). Of note,
1103 the enrichment in adipocytes was significant when we restricted this analysis to genes that
1104 were colocalized only with HDL and TG (FDR-corrected $P < 0.05$), consistent with the
1105 selective enrichments of adipose in HDL and TG (but not the other lipid traits) from our S-
1106 LDSC analysis. Evaluations at cellular resolution are required to understand the cell-type
1107 specific mechanisms underlying lipid GWAS loci, but our results could form a useful basis
1108 for future studies.

1109

1110 *Overlapping GWAS signals with binding sites highlights lipid-relevant TFs*

1111

1112 TFs have been implicated as a key mediator of linking genetic variation to complex traits ⁵³.

1113 To understand lipid GWAS in the context of TF activity, we assessed enrichment of genome-

1114 wide significant variants at TF binding sites using GREGOR ³⁷ and performed polygenic

1115 enrichment analysis of TF binding sites using S-LDSC.

1116

1117 Using ChIP-Seq data from 161 TFs across 91 cell types from the ENCODE project ⁷, 70.7%

1118 of lipid credible sets overlapped with at least one TF binding site. Using GREGOR ³⁷, we

1119 identified 137 TFs whose binding sites were significantly enriched in GWAS lead SNPs for

1120 at least one lipid phenotype (enrichment > 2; FDR adjusted P-value < 0.05; Figure S5; Table

1121 S7). Among these 137 enriched TFs, 69 of them (50%) showed significant enrichments

1122 across all five lipid phenotypes, suggesting a potential core regulatory circuit shared by all

1123 lipid traits (Figure S5). The TF with the strongest enrichment in all phenotypes was ESRRA

1124 (estrogen-related receptor alpha), a nuclear receptor active in metabolic tissues ⁵⁴; ESRRA

1125 has been implicated in adipogenesis and lipid metabolism, and ESRRA-null mice display an

1126 increase in fat mass and obesity ⁵⁴.

1127

1128 The GREGOR analysis also highlighted 68 TFs significantly enriched in specific subsets of

1129 (but not all five) lipid phenotypes (Figure S8). For example, we found 4 TFs (FOXM1,

1130 PBX3, ZKSCAN1, ZEB1) enriched in HDL and TG only, 4 TFs (EZH2, NFE2, NFATC1,

1131 KDM5A) enriched in HDL only and 11 TFs (FOSL1, IRF3, JUN, MEF2C, NANOG,

1132 PRDM1, RUNX3, SIRT6, SMC3, STAT3, ZNF217) enriched in TG only. Of these TFs, the

1133 central role of ZEB1 in adiposity ⁵⁵ and fat cell differentiation has been demonstrated ⁵⁶.

1134 Taken together, these TF-centric findings corroborate the selective enrichments of adipose in

1135 HDL and TG (but not the other lipid traits) identified in our previous tissue prioritization
1136 analyses.

1137

1138 Similar to tissue prioritization, we also performed polygenic enrichment analysis of TF
1139 binding sites using S-LDSC (Table S8), which differed from GREGOR analysis by looking at
1140 not only the genome-wide significant associations but also the polygenic signal irrespective
1141 of GWAS P-values. On the same 161 ENCODE TFs, this polygenic analysis identified 25
1142 TFs whose binding sites were significantly enriched in heritability (nominal $P < 0.05$) for at
1143 least one lipid phenotype (Figure S6); reassuringly, 24 of 25 TFs were also significant in
1144 GREGOR analysis. Among these enriched TFs, eight (34%) were significantly enriched in all
1145 five lipid traits (CEBPB, CEBPD, FOXA2, HDAC2, HNF4G, NFYA, RXRA, SP1; $P <$
1146 0.05). Of those TFs significant in both analyses, RXRA (retinoid X receptor alpha) is also
1147 encoded by a colocalized gene (*RXRA*) near a GWAS hit (chr9:137,268,682). RXRA is a
1148 ligand-activated transcription factor that forms heterodimers with other receptors (including
1149 PPARG) and is involved in lipid metabolism⁵⁷ and homeostasis. Moreover, 145 GWAS loci
1150 (Table S9) overlap RXRA binding peaks, suggesting that the GWAS variants might affect
1151 lipids (partially) through affecting the binding activity of RXRA. While the *RXRA*-associated
1152 variant has been previously implicated as a GWAS locus⁵⁸, our study demonstrates its role in
1153 lipid biology through its regulatory influence on other lipid-associated genes.

1154

1155 *Multi-layer functional integration reveals regulatory mechanisms at GWAS loci*

1156

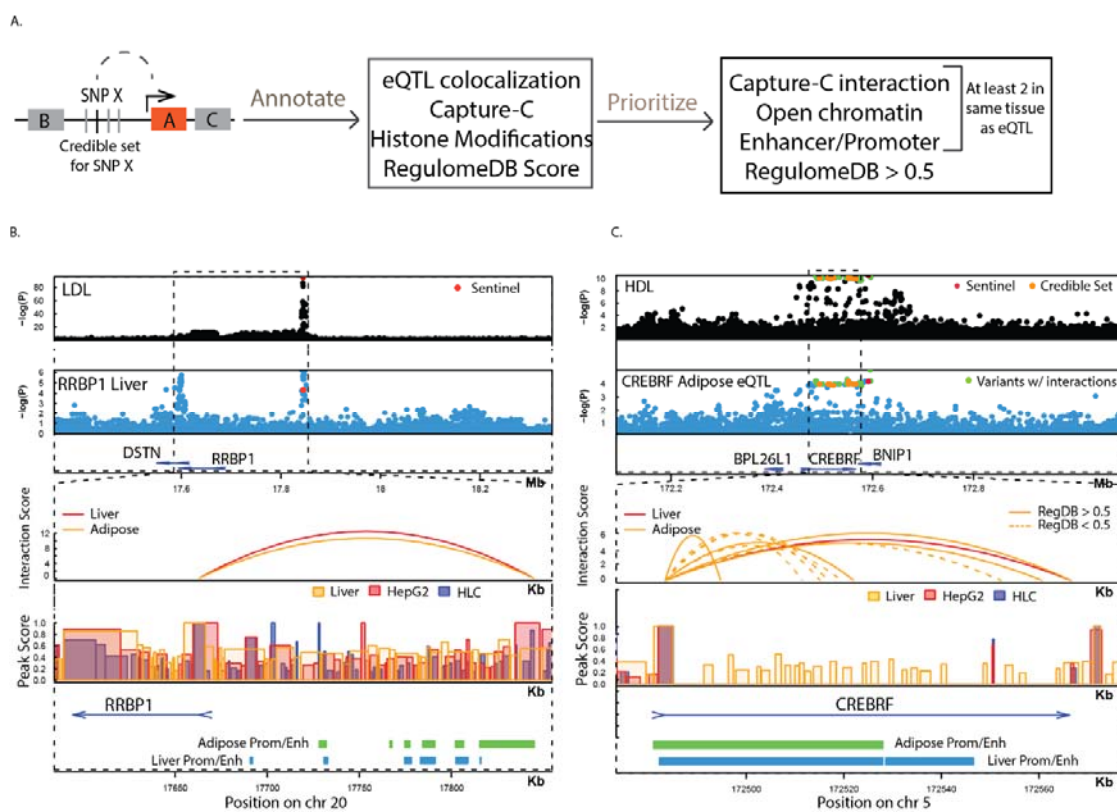
1157 Motivated by our finding that integrating chromatin interaction improved eQTL
1158 colocalizations, we further brought together multiple lines of functional evidence at each
1159 GWAS locus for mechanistic inference. We started with the list of genes with evidence for

1160 both eQTL colocalization in the liver or adipose and credible set physical interactions. We
1161 next annotated each variant in the 95% credible set with various indicators of regulatory
1162 function, including its open chromatin status in liver or adipose-related cell types, its
1163 proximity to a promoter or an enhancer, and its RegulomeDB regulation probability⁵⁹ (see
1164 Table S10 for the complete list of annotations used). To account for complexities of
1165 regulatory mechanisms and limitations of functional datasets, we combined evidence across
1166 these datasets to prioritize variants at GWAS loci (Figure 4A). Specifically, we prioritized
1167 variants with at least three independent lines of functional evidence (chromatin openness,
1168 physically interaction with target genes, and promoter/enhancer status in liver or adipose),
1169 with at least two being in the same tissue with colocalization with the target gene, and with a
1170 RegulomeDB score > 0.5. Applying this simple procedure to lipid GWAS we identified 13
1171 candidate loci, each with the strongest multi-layer evidence pointing to a single functional
1172 variant (Table 1). Below we describe two examples to highlight key features of this multi-
1173 layer integration framework.

1174

1175 *RRBP1* (ribosomal binding protein 1) could be identified from eQTL colocalization alone,
1176 but our multi-layer integration approach strengthened the conclusion via convergent evidence
1177 from various sources (Figure 4B). The *RRBP1* eQTL signals in the liver colocalize with LDL,
1178 TC, and nonHDL GWAS signals. The 'T' allele of the lead variant (chr20:17,844,684, hg19)
1179 decreases *RRBP1* expression levels and increases LDL, TC, and nonHDL levels. This lead
1180 variant is in open chromatin in HLC, and physically interacts with the *RRBP1* promoter
1181 (250kb away) in adipose and HepG2. All these data consistently point to *RRBP1* as the
1182 functional gene underlying this locus. *RRBP1* specifically tethers the endoplasmic reticulum
1183 to the mitochondria in the liver--an interaction that is enriched in hepatocytes--and regulates

1184 very low density lipoprotein (vLDL) levels⁶⁰. Rare variants in *RRBP1* are associated with
 1185 LDL in humans⁶¹ and silencing *RRBP1* in liver affects lipid homeostasis in mice⁶⁰.
 1186
 1187 *Figure 4. An easy-to-implement multi-layer framework to prioritize functional variants at*
 1188 *GWAS loci. A. Variant annotation and prioritization scheme at each credible set. B. Evidence*
 1189 *for gene RRBPI from functional genomics data. The LDL GWAS locus at this region is an*
 1190 *eQTL for gene RRBPI in the liver (second row). Variants in the credible set of this locus*
 1191 *interact with the gene promoter in both adipose and HepG2 Capture-C data. The interacting*
 1192 *variant is also in an open chromatin peak in three liver-related cell types. C. Multiple*
 1193 *sources of functional genomics data support CREBRF as a gene contributing to HDL levels.*
 1194 *The HDL GWAS locus at this region is an eQTL for gene CREBRF in adipose (second row).*
 1195 *Variants in the credible set at this locus interact with the CREBRF promoter in adipose. The*
 1196 *interacting variant is also in open chromatin in liver-related cell types.*



1197

1198

1199 *CREBRF* (CREB3 regulatory factor) demonstrates the power of our multi-layer integration
1200 framework in prioritizing functional variants (Figure 4C). The eQTL signals of *CREBRF*
1201 colocalized with a GWAS locus for HDL with 30 candidate variants. In contrast, our multi-
1202 layer approach identified a single candidate variant (chr5:172,566,698) at this locus that
1203 physically interacts with the *CREBRF* promoter in adipose, was predicted to be a regulatory
1204 element (RegulomeDB score=0.91). Consistent with the index variant (chr5:172,591,337),
1205 the allele 'A' at this functional variant increased HDL levels and increased *CREBRF*
1206 expression in adipose. Missense variants in *CREBRF* have been linked to body mass index,
1207 and the gene has been linked to obesity risk in Samoans ⁶².

1208

1209 Finally, to compare the power of functional fine-mapping with trans-ancestry fine-mapping,
1210 we applied our prioritization rule to credible sets derived from European-only meta-analysis.
1211 The 111 variants prioritized by our rule described above (including multiple variants in the
1212 same credible set) were all found in the multi-ancestry credible sets, representing a 3.7 fold
1213 enrichment ($P < 1e-04$ derived from 10000 permutations randomly sampling variants from
1214 the European-only credible sets). This convergence of complementary approaches to the
1215 same smaller set of variants highlights the power of multi-ancestry datasets as an approach to
1216 narrow in on functional variants.

1217

1218 **Discussion**

1219

1220 Here we integrate the largest multi-population lipid GWAS to date with a wide array of
1221 functional genomic resources to understand how noncoding genetic variation affects lipids
1222 through gene regulation. Specifically, we identify 1,076 genes whose eQTL signals

1223 colocalize with lipid GWAS signals and demonstrate how physical chromatin interaction can
1224 improve standard eQTL-based colocalization. We assess tissue-specific enrichments of lipid
1225 GWAS signals and demonstrate the selective importance of adipose in HDL and triglyceride
1226 biology. We examine binding site enrichments of 161 TFs in lipid GWAS and expand our
1227 understanding of lipid GWAS loci (e.g., *RXRA*) in the context of TF activity. Finally, we
1228 build a simple and interpretable prioritization framework that automatically combines
1229 multiple lines of evidence from orthogonal datasets, pinpointing a single functional variant at
1230 each of 13 lipid-associated loci (e.g., *RRBPI* and *CREBRF*). While there are studies that
1231 interpret lipid GWAS associations^{21,63,64}, the size of our multi-population GWAS and multi-
1232 layer functional integration represent a comprehensive effort and an important step forward in
1233 this direction.

1234

1235 Our multi-layer analysis has two key strengths. First, despite a large array of functional
1236 genomic resources being embedded, our analysis produces results with high consistency. For
1237 example, the selective enrichment of adipose in HDL and TG identified by S-LDSC is
1238 confirmed by our eQTL-based colocalization and TF binding site overlap. Another example
1239 of consistency is the multi-layer prioritization of *RRBPI*, which can be identified from eQTL-
1240 based colocalization alone and it is further validated by chromatin openness and interaction.
1241 Such convergent evidence from various sources improves the confidence of our findings.
1242 Second, our analysis highlights that combining multiple layers of regulatory information can
1243 improve sensitivity to prioritize functional genes and variants. For example, we refined eQTL
1244 colocalized genes (1,076) to a smaller set of functional genes (233) through integration with
1245 promoter Capture-C data. Another example of sensitivity is *CREBRF*, where eQTL-based
1246 colocalization implicates 30 candidate variants and adding other regulatory layers points to a

1247 single functional variant. Moving forward, we expect these two features will serve as useful
1248 guidelines for future integrative genomic analyses of other traits.

1249

1250 Our results rely on the breadth and accuracy of functional genomic datasets used in our
1251 analyses. First, unlike our lipid GWAS, current functional datasets⁶⁵ are limited both in
1252 sample size and ancestral diversity, which can affect discovery and replication of regulatory
1253 mechanisms in diverse populations. Second, some functional datasets are generated at limited
1254 resolution. For example, our colocalizations are based on eQTLs from bulk tissue RNA-seq⁸,
1255 which may miss detailed cell types and biological processes in which lipid-associated SNPs
1256 regulate gene expression⁶⁶. Third, some functional datasets are not available across the full
1257 spectrum of human tissues and cell types. For example, our chromatin-chromatin interaction
1258 analysis only examines a few cell types in two known lipid-related tissues, producing results
1259 that may be biased towards known lipid biology. As more comprehensive and accurate
1260 functional genomic resources are becoming publicly available in diverse cellular contexts and
1261 ancestry groups, the resolution and power of integrative analyses like ours will be markedly
1262 increased.

1263

1264 Other limitations of this study stem from computational methods embedded in our
1265 framework. First, the colocalization approach 'coloc' assumes one causal variant per locus,
1266 whereas recent studies suggest extensive allelic heterogeneity⁶⁷ consistent with a model of a
1267 milieu of related transcription factors binding within a single locus. Accounting for allelic
1268 heterogeneity in summary statistics-based colocalization typically requires modelling
1269 multiple correlated SNPs through LD matrix⁶⁸, which is computationally intensive in large-
1270 scale analyses derived from many cohorts with diverse ancestries, like the multi-population
1271 GWAS examined here. Second, due to restricted access to individual genotypes of 201

1272 cohorts, we cannot produce multi-population LD scores within GLGC but have to use
1273 European-based LD scores in all S-LDSC analyses. This approach, though less rigorous in
1274 principle, provides robust results in practice (as confirmed by our ancestry-specific analysis),
1275 largely because 79% of cohorts in GLGC are of European descent¹². That said, we caution
1276 that the same approach might fall short in ancestrally diverse studies with few European
1277 individuals⁶⁹. Third, our multi-layer variant prioritization framework is built on a series of
1278 simple rules that are easy to implement on large datasets. This approach could possibly be
1279 formalized as statistical models (e.g., priors in Bayesian methods⁴⁹), but certainly simplify
1280 computation and improve scalability of our framework. Despite the technical limitations, our
1281 approach here can serve as a useful benchmark for future development of methods with
1282 improved statistical rigor and computation efficiency.

1283 In summary, mapping noncoding genetic variation of complex traits to biological functions
1284 can benefit greatly from thorough integration of multiple layers of functional genomics, as
1285 demonstrated in the present study. Although tested on lipids only, our integrative framework
1286 is straightforward to implement more broadly on many other phenotypes, yielding functional
1287 insights of heritable traits and diseases in humans.

1288 **Description of Supplemental Data**

1289 Supplemental data include seven figures and ten tables, and study-specific
1290 acknowledgements.

1291 **Declaration of Interests**

1292 G.C-P. is currently an employee of 23andMe Inc. M.J.C. is the Chief Scientist for Genomics
1293 England, a UK Government company. B.M.P. serves on the steering committee of the Yale
1294 Open Data Access Project funded by Johnson & Johnson. G.T., A.H., D.F.G., H.H., U.T., and

1295 K.S. are employees of deCODE/Amgen Inc. V.S. has received honoraria for consultations
1296 from Novo Nordisk and Sanofi and has an ongoing research collaboration with Bayer Ltd.
1297 M.M. has served on advisory panels for Pfizer, NovoNordisk and Zoe Global, has received
1298 honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly, and research funding from
1299 Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk,
1300 Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. M.M. and A.M. are employees of
1301 Genentech and a holders of Roche stock. M.S. receives funding from Pfizer Inc. for a project
1302 unrelated to this work. M.E.K. is employed by SYNLAB MVZ Mannheim GmbH. W.M. has
1303 received grants from Siemens Healthineers, grants and personal fees from Aegerion
1304 Pharmaceuticals, grants and personal fees from AMGEN, grants from Astrazeneca, grants
1305 and personal fees from Sanofi, grants and personal fees from Alexion Pharmaceuticals, grants
1306 and personal fees from BASF, grants and personal fees from Abbott Diagnostics, grants and
1307 personal fees from Numares AG, grants and personal fees from Berlin-Chemie, grants and
1308 personal fees from Akzea Therapeutics, grants from Bayer Vital GmbH , grants from
1309 bestbion dx GmbH, grants from Boehringer Ingelheim Pharma GmbH Co KG, grants from
1310 Immundiagnostik GmbH, grants from Merck Chemicals GmbH, grants from MSD Sharp and
1311 Dohme GmbH, grants from Novartis Pharma GmbH, grants from Olink Proteomics, other
1312 from Synlab Holding Deutschland GmbH, all outside the submitted work. A.V.K. has served
1313 as a consultant to Sanofi, Medicines Company, Maze Pharmaceuticals, Navitor
1314 Pharmaceuticals, Verve Therapeutics, Amgen, and Color Genomics; received speaking fees
1315 from Illumina, the Novartis Institute for Biomedical Research; received sponsored research
1316 agreements from the Novartis Institute for Biomedical Research and IBM Research, and
1317 reports a patent related to a genetic risk predictor (20190017119). S.K. is an employee of
1318 Verve Therapeutics, and holds equity in Verve Therapeutics, Maze Therapeutics, Catabasis,
1319 and San Therapeutics. He is a member of the scientific advisory boards for Regeneron

1320 Genetics Center and Corvidia Therapeutics; he has served as a consultant for Acceleron, Eli
1321 Lilly, Novartis, Merck, Novo Nordisk, Novo Ventures, Ionis, Alnylam, Aegerion, Haug
1322 Partners, Noble Insights, Leerink Partners, Bayer Healthcare, Illumina, Color Genomics,
1323 MedGenome, Quest, and Medscape; he reports patents related to a method of identifying and
1324 treating a person having a predisposition to or afflicted with cardiometabolic disease
1325 (20180010185) and a genetics risk predictor (20190017119). D.K. accepts consulting fees
1326 from Regeneron Pharmaceuticals. D.O.M-K. is a part-time clinical research consultant for
1327 Metabolon, Inc. D.S. has received support from the British Heart Foundation, Pfizer,
1328 Regeneron, Genentech, and Eli Lilly pharmaceuticals. The spouse of C.J.W. is employed by
1329 Regeneron.

1330

1331 **Acknowledgments**

1332 GMP, PN and CW are supported by NHLBI R01HL127564. GMP and PN are supported by
1333 R01HL142711. AG acknowledge support from the Wellcome Trust (201543/B/16/Z),
1334 European Union Seventh Framework Programme FP7/2007-2013 under grant agreement no.
1335 HEALTH-F2-2013-601456 (CVGenes@Target) & the TriPartite Immunometabolism
1336 Consortium [TrIC]-Novo Nordisk Foundation's Grant number NNF15CC0018486. JMM is
1337 supported by American Diabetes Association Innovative and Clinical Translational Award 1-
1338 19-ICTS-068. SR was supported by the Academy of Finland Center of Excellence in
1339 Complex Disease Genetics (Grant No 312062), the Finnish Foundation for Cardiovascular
1340 Research, the Sigrid Juselius Foundation and University of Helsinki HiLIFE Fellow and
1341 Grand Challenge grants. EW was supported by the Finnish innovation fund Sitra (EW) and
1342 Finska Läkaresällskapet. CNS was supported by American Heart Association Postdoctoral
1343 Fellowships 15POST24470131 and 17POST33650016. Charles N Rotimi is supported by

1344 Z01HG200362. Zhe Wang, Michael Presuss, and Ruth JF Loos are supported by
1345 R01HL142302. NJT is a Wellcome Trust Investigator (202802/Z/16/Z), is the PI of the Avon
1346 Longitudinal Study of Parents and Children (MRC & WT 217065/Z/19/Z), is supported by
1347 the University of Bristol NIHR Biomedical Research Centre (BRC-1215-2001), the MRC
1348 Integrative Epidemiology Unit (MC_UU_00011) and works within the CRUK Integrative
1349 Cancer Epidemiology Programme (C18281/A19169). Ruth E Mitchell is a member of the
1350 MRC Integrative Epidemiology Unit at the University of Bristol funded by the MRC
1351 (MC_UU_00011/1). Simon Haworth is supported by the UK National Institute for Health
1352 Research Academic Clinical Fellowship. Paul S. de Vries was supported by American Heart
1353 Association grant number 18CDA34110116. Julia Ramierz acknowledges support by the
1354 People Programme of the European Union's Seventh Framework Programme grant n°
1355 608765 and Marie Skłodowska-Curie grant n° 786833. Maria Sabater-Lleal is supported by a
1356 Miguel Servet contract from the ISCIII Spanish Health Institute (CP17/00142) and co-
1357 financed by the European Social Fund. Jian Yang is funded by the Westlake Education
1358 Foundation. Olga Giannakopoulou has received funding from the British Heart Foundation
1359 (BHF) (FS/14/66/3129). Dr. Sander W. van der Laan is funded through grants from the
1360 Netherlands CardioVascular Research Initiative of the Netherlands Heart Foundation (CVON
1361 2011/B019 and CVON 2017-20: Generating the best evidence-based pharmaceutical targets
1362 for atherosclerosis [GENIUS I&II]). We are thankful for the support of the FP7 EU project
1363 CVgenes@target (HEALTH-F2-2013-601456), ERA-CVD program 'druggable-MI-targets'
1364 (grant number: 01KL1802) and the Leducq Fondation 'PlaqOmics'. Study-specific
1365 acknowledgements are available in the **Supplementary Material**.

1366

1367 **Web Resources**

- 1368 GLGC 2021 summary statistics: <http://csg.sph.umich.edu/willer/public/glgc-lipids2021/>
- 1369 GTEx v8 summary statistics: <https://www.gtexportal.org/home/datasets>
- 1370 coloc: <https://cran.r-project.org/web/packages/coloc>
- 1371 liftOver: <https://genome.ucsc.edu/cgi-bin/hgLiftOver>
- 1372 HiCUP: <https://www.bioinformatics.babraham.ac.uk/projects/hicup/>
- 1373 CHiCAGO: <https://www.bioconductor.org/packages/release/bioc/html/Chicago.html>
- 1374 GenomicRanges: <https://bioconductor.org/packages/release/bioc/html/GenomicRanges.html>
- 1375 bedtools: <https://bedtools.readthedocs.io/en/latest/>
- 1376 ClusterProfiler: <https://guangchuangyu.github.io/clusterProfiler>
- 1377 biomaRt: <https://bioconductor.org/packages/release/bioc/html/biomaRt.html>
- 1378 ClinVar: <https://www.ncbi.nlm.nih.gov/clinvar/>
- 1379 S-PrediXcan: <https://github.com/hakyimlab/MetaXcan>
- 1380 LDSC software: <https://github.com/bulik/ldsc>
- 1381 LD scores and related annotations: <https://data.broadinstitute.org/alkesgroup/LDSCORE/>
- 1382 DEPICT: <https://data.broadinstitute.org/mpg/depict>
- 1383 RSS-NET: <https://github.com/SUwonglab/rss-net>

1384 Adipose single cell data:

1385 https://singlecell.broadinstitute.org/single_cell/study/SCP133/human-adipose-svf-single-cell

1386 fgsea: <http://bioconductor.org/packages/release/bioc/html/fgsea.html>

1387 GREGOR: <https://genome.sph.umich.edu/wiki/GREGOR>

1388 RegulomeDB: <https://regulomedb.org/regulome-search/>

1389

1390 **Data and Code Availability**

1391 HLC Capture-C data is available at

1392 <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE189026>

1393 **References**

1394 1. Gallagher, M.D., and Chen-Plotkin, A.S. (2018). The Post-GWAS Era: From Association
1395 to Function. *Am. J. Hum. Genet.* *102*, 717–730.

1396 2. Cano-Gamez, E., and Trynka, G. (2020). From GWAS to Function: Using Functional
1397 Genomics to Identify the Mechanisms Underlying Complex Diseases. *Front. Genet.* *11*, 424.

1398 3. Schaid, D.J., Chen, W., and Larson, N.B. (2018). From genome-wide associations to
1399 candidate causal variants by statistical fine-mapping. *Nat. Rev. Genet.* *19*, 491–504.

1400 4. Smemo, S., Tena, J.J., Kim, K.-H., Gamazon, E.R., Sakabe, N.J., Gómez-Marín, C.,
1401 Aneas, I., Credidio, F.L., Sobreira, D.R., Wasserman, N.F., et al. (2014). Obesity-associated
1402 variants within FTO form long-range functional connections with IRX3. *Nature* *507*, 371–
1403 375.

1404 5. Musunuru, K., Strong, A., Frank-Kamenetsky, M., Lee, N.E., Ahfeldt, T., Sachs, K.V., Li,
1405 X., Li, H., Kuperwasser, N., Ruda, V.M., et al. (2010). From noncoding variant to phenotype
1406 via SORT1 at the 1p13 cholesterol locus. *Nature* *466*, 714–719.

1407 6. Hekselman, I., and Yeger-Lotem, E. (2020). Mechanisms of tissue and cell-type specificity
1408 in heritable traits and diseases. *Nat. Rev. Genet.* *21*, 137–150.

1409 7. ENCODE Project Consortium (2012). An integrated encyclopedia of DNA elements in the
1410 human genome. *Nature* *489*, 57–74.

1411 8. The GTEx Consortium (2020). The GTEx Consortium atlas of genetic regulatory effects

- 1412 across human tissues. *Science* *369*, 1318–1330.
- 1413 9. Loos, R.J.F., and Yeo, G.S.H. (2021). The genetics of obesity: from discovery to biology.
1414 *Nat. Rev. Genet.* doi: 10.1038/s41576-021-00414-z
- 1415 10. Huo, Y., Li, S., Liu, J., Li, X., and Luo, X.-J. (2019). Functional genomics reveal gene
1416 regulatory mechanisms underlying schizophrenia risk. *Nat. Commun.* *10*, 1–19.
- 1417 11. Willer, C.J., Sanna, S., Jackson, A.U., Scuteri, A., Bonnycastle, L.L., Clarke, R., Heath,
1418 S.C., Timpson, N.J., Najjar, S.S., Stringham, H.M., et al. (2008). Newly identified loci that
1419 influence lipid concentrations and risk of coronary artery disease. *Nat. Genet.* *40*, 161–169.
- 1420 12. Sarah E Graham, Shoa L Clarke, Kuan-Han H Wu, Stavroula Kanoni, Greg JM Zajac,
1421 Shweta Ramdas, Ida Surakka, Ioanna Ntalla, Sailaja Vedantam,, Thomas W Winkler, et al.
1422 (in press). The power of genetic diversity in genome-wide association studies of lipids.
1423 *Nature.* doi: 10.1038/s41586-021-04064-3
- 1424 13. McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A.R., Teumer, A., Kang,
1425 H.M., Fuchsberger, C., Danecek, P., Sharp, K., et al. (2016). A reference panel of 64,976
1426 haplotypes for genotype imputation. *Nat. Genet.* *48*, 1279–1283.
- 1427 14. 1000 Genomes Project Consortium, and Adam Auton, Lisa D Brooks, Richard M Durbin,
1428 Erik P Garrison, Hyun Min Kang, Jan O Korb, Jonathan L Marchini, Shane McCarthy, Gil
1429 A McVean, Gonçalo R Abecasis (2015). A global reference for human genetic variation.
1430 *Nature* *526*, 68–74.
- 1431 15. Mägi, R., Horikoshi, M., Sofer, T., Mahajan, A., Kitajima, H., Franceschini, N.,
1432 McCarthy, M.I., COGENT-Kidney Consortium, T2D-GENES Consortium, and Morris, A.P.
1433 (2017). Trans-ethnic meta-regression of genome-wide association studies accounting for
1434 ancestry increases power for discovery and improves fine-mapping resolution. *Hum. Mol.*
1435 *Genet.* *26*, 3639–3650.
- 1436 16. The International HapMap 3 Consortium (2010). Integrating common and rare genetic
1437 variation in diverse human populations. *Nature* *467*, 52–58.
- 1438 17. Giambartolomei, C., Vukcevic, D., Schadt, E.E., Franke, L., Hingorani, A.D., Wallace,
1439 C., and Plagnol, V. (2014). Bayesian test for colocalisation between pairs of genetic
1440 association studies using summary statistics. *PLoS Genet.* *10*, e1004383.
- 1441 18. Kuhn, R.M., Haussler, D., and Kent, W.J. (2013). The UCSC genome browser and
1442 associated tools. *Brief. Bioinform.* *14*, 144–161.
- 1443 19. Çalışkan, M., Manduchi, E., Rao, H.S., Segert, J.A., Beltrame, M.H., Trizzino, M., Park,
1444 Y., Baker, S.W., Chesi, A., Johnson, M.E., et al. (2019). Genetic and Epigenetic Fine
1445 Mapping of Complex Trait Associated Loci in the Human Liver. *Am. J. Hum. Genet.* *105*,
1446 89–107.
- 1447 20. Chesi, A., Wagley, Y., Johnson, M.E., Manduchi, E., Su, C., Lu, S., Leonard, M.E.,
1448 Hodge, K.M., Pippin, J.A., Hankenson, K.D., et al. (2019). Genome-scale Capture C
1449 promoter interactions implicate effector genes at GWAS loci for bone mineral density. *Nat.*
1450 *Commun.* *10*, 1260.

- 1451 21. Selvarajan, I., Toropainen, A., Garske, K.M., López Rodríguez, M., Ko, A., Miao, Z.,
1452 Kaminska, D., Öunap, K., Örd, T., Ravindran, A., et al. (2021). Integrative analysis of liver-
1453 specific non-coding regulatory SNPs associated with the risk of coronary artery disease. *Am.*
1454 *J. Hum. Genet.* *108*, 411–430.
- 1455 22. Pashos, E.E., Park, Y., Wang, X., Raghavan, A., Yang, W., Abbey, D., Peters, D.T.,
1456 Arbelaez, J., Hernandez, M., Kuperwasser, N., et al. (2017). Large, Diverse Population
1457 Cohorts of hiPSCs and Derived Hepatocyte-like Cells Reveal Functional Genetic Variation at
1458 Blood Lipid-Associated Loci. *Cell Stem Cell* *20*, 558–570.e10.
- 1459 23. Pan, D.Z., Garske, K.M., Alvarez, M., Bhagat, Y.V., Boocock, J., Nikkola, E., Miao, Z.,
1460 Raulerson, C.K., Cantor, R.M., Civelek, M., et al. (2018). Integration of human adipocyte
1461 chromosomal interactions with adipose gene expression prioritizes obesity-related genes from
1462 GWAS. *Nat. Commun.* *9*, 1512.
- 1463 24. Wingett, S., Ewels, P., Furlan-Magaril, M., Nagano, T., Schoenfelder, S., Fraser, P., and
1464 Andrews, S. (2015). HiCUP: pipeline for mapping and processing Hi-C data. *F1000Res.* *4*,
1465 1310.
- 1466 25. Cairns, J., Freire-Pritchett, P., Wingett, S.W., Várnai, C., Dimond, A., Plagnol, V.,
1467 Zerbino, D., Schoenfelder, S., Javierre, B.-M., Osborne, C., et al. (2016). CHiCAGO: robust
1468 detection of DNA looping interactions in Capture Hi-C data. *Genome Biol.* *17*, 127.
- 1469 26. Harrow, J., Frankish, A., Gonzalez, J.M., Tapanari, E., Diekhans, M., Kokocinski, F.,
1470 Aken, B.L., Barrell, D., Zadissa, A., Searle, S., et al. (2012). GENCODE: the reference
1471 human genome annotation for The ENCODE Project. *Genome Res.* *22*, 1760–1774.
- 1472 27. Lawrence, M., Huber, W., Pagès, H., Aboyoun, P., Carlson, M., Gentleman, R., Morgan,
1473 M.T., and Carey, V.J. (2013). Software for computing and annotating genomic ranges. *PLoS*
1474 *Comput. Biol.* *9*, e1003118.
- 1475 28. Leung, D., Jung, I., Rajagopal, N., Schmitt, A., Selvaraj, S., Lee, A.Y., Yen, C.-A., Lin,
1476 S., Lin, Y., Qiu, Y., et al. (2015). Integrative analysis of haplotype-resolved epigenomes
1477 across human tissues. *Nature* *518*, 350–354.
- 1478 29. Yu, G., Wang, L.-G., Han, Y., and He, Q.-Y. (2012). clusterProfiler: an R Package for
1479 Comparing Biological Themes Among Gene Clusters. *OMICS: A Journal of Integrative*
1480 *Biology* *16*, 284–287.
- 1481 30. Kanehisa, M., Sato, Y., Kawashima, M., Furumichi, M., and Tanabe, M. (2016). KEGG
1482 as a reference resource for gene and protein annotation. *Nucleic Acids Res.* *44*, D457–D462.
- 1483 31. Durinck, S., Spellman, P.T., Birney, E., and Huber, W. (2009). Mapping identifiers for
1484 the integration of genomic datasets with the R/Bioconductor package biomaRt. *Nat. Protoc.*
1485 *4*, 1184–1191.
- 1486 32. Landrum, M.J., Chitipiralla, S., Brown, G.R., Chen, C., Gu, B., Hart, J., Hoffman, D.,
1487 Jang, W., Kaur, K., Liu, C., et al. (2020). ClinVar: improvements to accessing data. *Nucleic*
1488 *Acids Res.* *48*, D835–D844.
- 1489 33. Barbeira, A.N., Dickinson, S.P., Bonazzola, R., Zheng, J., Wheeler, H.E., Torres, J.M.,
1490 Torstenson, E.S., Shah, K.P., Garcia, T., Edwards, T.L., et al. (2018). Exploring the

- 1491 phenotypic consequences of tissue specific gene expression variation inferred from GWAS
1492 summary statistics. *Nat. Commun.* *9*, 1825.
- 1493 34. Hindy, G., Dornbos, P., Chaffin, M.D., Liu, D.J., Wang, M.X., Selvaraj, M.S., Zhang, D.,
1494 Park, J., Aguilar-Salinas, C.A., Antonacci-Fulton, L., et al. (2021). Rare coding variants in 35
1495 genes associate with circulating lipid levels – a multi-ancestry analysis of 170,000 exomes.
1496 [bioRxiv 10.1101/2020.12.22.423783](https://doi.org/10.1101/2020.12.22.423783)
- 1497 35. Finucane, H.K., Bulik-Sullivan, B., Gusev, A., Trynka, G., Reshef, Y., Loh, P.-R.,
1498 Anttila, V., Xu, H., Zang, C., Farh, K., et al. (2015). Partitioning heritability by functional
1499 annotation using genome-wide association summary statistics. *Nat. Genet.* *47*, 1228.
- 1500 36. Kanai, M., Akiyama, M., Takahashi, A., Matoba, N., Momozawa, Y., Ikeda, M., Iwata,
1501 N., Ikegawa, S., Hirata, M., Matsuda, K., et al. (2018). Genetic analysis of quantitative traits
1502 in the Japanese population links cell types to complex human diseases. *Nat. Genet.* *50*, 390–
1503 400.
- 1504 37. Schmidt, E.M., Zhang, J., Zhou, W., Chen, J., Mohlke, K.L., Eugene Chen, Y., and
1505 Willer, C.J. (2015). GREGOR: evaluating global enrichment of trait-associated variants in
1506 epigenomic features using a systematic, data-driven approach. *Bioinformatics* *31*, 2601–
1507 2606.
- 1508 38. MacParland, S.A., Liu, J.C., Ma, X.-Z., Innes, B.T., Bartczak, A.M., Gage, B.K., Manuel,
1509 J., Khuu, N., Echeverri, J., Linares, I., et al. (2018). Single cell RNA sequencing of human
1510 liver reveals distinct intrahepatic macrophage populations. *Nat. Commun.* *9*, 4383.
- 1511 39. Korotkevich, G., Sukhov, V., Budin, N., Shpak, B., Artyomov, M.N., and Sergushichev,
1512 A. Fast gene set enrichment analysis. [bioRxiv https://doi.org/10.1101/060012](https://doi.org/10.1101/060012)
- 1513 40. Neumeyer, S., Hemani, G., and Zeggini, E. (2020). Strengthening Causal Inference for
1514 Complex Disease Using Molecular Quantitative Trait Loci. *Trends Mol. Med.* *26*, 232–241.
- 1515 41. Y C Loraine Tung, Giles S H Yeo, Stephen O’Rahilly, Anthony P Coll (2014). Obesity
1516 and FTO: Changing Focus at a Complex Locus. *Cell Metab.* *20*, 710–718.
- 1517 42. Blair, D.R., Lyttle, C.S., Mortensen, J.M., Bearden, C.F., Jensen, A.B., Khiabani, H.,
1518 Melamed, R., Rabadan, R., Bernstam, E.V., Brunak, S., et al. (2013). A nondegenerate code
1519 of deleterious variants in Mendelian loci contributes to complex disease risk. *Cell* *155*(1):70-
1520 80.
- 1521 43. Teslovich, T.M., Musunuru, K., Smith, A.V., Edmondson, A.C., Stylianou, I.M., Koseki,
1522 M., Pirruccello, J.P., Ripatti, S., Chasman, D.I., Willer, C.J., et al. (2010). Biological, clinical
1523 and population relevance of 95 loci for blood lipids. *Nature* *466*, 707–713.
- 1524 44. David U Gorkin, Danny Leung, Bing Ren (2014). The 3D Genome in Transcriptional
1525 Regulation and Pluripotency. *Cell Stem Cell* *14*, 762–775.
- 1526 45. Wakefield, J. (2009). Bayes factors for genome-wide association studies: comparison
1527 with P-values. *Genet. Epidemiol.* *33*, 79–86.
- 1528 46. Yu, J., Hu, M., and Li, C. (2019). Joint analyses of multi-tissue Hi-C and eQTL data
1529 demonstrate close spatial proximity between eQTLs and their target genes. *BMC Genet.* *20*,

- 1530 43.
- 1531 47. Matharu, N.K., and Ahanger, S.H. (2015). Chromatin Insulators and Topological
1532 Domains: Adding New Dimensions to 3D Genome Architecture. *Genes* 6, 790–811.
- 1533 48. Pers, T.H., Karjalainen, J.M., Chan, Y., Westra, H.-J., Wood, A.R., Yang, J., Lui, J.C.,
1534 Vedantam, S., Gustafsson, S., Esko, T., et al. (2015). Biological interpretation of genome-
1535 wide association studies using predicted gene functions. *Nat. Commun.* 6, 5890.
- 1536 49. Zhu, X., Duren, Z., and Wong, W.H. (2021). Modeling regulatory network topology
1537 improves genome-wide analyses of complex human traits. *Nat. Commun.* 12, 2851.
- 1538 50. Zhang, T., Chen, J., Tang, X., Luo, Q., Xu, D., and Yu, B. (2019). Interaction between
1539 adipocytes and high-density lipoprotein:new insights into the mechanism of obesity-induced
1540 dyslipidemia and atherosclerosis. *Lipids Health Dis.* 18, 223.
- 1541 51. A. D. Sniderman, K. Cianflone, P. Arner, L. K. M. Summers, and K. N. Frayn (1998) The
1542 Adipocyte, Fatty Acid Trapping, and Atherogenesis. *Arteriosclerosis, Thrombosis, and*
1543 *Vascular Biology.* 18:147–151.
- 1544 52. Subramanian, A., Tamayo, P., Mootha, V.K., Mukherjee, S., Ebert, B.L., Gillette, M.A.,
1545 Paulovich, A., Pomeroy, S.L., Golub, T.R., Lander, E.S., et al. (2005). Gene set enrichment
1546 analysis: a knowledge-based approach for interpreting genome-wide expression profiles.
1547 *Proc. Natl. Acad. Sci. U. S. A.* 102, 15545–15550.
- 1548 53. Degtyareva, A.O., Antontseva, E.V., and Merkulova, T.I. (2021). Regulatory SNPs:
1549 Altered Transcription Factor Binding Sites Implicated in Complex Traits and Diseases. *Int. J.*
1550 *Mol. Sci.* 22,.
- 1551 54. Tripathi, M., Yen, P.M., and Singh, B.K. (2020). Estrogen-Related Receptor Alpha: An
1552 Under-Appreciated Potential Target for the Treatment of Metabolic Diseases. *Int. J. Mol. Sci.*
1553 21,.
- 1554 55. Saykally, J.N., Dogan, S., Cleary, M.P., and Sanders, M.M. (2009). The ZEB1
1555 Transcription Factor Is a Novel Repressor of Adiposity in Female Mice. *PLoS One* 4, e8460.
- 1556 56. Gubelmann, C., Schwalie, P.C., Raghav, S.K., Röder, E., Delessa, T., Kiehlmann, E.,
1557 Waszak, S.M., Corsinotti, A., Udin, G., Holcombe, W., et al. (2014). Identification of the
1558 transcription factor ZEB1 as a central component of the adipogenic gene regulatory network.
1559 *Elife* 3, e03346.
- 1560 57. Neuschwander-Tetri, B.A. (2015). Retinoid X receptor: the forgotten partner in regulating
1561 lipid metabolism? *Am. J. Clin. Nutr.* 102, 5–6.
- 1562 58. Peloso, G.M., Demissie, S., Collins, D., Mirel, D.B., Gabriel, S.B., Cupples, L.A.,
1563 Robins, S.J., Schaefer, E.J., and Brousseau, M.E. (2010). Common genetic variation in
1564 multiple metabolic pathways influences susceptibility to low HDL-cholesterol and coronary
1565 heart disease. *J. Lipid Res.* 51, 3524–3532.
- 1566 59. Boyle, A.P., Hong, E.L., Hariharan, M., Cheng, Y., Schaub, M.A., Kasowski, M.,
1567 Karczewski, K.J., Park, J., Hitz, B.C., Weng, S., et al. (2012). Annotation of functional
1568 variation in personal genomes using RegulomeDB. *Genome Research* 22, 1790–1797.

- 1569 60. Anastasia, I., Ilacqua, N., Raimondi, A., Lemieux, P., Ghandehari-Alavijeh, R., Faure, G.,
1570 Mekhedov, S.L., Williams, K.J., Caicci, F., Valle, G., et al. (2021). Mitochondria-rough-ER
1571 contacts in the liver regulate systemic lipid homeostasis. *Cell Rep.* *34*, 108873.
- 1572 61. Jurgens, S.J., Choi, S.H., Morrill, V.N., Chaffin, M., Pirruccello, J.P., Halford, J.L.,
1573 Weng, L.-C., Nauffal, V., Roselli, C., Hall, A.W., et al. (2020). Rare Genetic Variation
1574 Underlying Human Diseases and Traits: Results from 200,000 Individuals in the UK
1575 Biobank.
- 1576 62. Minster, R.L., Hawley, N.L., Su, C.-T., Sun, G., Kershaw, E.E., Cheng, H., Buhule, O.D.,
1577 Lin, J., Reupena, M.S., Viali, S. 'itea, et al. (2016). A thrifty variant in CREBRF strongly
1578 influences body mass index in Samoans. *Nat. Genet.* *48*, 1049–1054.
- 1579 63. Klarin, D., Damrauer, S.M., Cho, K., Sun, Y.V., Teslovich, T.M., Honerlaw, J., Gagnon,
1580 D.R., DuVall, S.L., Li, J., Peloso, G.M., et al. (2018). Genetics of blood lipids among
1581 ~300,000 multi-ethnic participants of the Million Veteran Program. *Nat. Genet.* *50*, 1514–
1582 1523.
- 1583 64. Li, Z., Votava, J.A., Zajac, G.J.M., Nguyen, J.N., Leyva Jaimes, F.B., Ly, S.M.,
1584 Brinkman, J.A., De Giorgi, M., Kaul, S., Green, C.L., et al. (2020). Integrating Mouse and
1585 Human Genetic Data to Move beyond GWAS and Identify Causal Genes in Cholesterol
1586 Metabolism. *Cell Metab.* *31*, 741–754.e5.
- 1587 65. Varshney, A., VanRenterghem, H., Orchard, P., Boyle, A.P., Stitzel, M.L., Ucar, D., and
1588 Parker, S.C.J. (2019). Cell Specificity of Human Regulatory Annotations and Their Genetic
1589 Effects on Gene Expression. *Genetics* *211*, 549–562.
- 1590 66. van der Wijst, M.G.P., de Vries, D.H., Groot, H.E., Trynka, G., Hon, C.C., Bonder, M.J.,
1591 Stegle, O., Nawijn, M.C., Idaghdour, Y., van der Harst, P., et al. (2020). Science Forum: The
1592 single-cell eQTLGen consortium. *eLife* 2020;9:e52155.
- 1593 67. Arvanitis, M., Tayeb, K., Strober, B.J., and Battle, A. (2021). Redefining tissue
1594 specificity of genetic regulation of gene expression in the presence of allelic heterogeneity.
1595 medRxiv 2021.06.28.21259545.
- 1596 68. Zhu, X., and Stephens, M. (2017). Bayesian large-scale multiple regression with
1597 summary statistics from genome-wide association studies. *Ann. Appl. Stat.* *11*, 1561–1592.
- 1598 69. Wojcik, G.L., Graff, M., Nishimura, K.K., Tao, R., Haessler, J., Gignoux, C.R., Highland,
1599 H.M., Patel, Y.M., Sorokin, E.P., Avery, C.L., et al. (2019). Genetic analyses of diverse
1600 populations improves discovery for complex traits. *Nature* *570*, 514–518.
- 1601

Tables

Table 1. Thirteen prioritized loci with highest confidence of a single functional variant in the credible set. The ‘sentinel’ column represents the lead variant at the locus. ‘Prioritized var’ 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 datasets. The ‘RegDB’ column represents the RegulomeDB score of the prioritized variant.

<i>Gene Name</i>	<i>Tissue</i>	<i>Sentinel</i>	<i>Prioritized Var</i>	<i>Open</i>	<i>CapC</i>	<i>Enhancer</i>	<i>Promoter</i>	<i>RegDB</i>
<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	Both	Ad	0.705
<i>MICAL2</i>	Liver	11:12071855	12221016	Liver	Liver	Liver	Ad	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	Both	Ad	0.60906
<i>FAM210A</i>	Liver	18:13725674	13725674	Liver	Liver	Both	Ad	0.7571
<i>RRBP1</i>	Liver	20:17844684	17844684	Both	Ad	Both	Ad	0.6091