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Supplemental Data

Efficient Variant Set Mixed Model Association Tests for Continuous and Binary Traits in Large-Scale Whole-Genome Sequencing Studies

Han Chen, Jennifer E. Huffman, Jennifer A. Brody, Chaolong Wang, Seunggeun Lee, Zilin Li, Stephanie M. Gogarten, Tamar Sofer, Lawrence F. Bielak, Joshua C. Bis, John Blangero, Russell P. Bowler, Brian E. Cade, Michael H. Cho, Adolfo Correa, Joanne E. Curran, Paul S. de Vries, David C. Glahn, Xiuqing Guo, Andrew D. Johnson, Sharon Kardia, Charles Kooperberg, Joshua P. Lewis, Xiaoming Liu, Rasika A. Mathias, Braxton D. Mitchell, Jeffrey R. O'Connell, Patricia A. Peyser, Wendy S. Post, Alex P. Reiner, Stephen S. Rich, Jerome I. Rotter, Edwin K. Silverman, Jennifer A. Smith, Ramachandran S. Vasan, James G. Wilson, Lisa R. Yanek, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, TOPMed Hematology and Hemostasis Working Group, Susan Redline, Nicholas L. Smith, Eric Boerwinkle, Ingrid B. Borecki, L. Adrienne Cupples, Cathy C. Laurie, Alanna C. Morrison, Kenneth M. Rice, and Xihong Lin

Supplemental Data

Supplemental Figures

Figure S1. Empirical power of mixed model based SMMAT-B (B), SMMAT-S (S), SMMAT-O (O), SMMAT-E (E) and GLMM-MiST (M) in the presence of large genetic effects. The total sample size was 2,000, and all genetic variants were causal, with effects in the same direction. (A) Power at the significance level of 2.5×10^{-6} for continuous traits in linear mixed models. (B) Power at the significance level of 2.5×10^{-6} for binary traits in logistic mixed models. (C) P value comparison of SMMAT-E and GLMM-MiST for continuous traits in linear mixed models. (D) P value comparison of SMMAT-E and GLMM-MiST for binary traits in logistic mixed models.

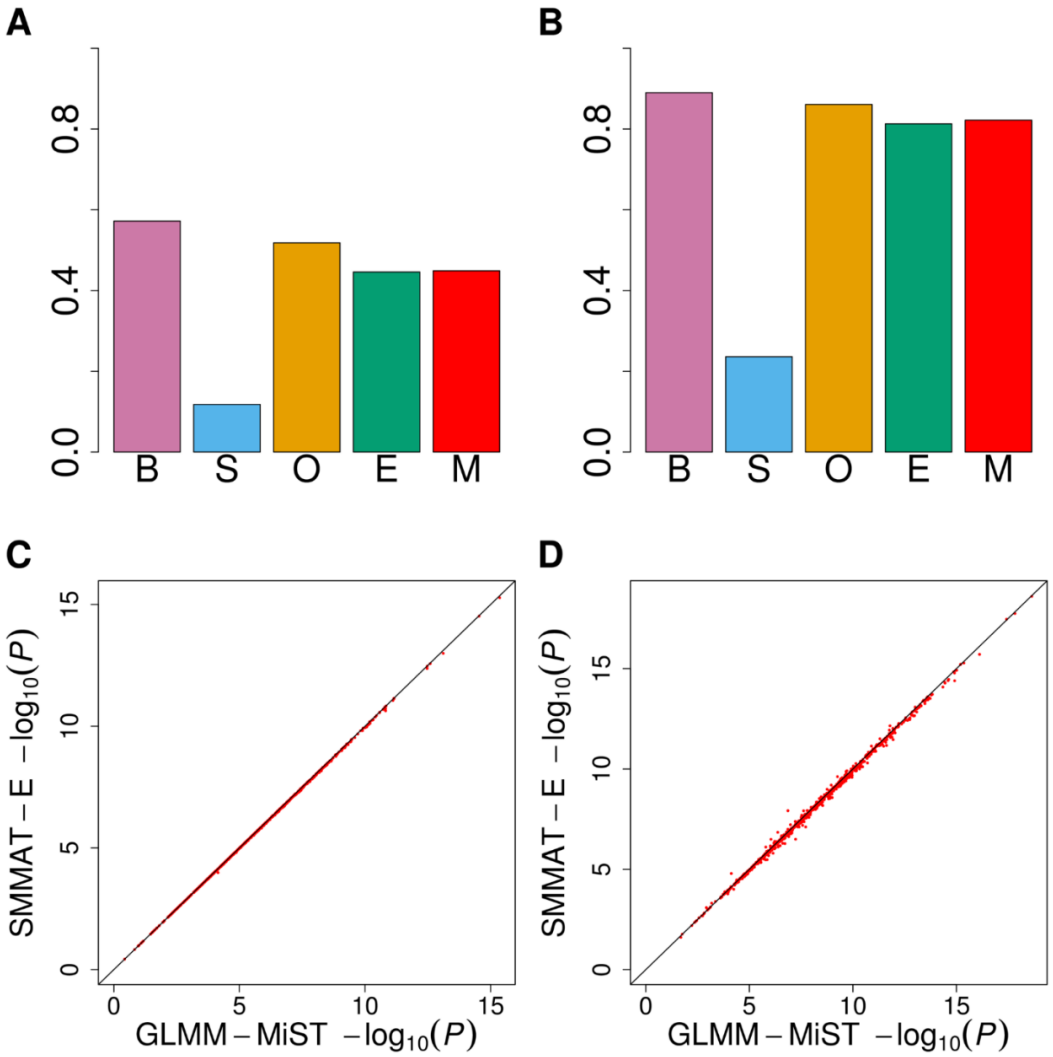


Figure S2. Quantile-quantile plots of SMMAT-B, SMMAT-S, SMMAT-O and SMMAT-E in the analysis of 10,000 samples in the presence of both population-level and familial random effects, under the null hypothesis of no genetic association. (A) Continuous traits in linear mixed models with GRM random effects and no ancestry PC adjustment. (B) Binary traits in logistic mixed models with GRM random effects and no ancestry PC adjustment. (C) Continuous traits in linear mixed models with GRM random effects and 10 ancestry PCs. (D) Binary traits in logistic mixed models with GRM random effects and 10 ancestry PCs. (E) Continuous traits in linear mixed models with GRM and population random effects, but no ancestry PC adjustment. (F) Binary traits in logistic mixed models with GRM and population random effects, but no ancestry PC adjustment.

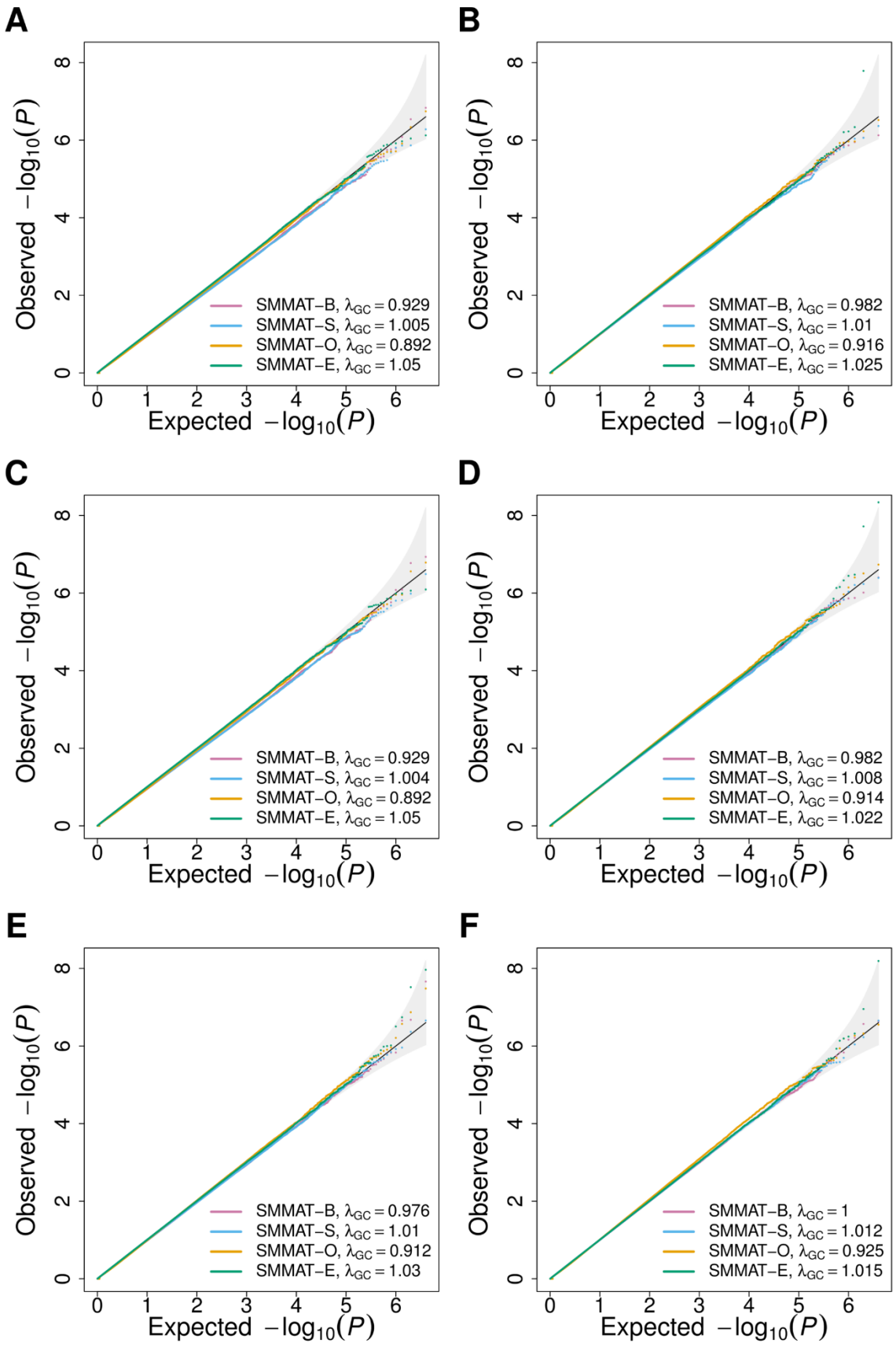

A
Observed $-\log_{10}(P)$
Expected $-\log_{10}(P)$
SMMAT–B, $\lambda_{GC} = 0.929$
SMMAT–S, $\lambda_{GC} = 1.005$
SMMAT–O, $\lambda_{GC} = 0.892$
SMMAT–E, $\lambda_{GC} = 1.05$
B
Observed $-\log_{10}(P)$
Expected $-\log_{10}(P)$
SMMAT–B, $\lambda_{GC} = 0.982$
SMMAT–S, $\lambda_{GC} = 1.01$
SMMAT–O, $\lambda_{GC} = 0.916$
SMMAT–E, $\lambda_{GC} = 1.025$
C
Observed $-\log_{10}(P)$
Expected $-\log_{10}(P)$
SMMAT–B, $\lambda_{GC} = 0.929$
SMMAT–S, $\lambda_{GC} = 1.004$
SMMAT–O, $\lambda_{GC} = 0.892$
SMMAT–E, $\lambda_{GC} = 1.05$
D
Observed $-\log_{10}(P)$
Expected $-\log_{10}(P)$
SMMAT–B, $\lambda_{GC} = 0.982$
SMMAT–S, $\lambda_{GC} = 1.008$
SMMAT–O, $\lambda_{GC} = 0.914$
SMMAT–E, $\lambda_{GC} = 1.022$
E
Observed $-\log_{10}(P)$
Expected $-\log_{10}(P)$
SMMAT–B, $\lambda_{GC} = 0.976$
SMMAT–S, $\lambda_{GC} = 1.01$
SMMAT–O, $\lambda_{GC} = 0.912$
SMMAT–E, $\lambda_{GC} = 1.03$
F
Observed $-\log_{10}(P)$
Expected $-\log_{10}(P)$
SMMAT–B, $\lambda_{GC} = 1$
SMMAT–S, $\lambda_{GC} = 1.012$
SMMAT–O, $\lambda_{GC} = 0.925$
SMMAT–E, $\lambda_{GC} = 1.015$

Figure S3. Empirical power of linear mixed model based SMMAT-B (B), SMMAT-S (S), SMMAT-O (O) and SMMAT-E (E) in continuous trait analysis of 5,000 samples, using three models: GRM random effects with no ancestry PC adjustment (1 RE no PC), GRM random effects with 10 ancestry PCs as fixed effects (1 RE 10 PC), GRM and population random effects with no ancestry PC adjustment (2 RE no PC). (A) 10% causal variants with 100% negative effects. (B) 10% causal variants with 80% negative effects. (C) 10% causal variants with 50% negative effects. (D) 20% causal variants with 100% negative effects. (E) 20% causal variants with 80% negative effects. (F) 20% causal variants with 50% negative effects. (G) 50% causal variants with 100% negative effects. (H) 50% causal variants with 80% negative effects. (I) 50% causal variants with 50% negative effects. Effect sizes were simulated using the same parameter in each row, but different across rows.

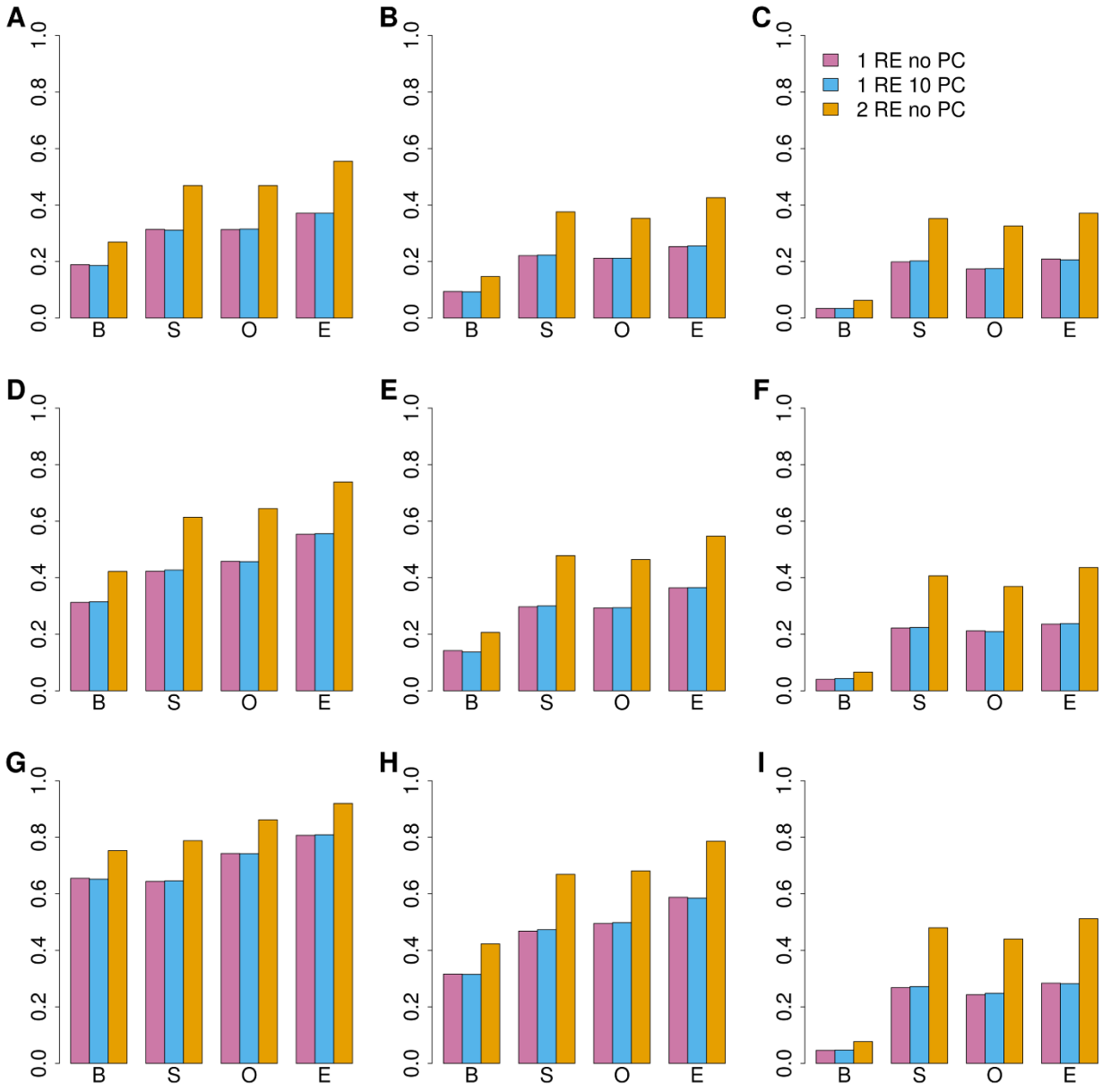

A
B
C
D
E
F
G
H
I
1 RE no PC
1 RE 10 PC
2 RE no PC
0.0
0.2
0.4
0.6
0.8
1.0
B
S
O
E

Figure S4. Empirical power of logistic mixed model based SMMAT-B (B), SMMAT-S (S), SMMAT-O (O) and SMMAT-E (E) in binary trait analysis of 5,000 samples, using three models: GRM random effects with no ancestry PC adjustment (1 RE no PC), GRM random effects with 10 ancestry PCs as fixed effects (1 RE 10 PC), GRM and population random effects with no ancestry PC adjustment (2 RE no PC). (A) 10% causal variants with 100% negative effects. (B) 10% causal variants with 80% negative effects. (C) 10% causal variants with 50% negative effects. (D) 20% causal variants with 100% negative effects. (E) 20% causal variants with 80% negative effects. (F) 20% causal variants with 50% negative effects. (G) 50% causal variants with 100% negative effects. (H) 50% causal variants with 80% negative effects. (I) 50% causal variants with 50% negative effects. Effect sizes were simulated using the same parameter in each row, but different across rows.

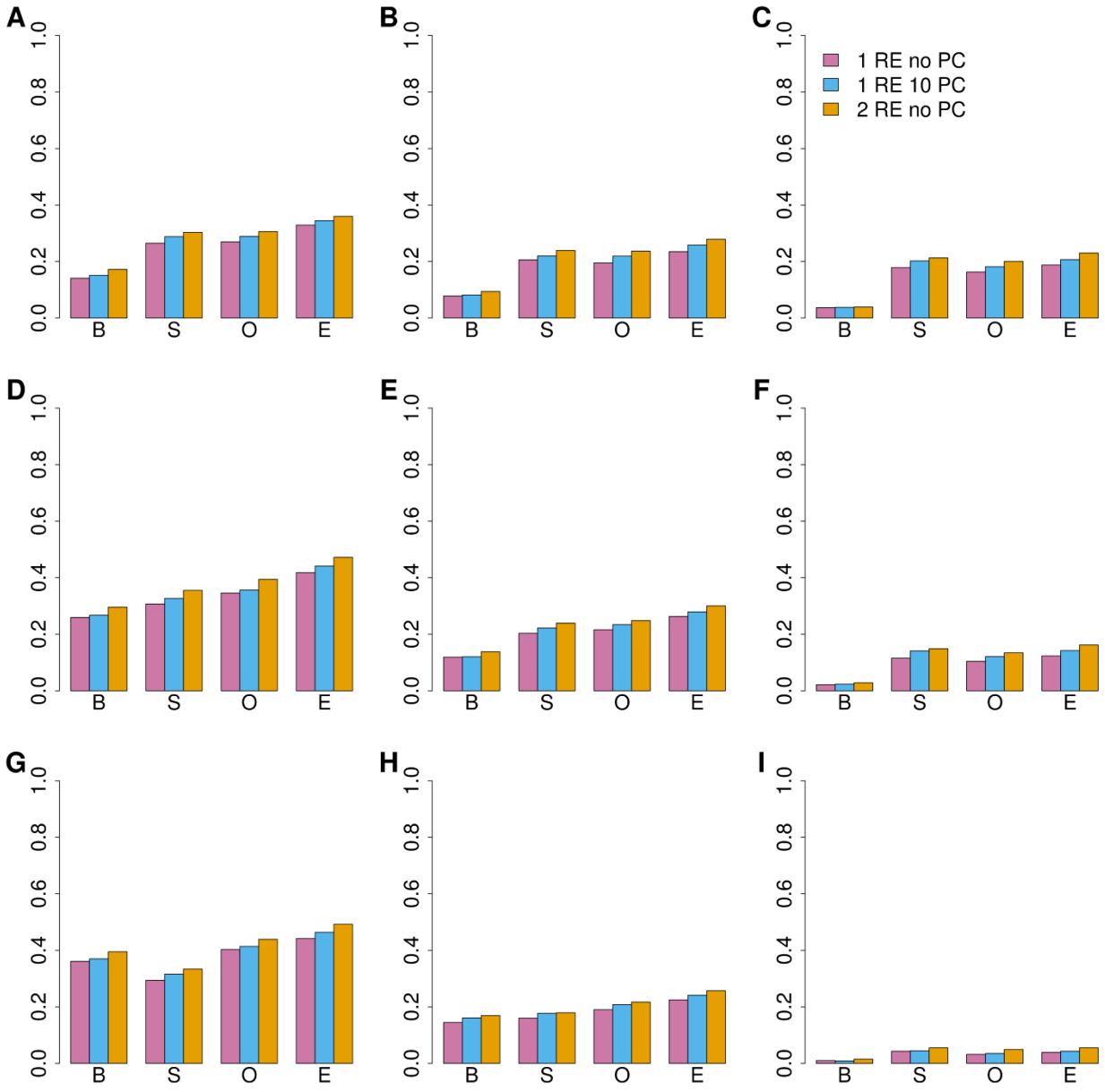

A
B
C
D
E
F
G
H
I
1 RE no PC
1 RE 10 PC
2 RE no PC
0.0
0.2
0.4
0.6
0.8
1.0
B
S
O
E

Figure S5. P value comparison of TOPMed fibrinogen level SMMAT analysis results using heteroscedastic linear mixed models with and without adjusting for 10 ancestry PCs as fixed effects, using rare variants with MAF < 5% in non-overlapping 4 kb sliding windows on chromosome 4 (n = 23,763). (A) SMMAT-B. (B) SMMAT-S. (C) SMMAT-O. (D) SMMAT-E.

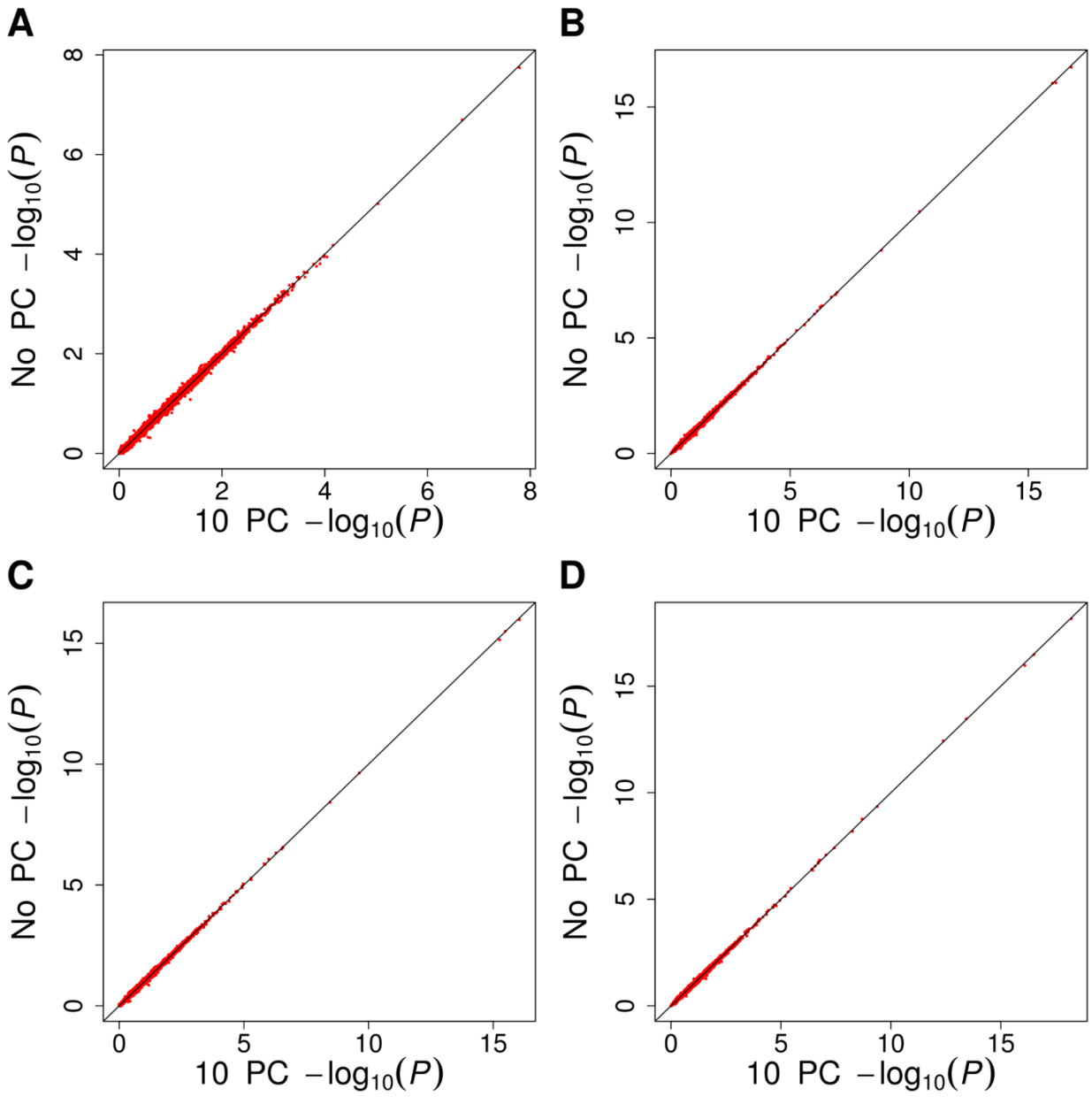


Figure S6. TOPMed fibrinogen level SMMAT analysis results using a heteroscedastic linear mixed model on rare variants with MAF < 5% in non-overlapping 1 kb sliding windows on chromosome 4 (n = 23,763). (A) Quantile-quantile plot. (B) P values on the log scale versus physical positions of the windows on chromosome 4 (build hg38).

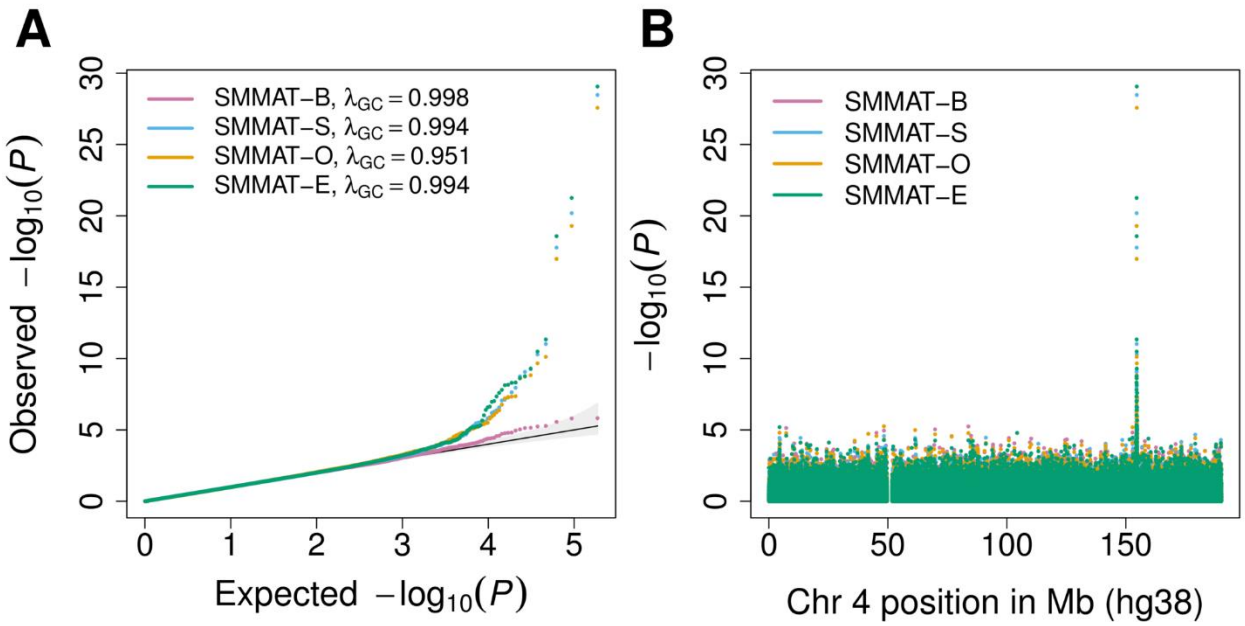


Figure S7. TOPMed fibrinogen level SMMAT analysis results using a heteroscedastic linear mixed model on rare variants with MAF < 5% in non-overlapping 10 kb sliding windows on chromosome 4 (n = 23,763). (A) Quantile-quantile plot. (B) P values on the log scale versus physical positions of the windows on chromosome 4 (build hg38).

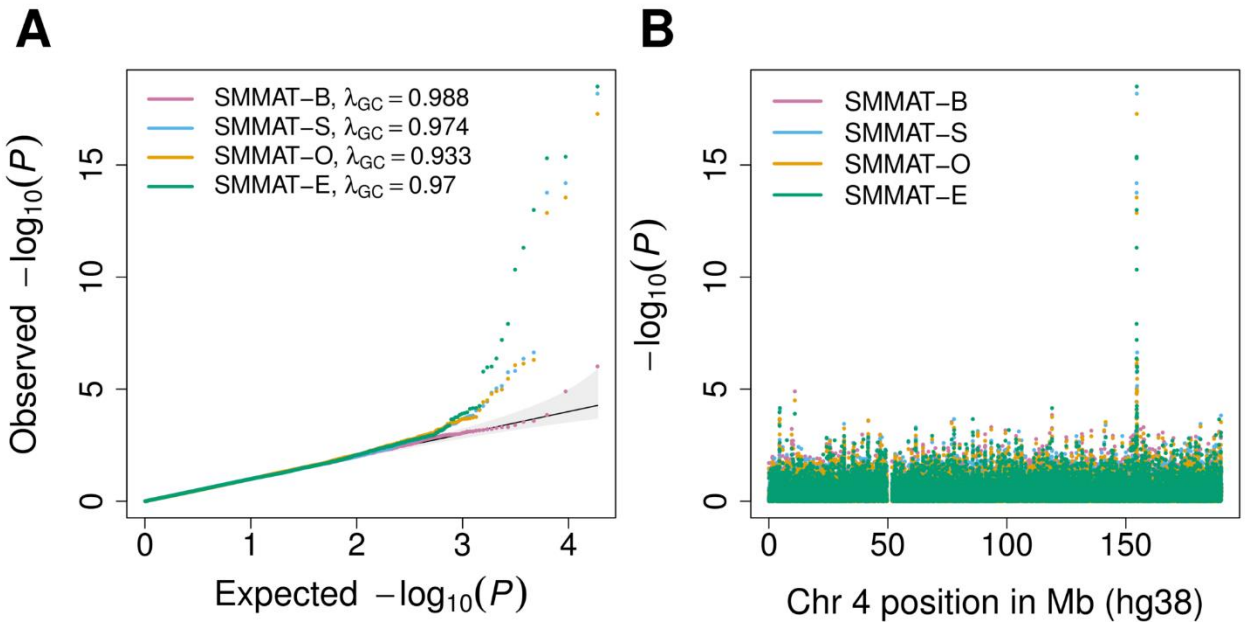
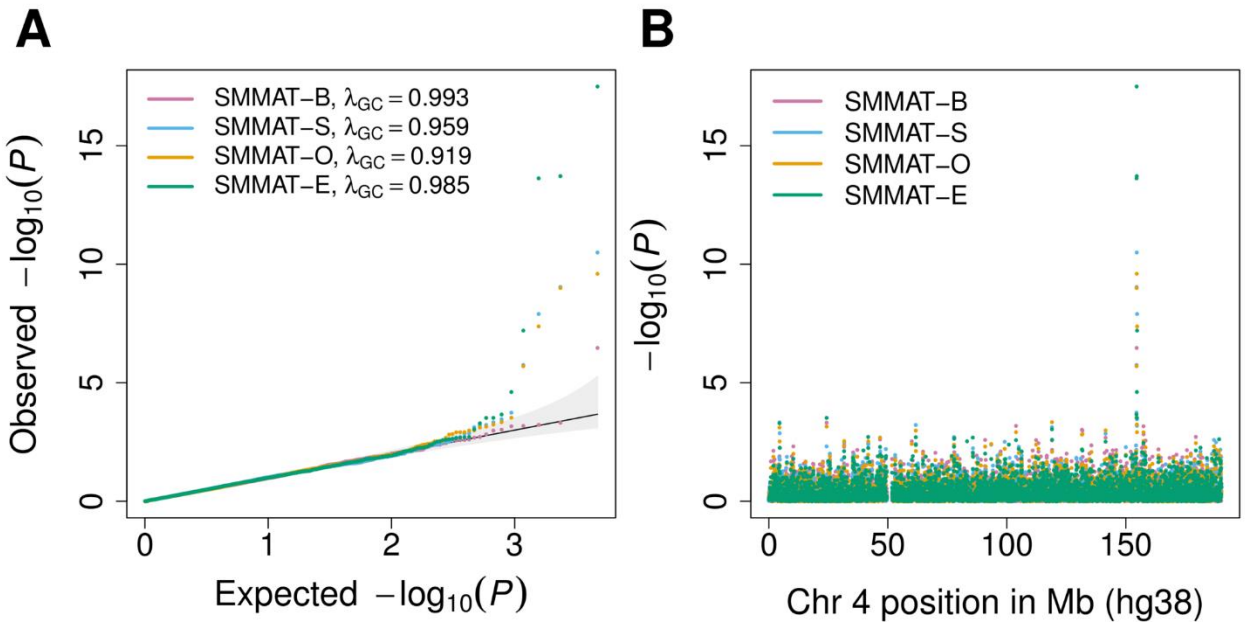


Figure S8. TOPMed fibrinogen level SMMAT analysis results using a heteroscedastic linear mixed model on rare variants with MAF < 5% in non-overlapping 40 kb sliding windows on chromosome 4 (n = 23,763). (A) Quantile-quantile plot. (B) P values on the log scale versus physical positions of the windows on chromosome 4 (build hg38).



Supplemental Tables

Table S1. TOPMed fibrinogen level SMMAT p values covering two known association variants rs6054 (hg38 position 154,568,456) and rs201909029 (hg 38 position 154,567,636) in gene *FGB* on chromosome 4, using a heteroscedastic linear mixed model on rare variants with MAF < 5% (n = 23,763). Physical positions of each window are on build hg38.

Window (kb)	Length	No. of variants	SMMAT-B	SMMAT-S	SMMAT-O	SMMAT-E
154,567-154,568[a]	1 kb	78	0.097	0.0047	0.0076	0.0086
154,568-154,569[b]	1 kb	86	8.1×10^{-5}	1.7×10^{-18}	1.0×10^{-17}	2.7×10^{-19}
154,566-154,570	4 kb	309	1.6×10^{-8}	9.7×10^{-17}	3.3×10^{-16}	3.1×10^{-17}
154,560-154,570	10 kb	846	0.0011	1.7×10^{-14}	1.4×10^{-13}	4.3×10^{-16}
154,560-154,600	40 kb	3,399	3.4×10^{-7}	9.2×10^{-10}	1.0×10^{-9}	3.2×10^{-18}

[a] This window covers rs201909029, which has 33 minor allele counts in our TOPMed samples.

[b] This window covers rs6054, which has 179 minor allele counts in our TOPMed samples.

Supplemental Methods: Additional Simulation Studies

Impact of Large Genetic Effects on SMMAT-E Power

The efficient hybrid test SMMAT-E is developed based on the assumption that the mean of genetic effects β_0 is not large. To investigate the impact of large genetic effects on SMMAT-E power, we performed additional simulation studies in which all variants in a test unit are causal, with the effects in the same direction. This simulation setting is in favor of SMMAT-B. We used the same genotype data as that in the single-cohort type I error simulations and evaluated the empirical power of SMMAT-B, SMMAT-S, SMMAT-O, SMMAT-E, and GLMM-MiST that combines the p value of SMMAT-B (Equation 2 in Methods) and the p value of SMMAT-S (Equation 3 in Methods) using Fisher's method. All tests were performed using weights equal to a beta distribution density function with parameters 1 and 25 on the MAF of each variant.

For continuous traits, we simulated the phenotype y_{ij} for individual j in family i from

$$y_{ij} = \alpha_1 Z_i + \beta_0 T_{ij} + b_{ij} + \epsilon_{ij},$$

where $\alpha_1 = 1$, the population indicator $Z_i = 1$ if family i was from Population 1, and $Z_i = 0$ if from Population 2, the genetic effect $\beta_0 = 0.15$. The burden score T_{ij} of individual j in family i was the weighted sum of causal variant genotypes (with weights equal to a beta distribution density function with parameters 1 and 25 on the MAF of each variant), normalized to have mean 0 and variance 1. The familial random effects b_{ij} were simulated using Equation 5 in Methods, and the random error $\epsilon_{ij} \sim N(0, 1)$. In this parameter setting, the burden score T_{ij} explains 1.3% of the total phenotypic variance. We randomly sampled 35% individuals from Population 1, and 65% individuals from Population 2.

For binary traits, we simulated the phenotype y_{ij} for individual j in family i from

$$\log\left(\frac{P(y_{ij}=1)}{1-P(y_{ij}=1)}\right)=\alpha_0+\beta_0 T_{ij}+b_{ij},$$

where α_0 was chosen such that the disease prevalence was 0.01 in all populations, the genetic effect $\beta_0 = 0.3$. The burden score T_{ij} of individual j in family i was calculated in the same way as for continuous traits, and the familial random effects b_{ij} were simulated using Equation 5 in Methods. We randomly sampled 35% individuals (with 25% cases and 10% controls out of the total sample size) from Population 1, and 65% individuals (with 25% cases and 40% controls out of the total sample size) from Population 2 to form a hypothetical study with balanced cases and controls in combined populations.

We used the sample size of 2,000 for both continuous and binary traits, since the simulated genetic effect was large. We repeated 1,000 simulation replicates, and compared the empirical power at the significance level of 2.5×10^{-6}, as well as the p values from SMMAT-E and GLMM-MiST (Figure S1).

Impact of Multiple Random Effects

One advantage of the SMMAT framework is that it can flexibly use multiple random effects to model between-subject correlation from different sources in the model. We considered two sources of genetic relatedness in our simulation, one from population structure and one from family membership. The population membership matrix has 400 population blocks corresponding to the 20×20 grid in Figure 1A, with elements equal to 1 if two individuals are from the same population grid, 0 otherwise. We included a population-level random intercept with mean 0 and variance 1, which is the same for individuals from the same population grid, in the true models for both

continuous and binary traits. We also included the familial random effects from Equation 5 in Methods.

We evaluated the performance of three analytical strategies in the presence of sample correlation due to both population-level and familial random effects: 1) including a single random effects term with the covariance matrix proportional to the GRM, without adjusting for ancestry PCs; 2) including a single random effects term with the covariance matrix proportional to the GRM, and adjusting for the first 10 ancestry PCs as fixed effects; and 3) including two random effects terms, one with the covariance matrix proportional to the GRM, and the other with the covariance matrix proportional to the block-diagonal population membership matrix, without adjusting for ancestry PCs. We evaluated the type I error rate and power as described in Methods.

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Full Authorship List of the Trans-Omics for Precision Medicine (TOPMed) Consortium

Name	Institution(s)
Abe, Namiko	New York Genome Center
Abecasis, Goncalo	University of Michigan
Albert, Christine	Massachusetts General Hospital
Allred, Nicholette (Nichole) Palmer	Wake Forest Baptist Health
Almasy, Laura	Children's Hospital of Philadelphia, University of Pennsylvania
Alonso, Alvaro	Emory University
Ament, Seth	University of Maryland
Anderson, Peter	University of Washington
Anugu, Pramod	University of Mississippi
Applebaum-Bowden, Deborah	National Institutes of Health
Arking, Dan	Johns Hopkins University
Arnett, Donna K	University of Kentucky
Ashley-Koch, Allison	Duke University
Aslibekyan, Stella	University of Alabama
Assimes, Tim	Stanford University
Auer, Paul	University of Wisconsin Milwaukee
Avramopoulos, Dimitrios	Johns Hopkins University
Barnard, John	Cleveland Clinic
Barnes, Kathleen	University of Colorado at Denver
Barr, R. Graham	Columbia University
Barron-Casella, Emily	Johns Hopkins University
Beaty, Terri	Johns Hopkins University
Becker, Diane	Johns Hopkins University
Becker, Lewis	Johns Hopkins University
Beer, Rebecca	National Heart, Lung, and Blood Institute, National Institutes of Health
Begum, Ferdouse	Johns Hopkins University
Beitelshees, Amber	University of Maryland
Benjamin, Emelia	Boston University, Massachusetts General Hospital
Bezerra, Marcos	Fundação de Hematologia e Hemoterapia de Pernambuco - Hemope
Bielak, Larry	University of Michigan
Bis, Joshua	University of Washington
Blackwell, Thomas	University of Michigan

Name	Institution(s)
Blangero, John	University of Texas Rio Grande Valley School of Medicine
Boerwinkle, Eric	University of Texas Health at Houston
Borecki, Ingrid	University of Washington
Bowler, Russell	National Jewish Health
Brody, Jennifer	University of Washington
Broeckel, Ulrich	Medical College of Wisconsin
Broome, Jai	University of Washington
Bunting, Karen	New York Genome Center
Burchard, Esteban	University of California, San Francisco
Cardwell, Jonathan	University of Colorado at Denver
Carty, Cara	Women's Health Initiative
Casaburi, Richard	University of California, Los Angeles
Casella, James	Johns Hopkins University
Chaffin, Mark	The Broad Institute
Chang, Christy	University of Maryland
Chasman, Daniel	Brigham & Women's Hospital
Chavan, Sameer	University of Colorado at Denver
Chen, Bo-Juen	New York Genome Center
Chen, Wei-Min	University of Virginia
Chen, Yii-Der Ida	Los Angeles Biomedical Research Institute
Cho, Michael	Brigham & Women's Hospital
Choi, Seung Hoan	The Broad Institute
Chuang, Lee-Ming	National Taiwan University
Chung, Mina	Cleveland Clinic
Cornell, Elaine	University of Vermont
Correa, Adolfo	University of Mississippi
Crandall, Carolyn	University of California, Los Angeles
Crapo, James	National Jewish Health
Cupples, L Adrienne	Boston University
Curran, Joanne	University of Texas Rio Grande Valley School of Medicine
Curtis, Jeffrey	University of Michigan
Custer, Brian	Blood Systems Research Institute UCSF
Damcott, Coleen	University of Maryland
Darbar, Dawood	University of Illinois at Chicago
Das, Sayantan	University of Michigan
David, Sean	Stanford University
Davis, Colleen	University of Washington

Name	Institution(s)
Daya, Michelle	University of Colorado at Denver
de Andrade, Mariza	Mayo Clinic
DeBaun, Michael	Vanderbilt University
Deka, Ranjan	University of Cincinnati
DeMeo, Dawn	Brigham & Women's Hospital
Devine, Scott	University of Maryland
Do, Ron	Icahn School of Medicine at Mount Sinai
Duan, Qing	University of North Carolina
Duggirala, Ravi	University of Texas Rio Grande Valley School of Medicine
Durda, Peter	University of Vermont
Dutcher, Susan	Washington University in St Louis
Eaton, Charles	Brown University
Ekunwe, Lynette	University of Mississippi
Ellinor, Patrick	Massachusetts General Hospital
Emery, Leslie	University of Washington
Farber, Charles	University of Virginia
Farnam, Leanna	Brigham & Women's Hospital
Fingerlin, Tasha	National Jewish Health
Flickinger, Matthew	University of Michigan
Fornage, Myriam	University of Texas Health at Houston
Franceschini, Nora	University of North Carolina
Fu, Mao	University of Maryland
Fullerton, Stephanie M.	University of Washington
Fulton, Lucinda	Washington University in St Louis
Gabriel, Stacey	The Broad Institute
Gan, Weiniu	National Heart, Lung, and Blood Institute, National Institutes of Health
Gao, Yan	University of Mississippi
Gass, Margery	Fred Hutchinson Cancer Research Center
Gelb, Bruce	Icahn School of Medicine at Mount Sinai
Geng, Xiaoqi (Priscilla)	University of Michigan
Germer, Soren	New York Genome Center
Gignoux, Chris	Stanford University
Gladwin, Mark	University of Pittsburgh
Glahn, David	Yale University
Gogarten, Stephanie	University of Washington
Gong, Da-Wei	University of Maryland

Name	Institution(s)
Goring, Harald	University of Texas Rio Grande Valley School of Medicine
Gu, C. Charles	Washington University in St Louis
Guan, Yue	University of Maryland
Guo, Xiuqing	Los Angeles Biomedical Research Institute
Haessler, Jeff	Fred Hutchinson Cancer Research Center, Women's Health Initiative
Hall, Michael	University of Mississippi
Harris, Daniel	University of Maryland
Hawley, Nicola	Yale University
He, Jiang	Tulane University
Heavner, Ben	University of Washington
Heckbert, Susan	University of Washington
Hernandez, Ryan	University of California, San Francisco
Herrington, David	Wake Forest Baptist Health
Hersh, Craig	Brigham & Women's Hospital
Hidalgo, Bertha	University of Alabama
Hixson, James	University of Texas Health at Houston
Hokanson, John	University of Colorado at Denver
Holly, Kramer	Loyola University
Hong, Elliott	University of Maryland
Hoth, Karin	University of Iowa
Hsiung, Chao (Agnes)	National Health Research Institute Taiwan
Huston, Haley	Blood Works Northwest
Hwu, Chii Min	Taichung Veterans General Hospital Taiwan
Irvin, Marguerite Ryan	University of Alabama
Jackson, Rebecca	Ohio State University Wexner Medical Center
Jain, Deepti	University of Washington
Jaquish, Cashell	National Heart, Lung, and Blood Institute, National Institutes of Health
Jhun, Min A	University of Michigan
Johnsen, Jill	Blood Works Northwest, University of Washington
Johnson, Andrew	National Heart, Lung, and Blood Institute, National Institutes of Health
Johnson, Craig	University of Washington
Johnston, Rich	Emory University
Jones, Kimberly	Johns Hopkins University
Kang, Hyun Min	University of Michigan
Kaplan, Robert	Albert Einstein College of Medicine

Name	Institution(s)
Kardia, Sharon	University of Michigan
Kathiresan, Sekar	The Broad Institute
Kaufman, Laura	Brigham & Women's Hospital
Kelly, Shannon	Blood Systems Research Institute UCSF
Kenny, Eimear	Icahn School of Medicine at Mount Sinai
Kessler, Michael	University of Maryland
Khan, Alyna	University of Washington
Kinney, Greg	University of Colorado at Denver
Konkle, Barbara	Blood Works Northwest
Kooperberg, Charles	Fred Hutchinson Cancer Research Center
Krauter, Stephanie	University of Washington
Lange, Christoph	Harvard School of Public Health
Lange, Ethan	University of Colorado at Denver
Lange, Leslie	University of Colorado at Denver
Laurie, Cathy	University of Washington
Laurie, Cecelia	University of Washington
LeBoff, Meryl	Brigham & Women's Hospital
Lee, Seunggeun Shawn	University of Michigan
Lee, Wen-Jane	Taichung Veterans General Hospital Taiwan
LeFaive, Jonathon	University of Michigan
Levine, David	University of Washington
Levy, Dan	National Heart, Lung, and Blood Institute, National Institutes of Health
Lewis, Joshua	University of Maryland
Li, Yun	University of North Carolina
Lin, Honghuang	Boston University
Lin, Keng Han	University of Michigan
Liu, Simin	Brown University, Women's Health Initiative
Liu, Yongmei	Wake Forest Baptist Health
Loos, Ruth	Icahn School of Medicine at Mount Sinai
Lubitz, Steven	Massachusetts General Hospital
Lunetta, Kathryn	Boston University
Luo, James	National Heart, Lung, and Blood Institute, National Institutes of Health
Mahaney, Michael	University of Texas Rio Grande Valley School of Medicine
Make, Barry	Johns Hopkins University
Manichaikul, Ani	University of Virginia

Name	Institution(s)
Manson, JoAnn	Brigham & Women's Hospital
Margolin, Lauren	The Broad Institute
Martin, Lisa	George Washington University
Mathai, Susan	University of Colorado at Denver
Mathias, Rasika	Johns Hopkins University
McArdle, Patrick	University of Maryland
McDonald, Merry-Lynn	University of Alabama
McFarland, Sean	Harvard University
McGarvey, Stephen	Brown University
Mei, Hao	University of Mississippi
Meyers, Deborah A	University of Arizona
Mikulla, Julie	National Heart, Lung, and Blood Institute, National Institutes of Health
Min, Nancy	University of Mississippi
Minear, Mollie	National Heart, Lung, and Blood Institute, National Institutes of Health
Minster, Ryan L	University of Pittsburgh
Mitchell, Braxton	University of Maryland
Montasser, May E.	University of Maryland
Musani, Solomon	University of Mississippi
Mwasongwe, Stanford	University of Mississippi
Mychaleckyj, Josyf C	University of Virginia
Nadkarni, Girish	Icahn School of Medicine at Mount Sinai
Naik, Rakhi	Johns Hopkins University
Natarajan, Pradeep	The Broad Institute, Harvard University, Massachusetts General Hospital
Nekhai, Sergei	Howard University
Nickerson, Deborah	University of Washington
North, Kari	University of North Carolina
O'Connell, Jeff	University of Maryland
O'Connor, Tim	University of Maryland
Ochs-Balcom, Heather	University at Buffalo
Pankow, James	University of Minnesota
Papanicolaou, George	National Heart, Lung, and Blood Institute, National Institutes of Health
Parker, Margaret	Brigham & Women's Hospital
Parsa, Afshin	University of Maryland
Penchev, Sara	National Jewish Health

Name	Institution(s)
Peralta, Juan Manuel	University of Texas Rio Grande Valley School of Medicine
Perez, Marco	Stanford University
Perry, James	University of Maryland
Peters, Ulrike	Fred Hutchinson Cancer Research Center, University of Washington
Peyser, Patricia	University of Michigan
Phillips, Larry	Emory University
Phillips, Sam	University of Washington
Pollin, Toni	University of Maryland
Post, Wendy	Johns Hopkins University
Powers Becker, Julia	University of Colorado at Denver
Preethi Boorgula, Meher	University of Colorado at Denver
Preuss, Michael	Icahn School of Medicine at Mount Sinai
Prokopenko, Dmitry	Harvard University
Psaty, Bruce	University of Washington
Qasba, Pankaj	National Heart, Lung, and Blood Institute, National Institutes of Health
Qiao, Dandi	Brigham & Women's Hospital
Qin, Zhaohui	Emory University
Rafaels, Nicholas	University of Colorado at Denver
Raffield, Laura	University of North Carolina
Ramachandran, Vasan	Boston University
Rao, D.C.	Washington University in St Louis
Rasmussen-Torvik, Laura	Northwestern University
Ratan, Aakrosh	University of Virginia
Redline, Susan	Brigham & Women's Hospital
Reed, Robert	University of Maryland
Regan, Elizabeth	National Jewish Health
Reiner, Alex	Fred Hutchinson Cancer Research Center, University of Washington
Rice, Ken	University of Washington
Rich, Stephen	University of Virginia
Roden, Dan	Vanderbilt University
Roselli, Carolina	The Broad Institute
Rotter, Jerome	Los Angeles Biomedical Research Institute
Ruczinski, Ingo	Johns Hopkins University
Russell, Pamela	University of Colorado at Denver
Ruuska, Sarah	Blood Works Northwest

Name	Institution(s)
Ryan, Kathleen	University of Maryland
Sakornsakolpat, Phuwanat	Brigham & Women's Hospital
Salimi, Shabnam	University of Maryland
Salzberg, Steven	Johns Hopkins University
Sandow, Kevin	Los Angeles Biomedical Research Institute
Sankaran, Vijay	Harvard University
Scheller, Christopher	University of Michigan
Schmidt, Ellen	University of Michigan
Schwander, Karen	Washington University in St Louis
Schwartz, David	University of Colorado at Denver
Sciurba, Frank	University of Pittsburgh
Seidman, Christine	Harvard Medical School
Sheehan, Vivien	Baylor College of Medicine
Shetty, Amol	University of Maryland
Shetty, Aniket	University of Colorado at Denver
Sheu, Wayne Hui-Heng	Taichung Veterans General Hospital Taiwan
Shoemaker, M. Benjamin	Vanderbilt University
Silver, Brian	UMass Memorial Medical Center
Silverman, Edwin	Brigham & Women's Hospital
Smith, Jennifer	University of Michigan
Smith, Josh	University of Washington
Smith, Nicholas	University of Washington
Smith, Tanja	New York Genome Center
Smoller, Sylvia	Albert Einstein College of Medicine
Snively, Beverly	Wake Forest Baptist Health
Sofer, Tamar	Brigham & Women's Hospital
Sotoodehnia, Nona	University of Washington
Stilp, Adrienne	University of Washington
Streeten, Elizabeth	University of Maryland
Sung, Yun Ju	Washington University in St Louis
Sylvia, Jody	Brigham & Women's Hospital
Szpiro, Adam	University of Washington
Sztalryd, Carole	University of Maryland
Taliun, Daniel	University of Michigan
Tang, Hua	Stanford University
Taub, Margaret	Johns Hopkins University
Taylor, Kent	Los Angeles Biomedical Research Institute

Name	Institution(s)
Taylor, Simeon	University of Maryland
Telen, Marilyn	Duke University
Thornton, Timothy A.	University of Washington
Tinker, Lesley	Women's Health Initiative
Tirschwell, David	University of Washington
Tiwari, Hemant	University of Alabama
Tracy, Russell	University of Vermont
Tsai, Michael	University of Minnesota
Vaidya, Dhananjay	Johns Hopkins University
VandeHaar, Peter	University of Michigan
Vrieze, Scott	University of Colorado at Boulder, University of Minnesota
Walker, Tarik	University of Colorado at Denver
Wallace, Robert	University of Iowa
Walts, Avram	University of Colorado at Denver
Wan, Emily	Brigham & Women's Hospital
Wang, Fei Fei	University of Washington
Watson, Karol	University of California, Los Angeles
Weeks, Daniel E.	University of Pittsburgh
Weir, Bruce	University of Washington
Weiss, Scott	Brigham & Women's Hospital
Weng, Lu-Chen	Massachusetts General Hospital
Willer, Cristen	University of Michigan
Williams, Kayleen	University of Washington
Williams, L. Keoki	Henry Ford Health System
Wilson, Carla	Brigham & Women's Hospital
Wilson, James	University of Mississippi
Wong, Quenna	University of Washington
Xu, Huichun	University of Maryland
Yanek, Lisa	Johns Hopkins University
Yang, Ivana	University of Colorado at Denver
Yang, Rongze	University of Maryland
Zaghloul, Norann	University of Maryland
Zekavat, Maryam	The Broad Institute
Zhang, Yingze	University of Pittsburgh
Zhao, Snow Xueyan	National Jewish Health
Zhao, Wei	University of Michigan
Zheng, Xiuwen	University of Washington

Name	Institution(s)
Zhi, Degui	University of Texas Health at Houston
Zhou, Xiang	University of Michigan
Zody, Michael	New York Genome Center
Zoellner, Sebastian	University of Michigan