

Supplemental Data

Efficient Variant Set Mixed Model Association

Tests for Continuous and Binary Traits

in Large-Scale Whole-Genome Sequencing Studies

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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.

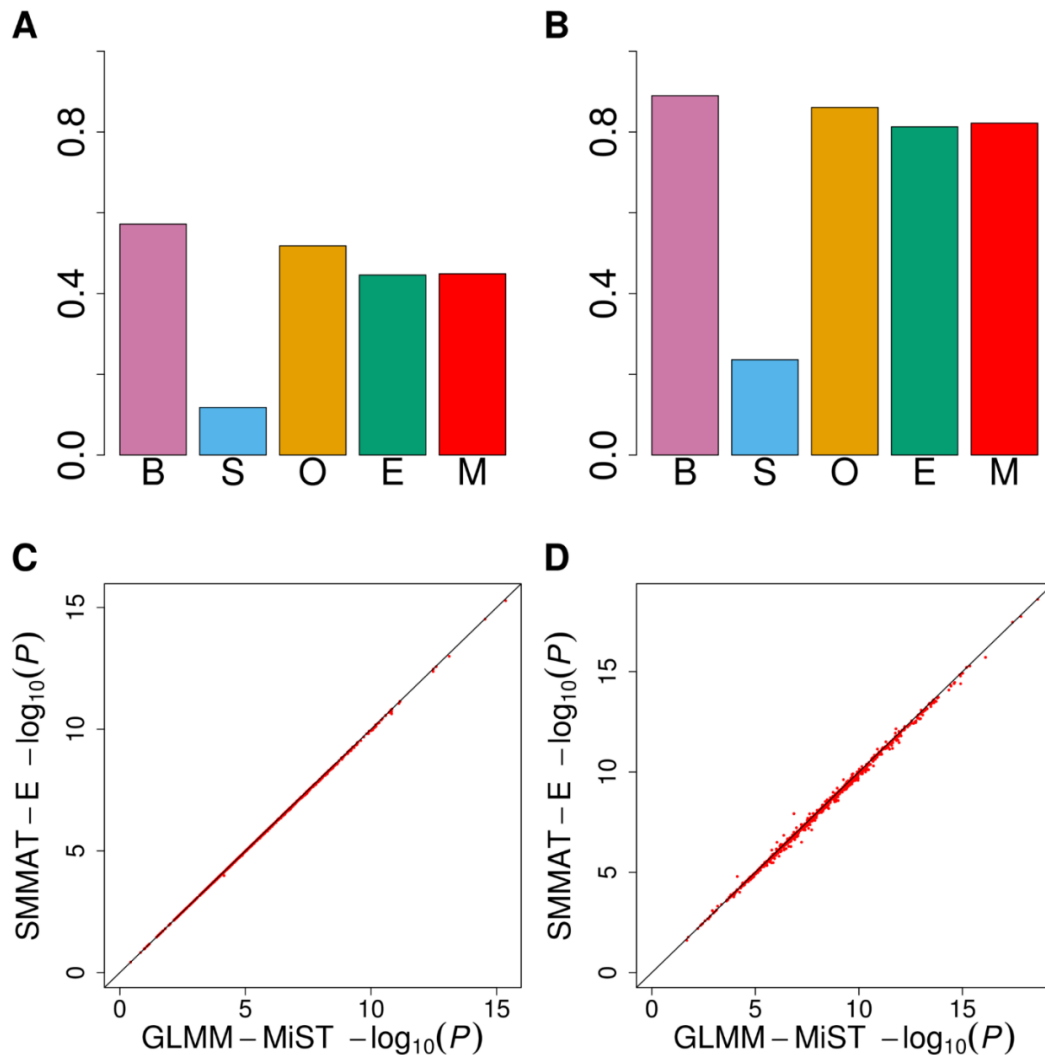


Figure S2. Quantile-quantile plots of SMMAT-B, SMMAT-S, SMMAT-O and SMMAT-E in the analysis of 10,000 samples in the presence of both population-level and familial random effects, under the null hypothesis of no genetic association. (A) Continuous traits in linear mixed models with GRM random effects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

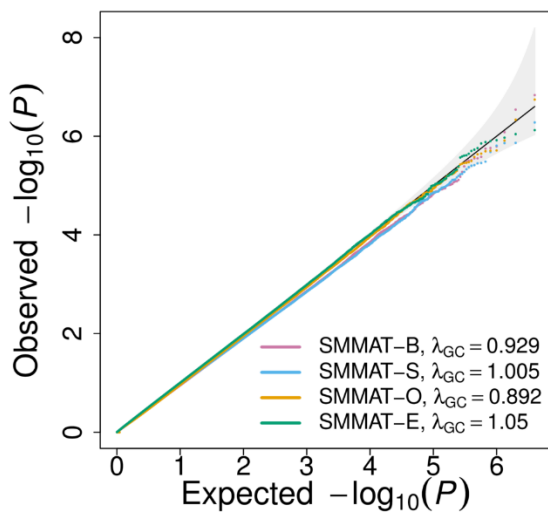
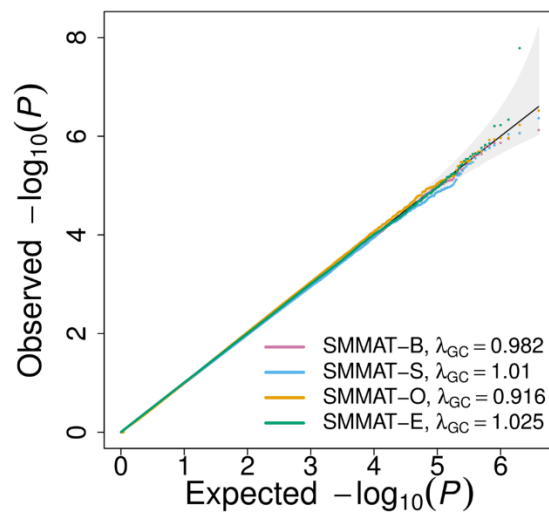
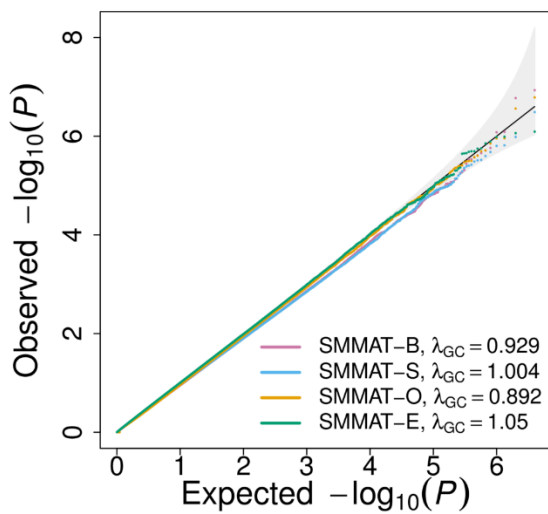
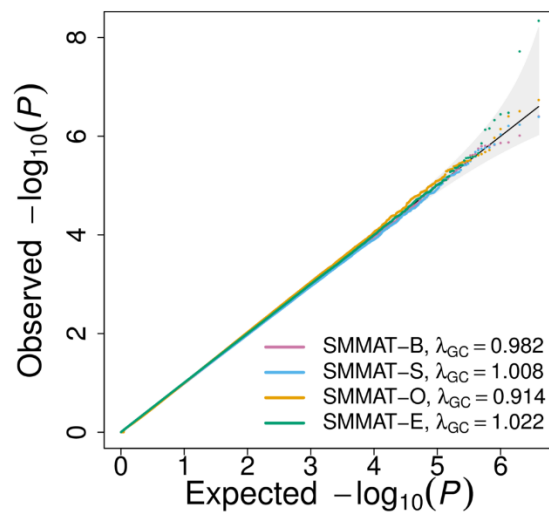
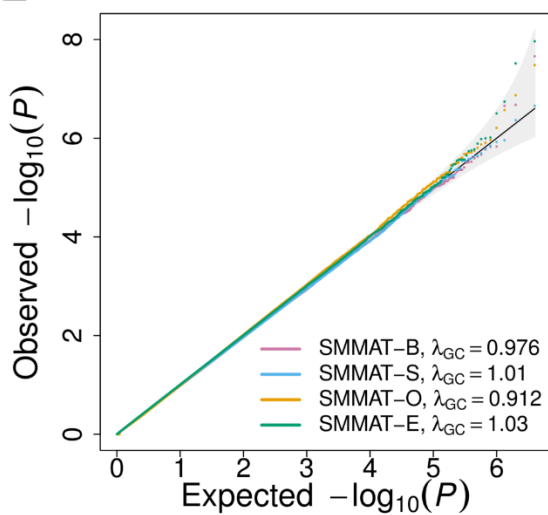
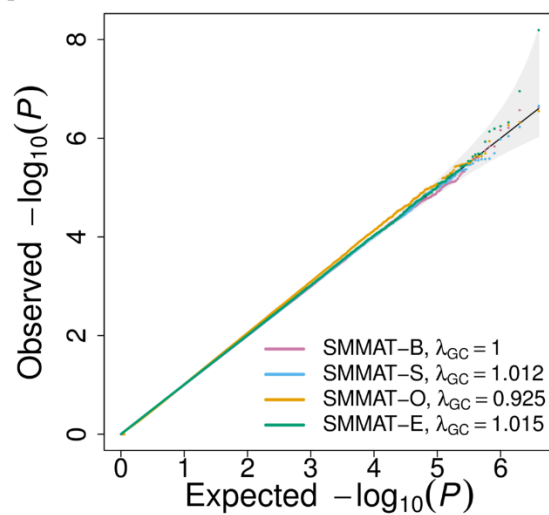
A**B****C****D****E****F**

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.

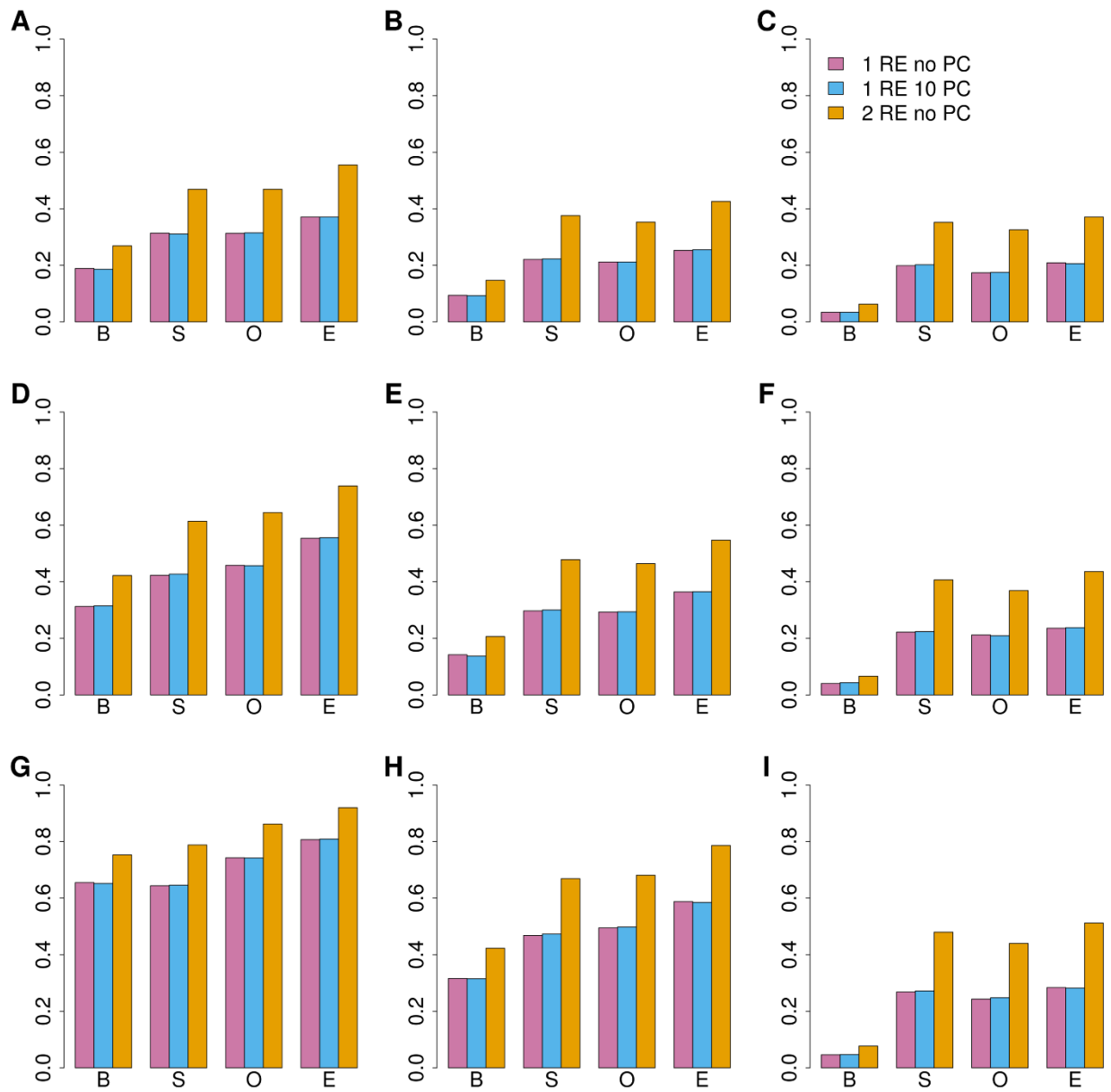


Figure S4. Empirical power of logistic mixed model based SMMAT-B (B), SMMAT-S (S), SMMAT-O (O) and SMMAT-E (E) in binary trait analysis of 5,000 samples, using three models: GRM random effects with no ancestry PC adjustment (1 RE no PC), GRM random effects with 10 ancestry PCs as fixed effects (1 RE 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.

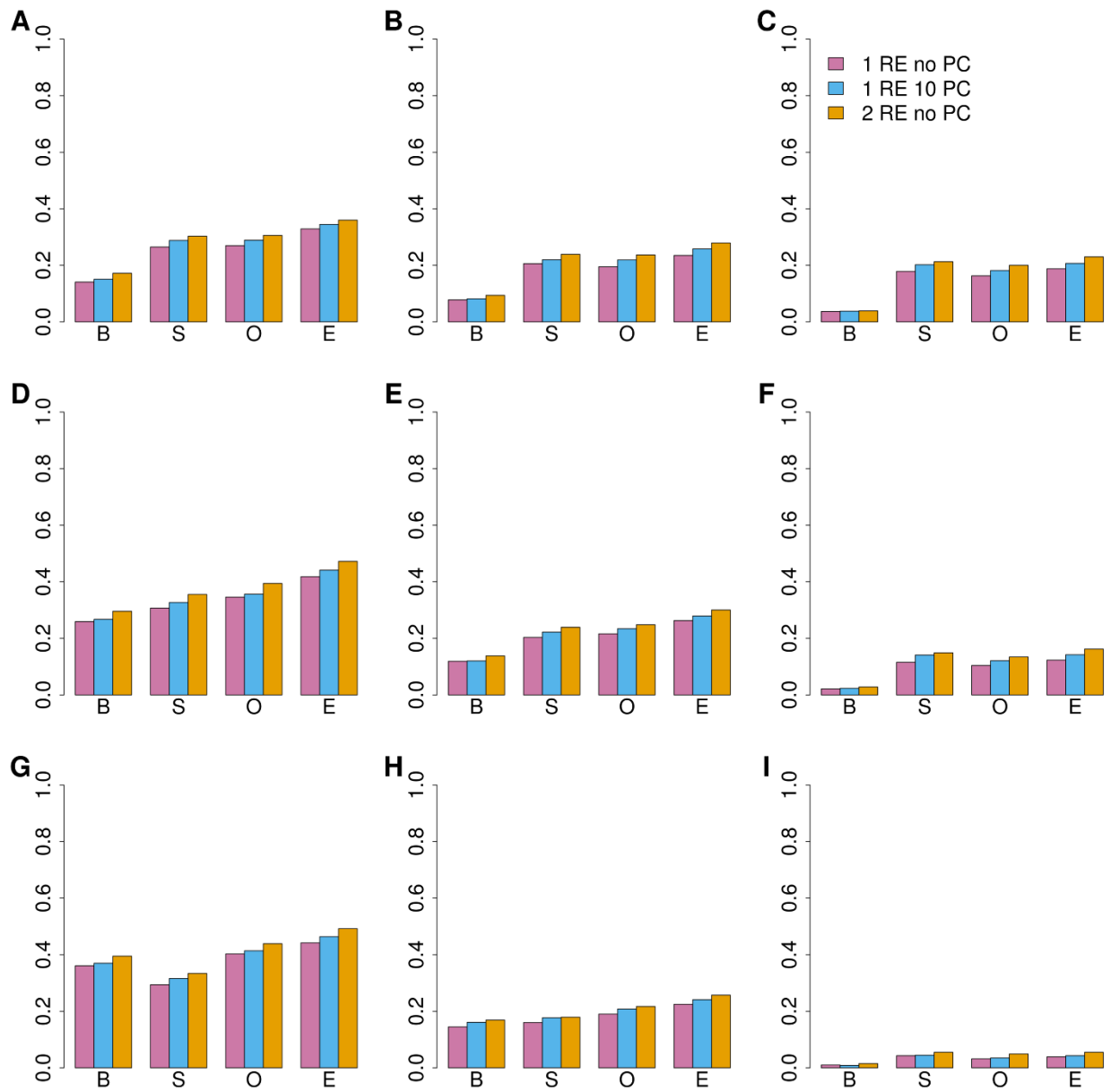


Figure S5. P value comparison of TOPMed fibrinogen level SMMAT analysis results using heteroscedastic linear mixed models with and without adjusting for 10 ancestry PCs as fixed effects, using rare variants with $MAF < 5\%$ in non-overlapping 4 kb sliding windows on chromosome 4 ($n = 23,763$). (A) SMMAT-B.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

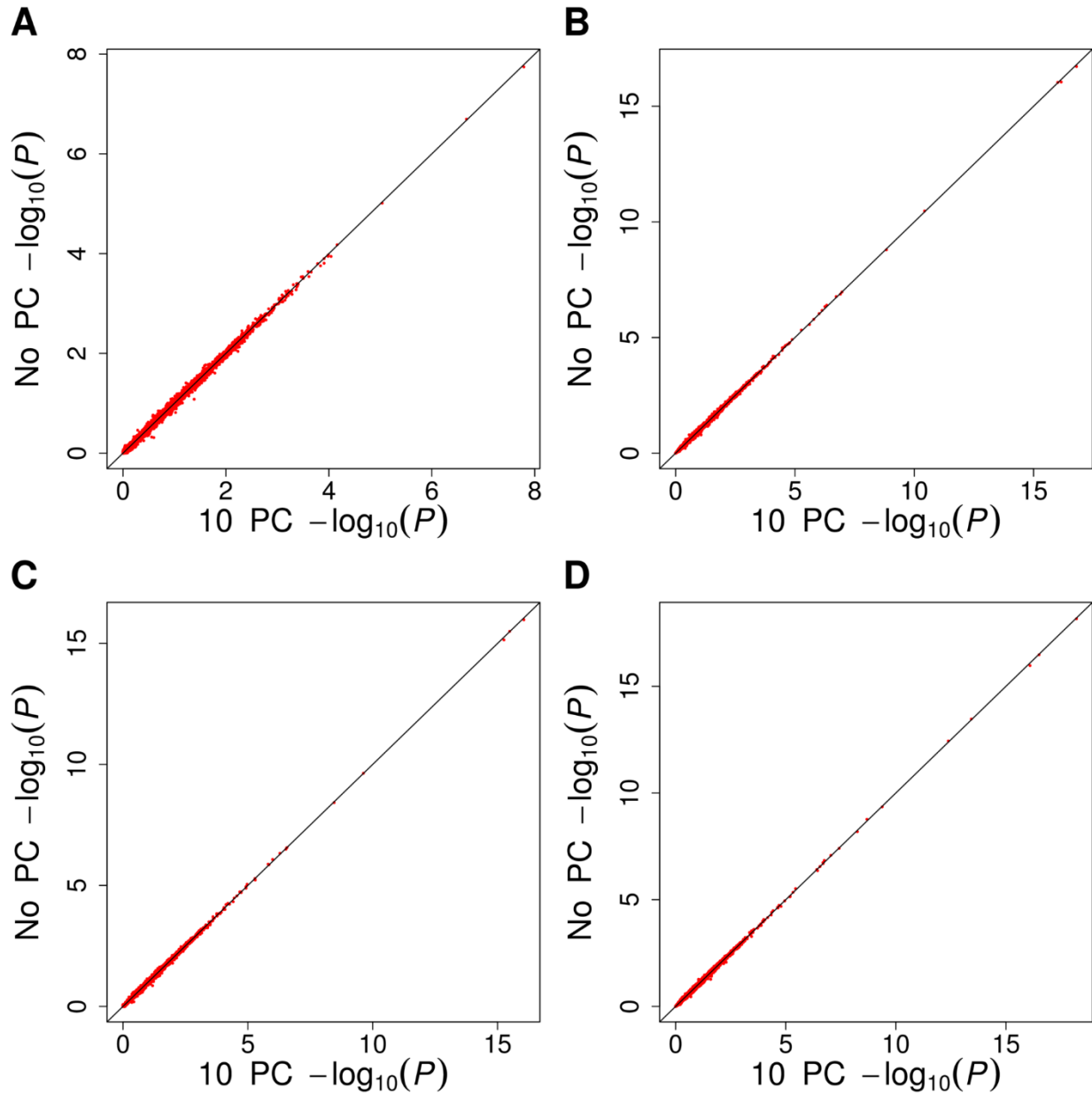


Figure S6. TOPMed fibrinogen level SMMAT analysis results using a heteroscedastic linear mixed model on rare variants with $MAF < 5\%$ in non-overlapping 1 kb sliding windows on chromosome 4 ($n = 23,763$). (A) Quantile-quantile plot. (B) P values on the log scale versus physical positions of the windows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

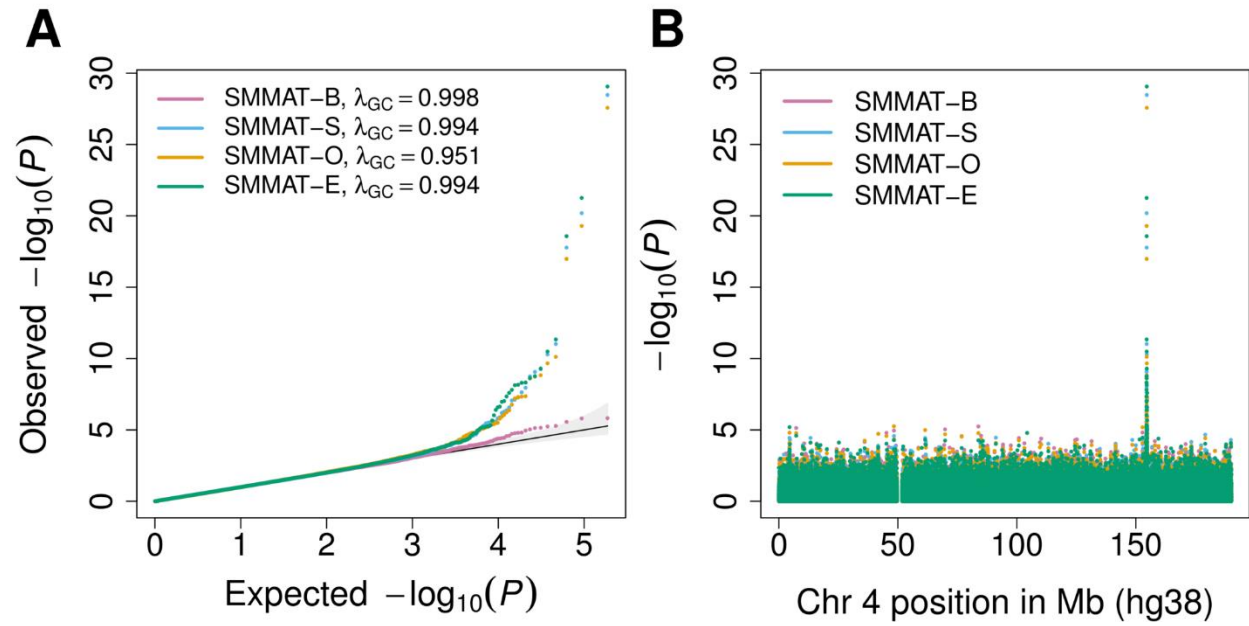


Figure S7. TOPMed fibrinogen level SMMAT analysis results using a heteroscedastic linear mixed model on rare variants with $MAF < 5\%$ in non-overlapping 10 kb sliding windows on chromosome 4 ($n = 23,763$). (A) Quantile-quantile plot. (B) P values on the log scale versus physical positions of the windows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

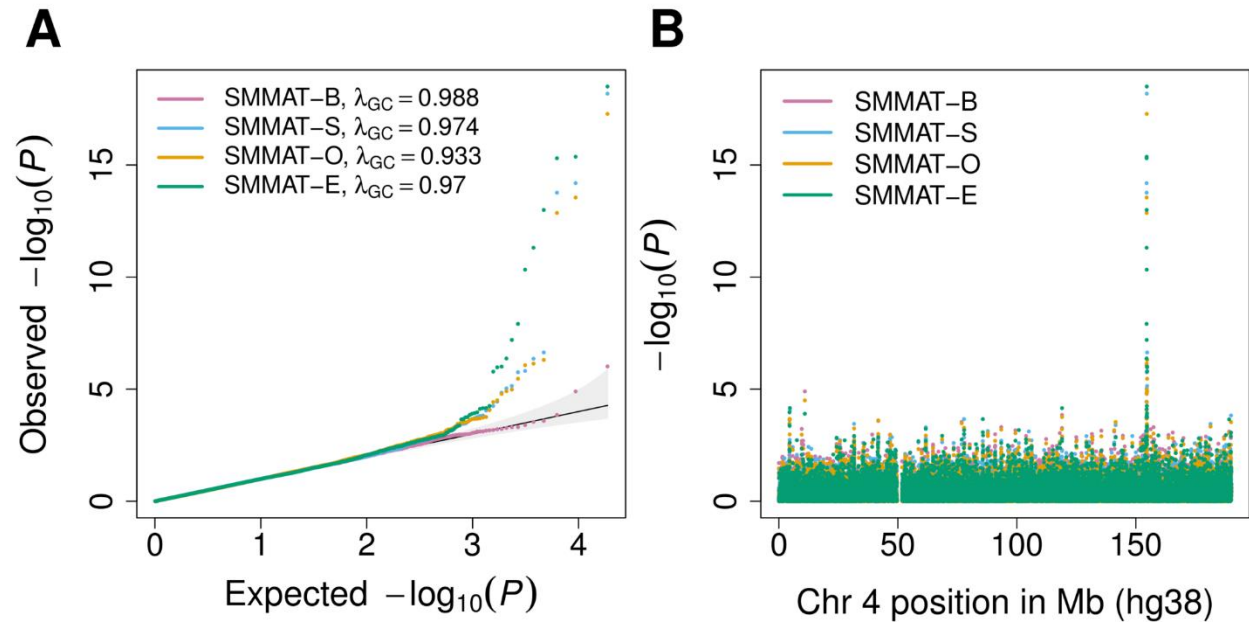
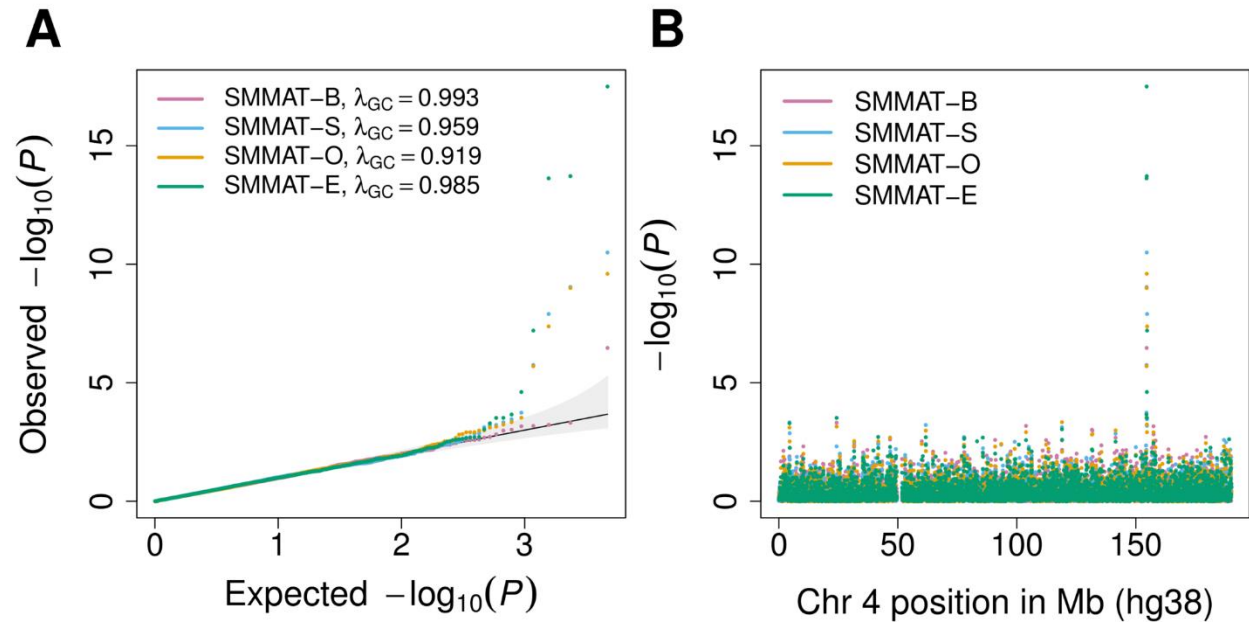


Figure S8. TOPMed fibrinogen level SMMAT analysis results using a heteroscedastic linear mixed model on rare variants with $MAF < 5\%$ in non-overlapping 40 kb sliding windows on chromosome 4 ($n = 23,763$). (A) Quantile-quantile plot. (B) P values on the log scale versus physical positions of the windows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

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Sakornsakolpat, Phuwanat	Brigham & Women's Hospital
Salimi, Shabnam	University of Maryland
Salzberg, Steven	Johns Hopkins University
Sadow, 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
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Taliun, Daniel	University of Michigan
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Taub, Margaret	Johns Hopkins University
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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
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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

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Zhou, Xiang	University of Michigan
Zody, Michael	New York Genome Center
Zoellner, Sebastian	University of Michigan