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Supplemental Data

Optimal Unified Approach for Rare-Variant

Association Testing with Application to Small-Sample

Case-Control Whole-Exome Sequencing Studies

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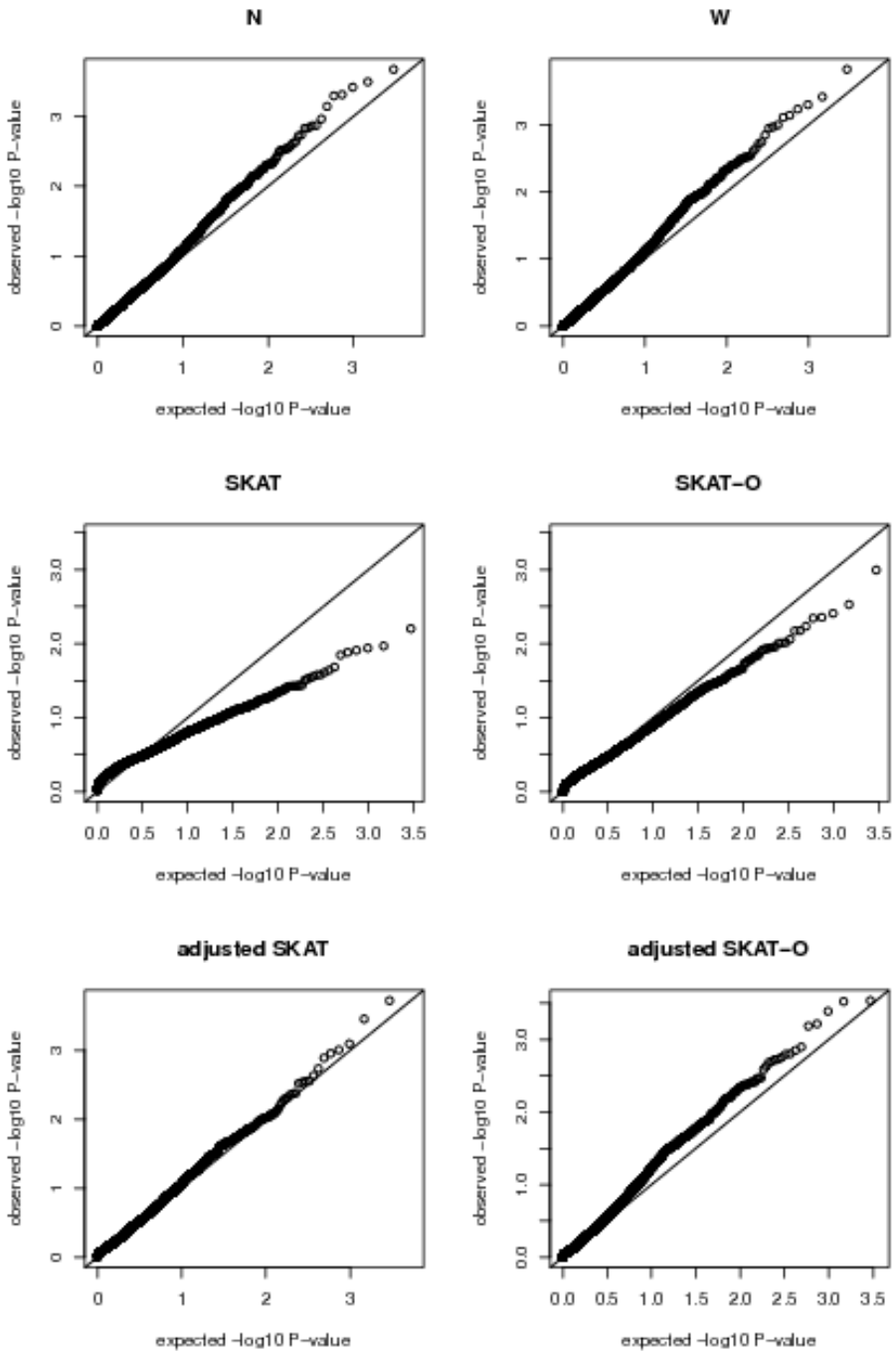

Figure S1. Analysis of Functional Variants of the ALI Exome-Sequence Data
$-\log_{10}$ QQ plots of observed vs. expected p-values for the ALI whole exome sequence data using the six methods: burden tests (W,N), SKAT, SKAT-O, adjusted SKAT, adjusted SKAT-O. X-axis represents $-\log_{10}$ expected p-values, and Y-axis represents $-\log_{10}$ observed p-values. Total 2,939 genes with at least four rare functional variants were tested for associations with ALI severity.

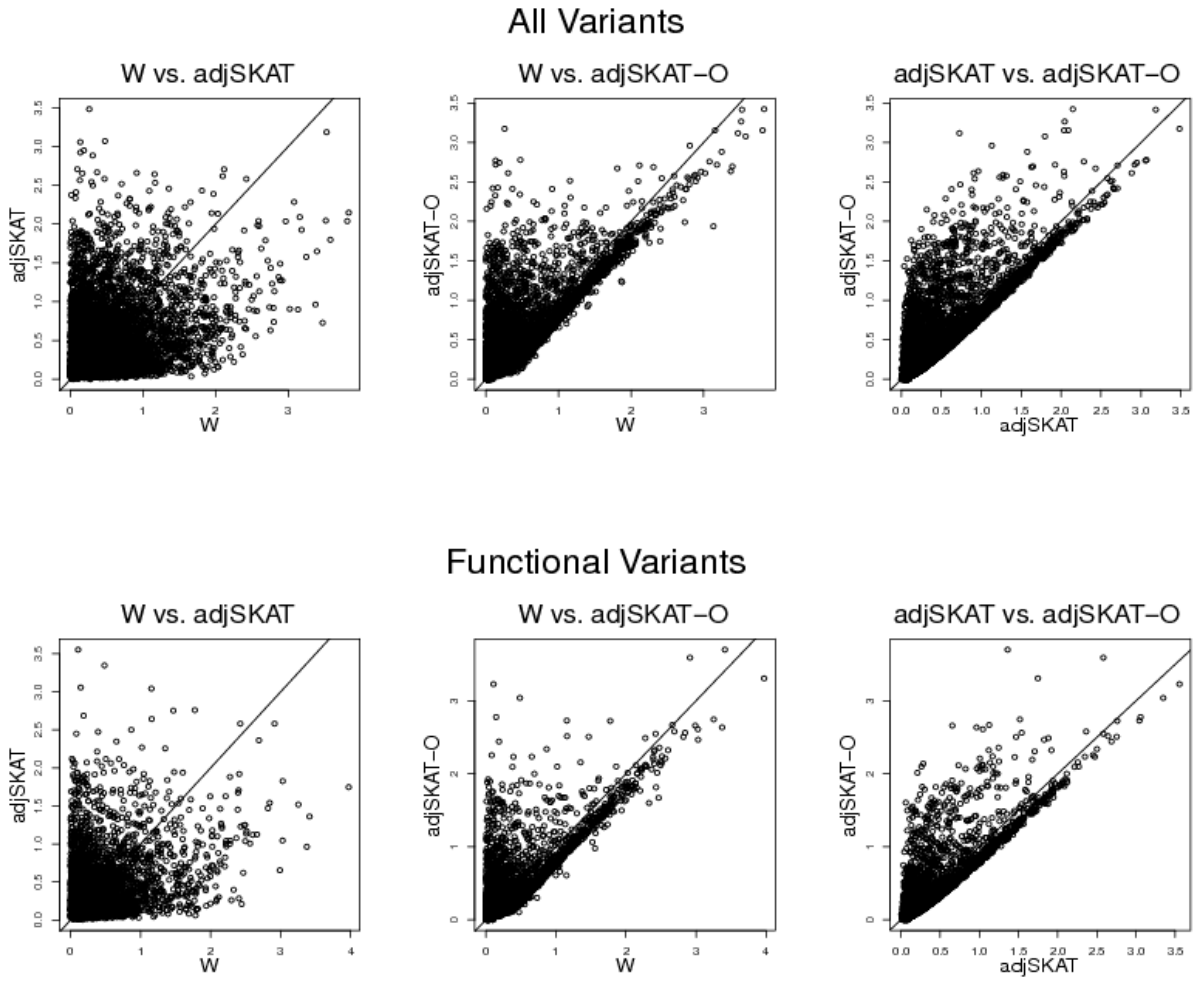

Figure S2. Comparison of Burden Test (W), Adjusted SKAT, and Adjusted SKAT-O
Scatter plots of $-\log_{10}$ p-values to compare burden test (W), adjusted SKAT, adjusted SKAT-O. The top panel considers testing all variants, and bottom panel considers testing functional variants.

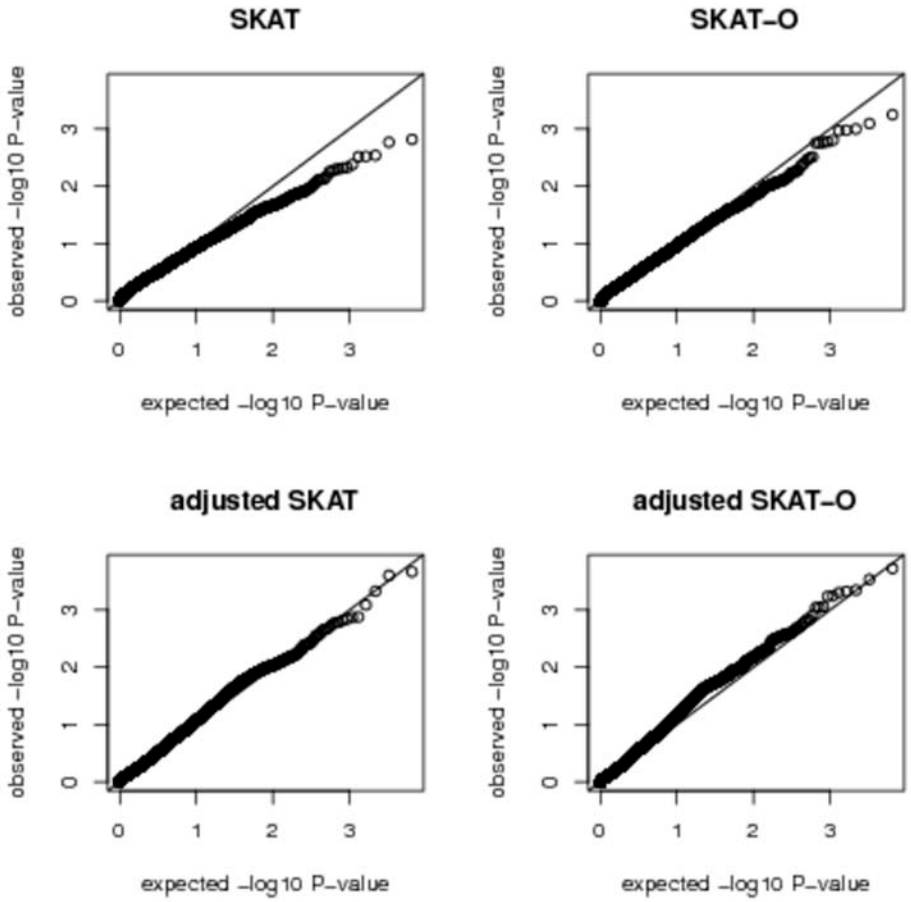

Figure S3. Analysis of the ALI Exome-Sequence Data with Logistic Weight
$-\log_{10}$ QQ plots of observed vs. expected p-values for the ALI whole exome sequence data with logistic weight ($w_j = exp((a1 - pj)a2)/\{1+exp((a1 - pj)a2\}$) with $a_1 = 0.07$ and $a_2 = 150$. X-axis represents $-\log_{10}$ expected p-values, and Y-axis represents $-\log_{10}$ observed p-values. Total 6,488 genes with at least four rare variants were tested for associations with ALI severity.

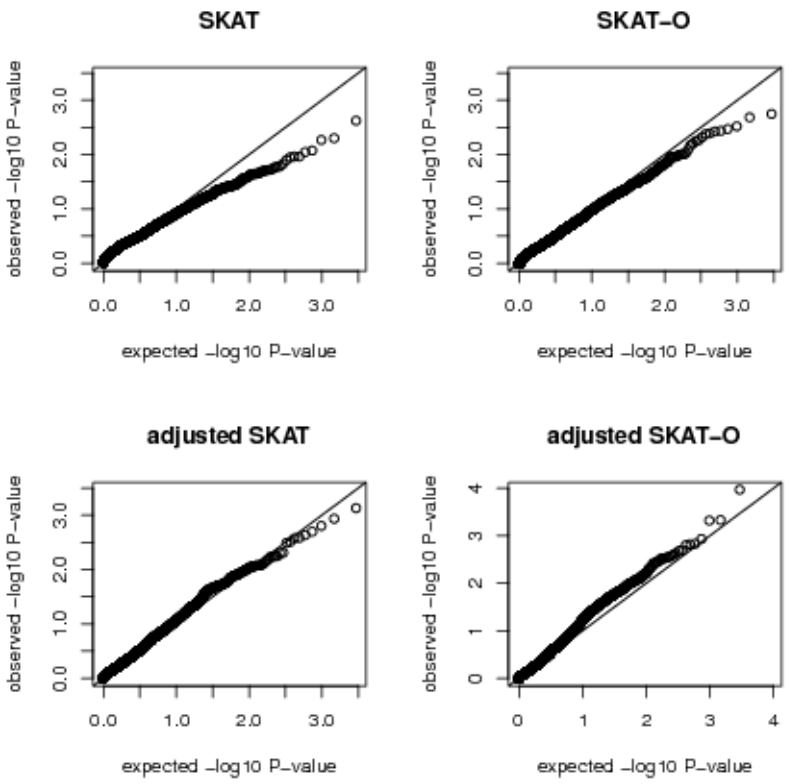

Figure S4. Analysis of the Functional Variants of the ALI Exome-Sequence Data with Logistic Weight

$-\log_{10}$ QQ plots of observed vs. expected p-values for the ALI whole exome sequence data with logistic weight ($w_j = exp((a1 - pj)a2)/\{1+exp((a1 - pj)a2\}$) with $a_1 = 0.07$ and $a_2 = 150$. X-axis represents $-\log_{10}$ expected p-values, and Y-axis represents $-\log_{10}$ observed p-values. Total 2,939 genes with at least four rare variants were tested for associations with ALI severity.

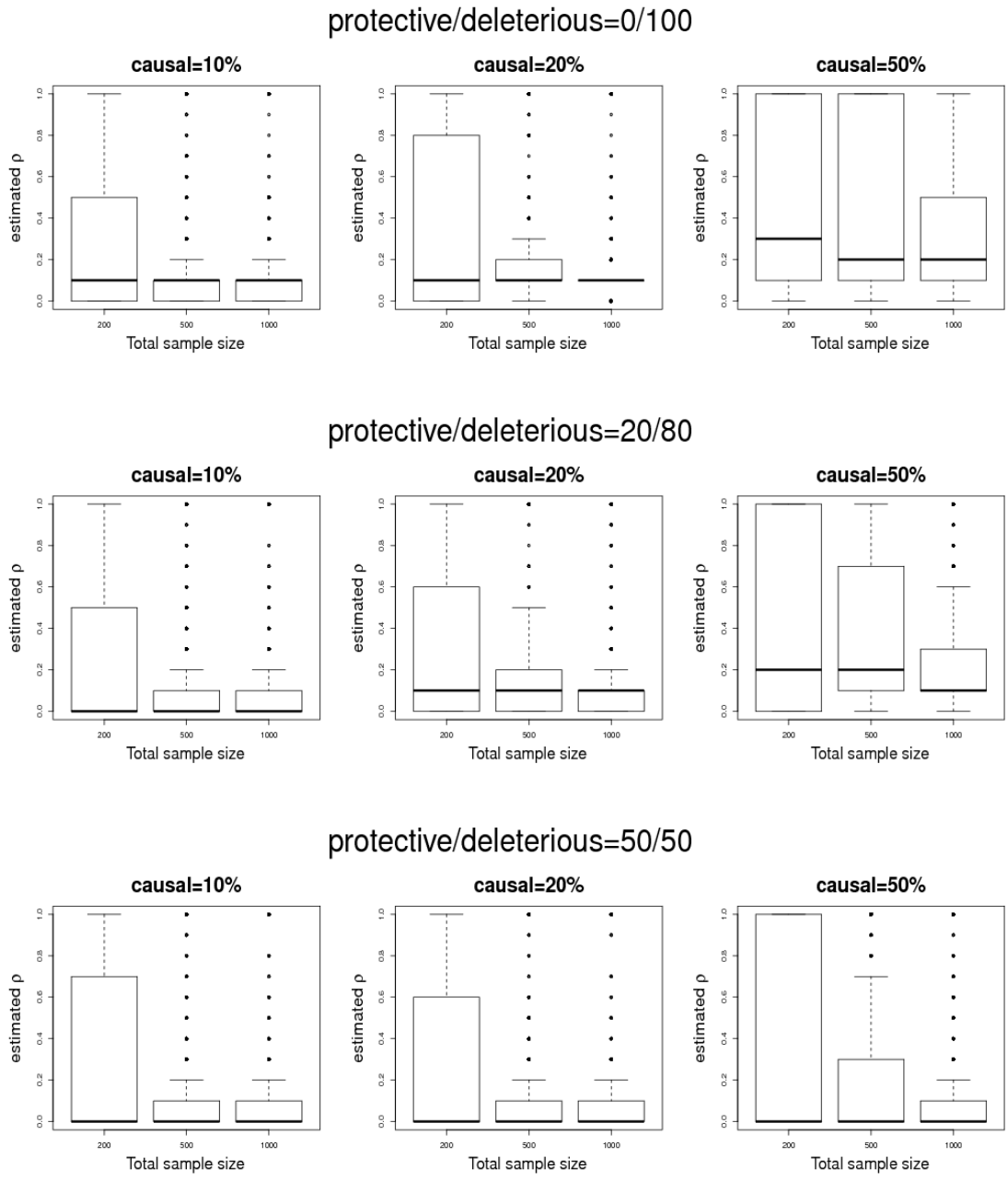

Figure S5. Estimated Optimal *ρ* of the Power Simulation
Box plots of the estimated optimal *ρ* in the power simulation studies. From top to bottom, the plots consider the setting in which percentage of protective/deleterious causal variants= 0/100, = 20/80 and = 50/50, respectively. From left to right, the plots consider the settings in which 10%, 20% and 50% of the rare variants were causal, respectively.

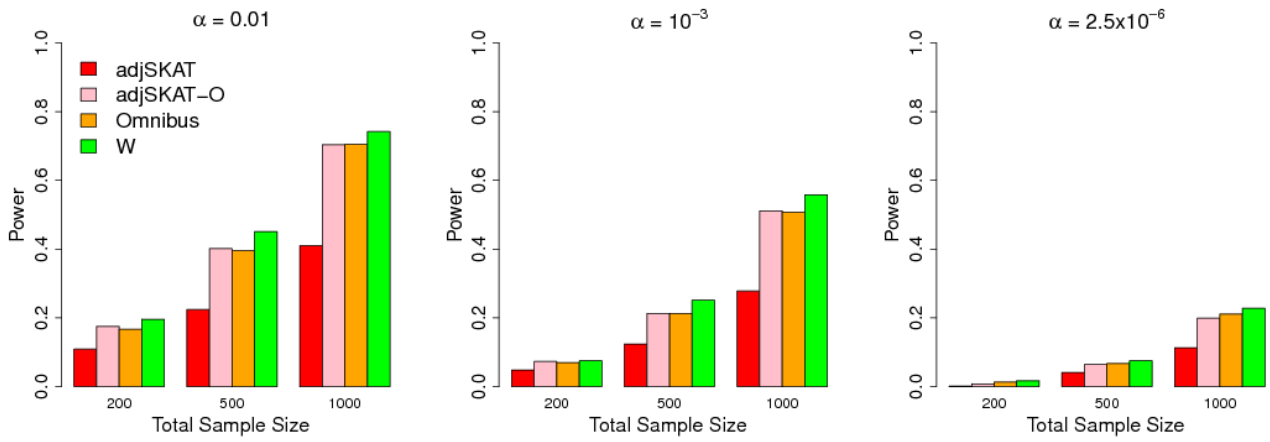

Figure S6. Power Comparison for SKAT, Omnibus, and Burden Tests when All Rare Variants Are Deleterious Causal Variants

Empirical power of the four methods for randomly selected 3kb regions with all the rare variants being deleterious causal variants, i.e., 100% causal. "Ominbus" represents the simple omnibus test that uses the smallest p-value of adjusted SKAT (adjSKAT) and W as the test statistics. Since it used the minimum p-value of two different tests, the multiple tests was corrected by the Bonferroni correction. From left to right, the plots consider the significance levels 0.01, 10^{-3}, and 2.5×10^{-6}, respectively. For causal variants, we assumed $|\beta_j| = c|\ log10(p_j)|/2$, where p_j was the MAF of the j_{th} variant, and c = log(1.5). Total sample sizes considered were 200, 500, and 1000, with half being cases in case-control studies.

Table S1. Type I Error Rates of the Burden Tests and the SKAT-Family Methods

α	N	W	SKAT	SKAT-O	adjusted SKAT	adjusted SKAT-O
SampleSize = 200						
0.05	5.72×10^{-2}	5.55×10^{-2}	3.36×10^{-2}	4.26×10^{-2}	5.34×10^{-2}	5.96×10^{-2}
0.01	1.28×10^{-2}	1.32×10^{-2}	2.90×10^{-3}	5.80×10^{-3}	9.75×10^{-3}	1.14×10^{-2}
SampleSize = 500						
0.05	5.53×10^{-2}	5.29×10^{-2}	4.59×10^{-2}	4.76×10^{-2}	5.26×10^{-2}	5.39×10^{-2}
0.01	1.09×10^{-2}	1.06×10^{-2}	7.95×10^{-3}	9.00×10^{-3}	1.13×10^{-2}	1.12×10^{-2}
SampleSize = 1000						
0.05	5.05×10^{-2}	5.14×10^{-2}	4.45×10^{-2}	4.71×10^{-2}	4.73×10^{-2}	4.91×10^{-2}
0.01	1.05×10^{-2}	1.14×10^{-2}	8.30×10^{-3}	1.00×10^{-2}	9.70×10^{-3}	1.11×10^{-2}

Simulation Studies of type I error estimates of six different methods to test an association between randomly selected 3kb regions with dichotomous traits at $\alpha = 0.01$ and 0.05. Each entry represents type I error rate estimates as the proportion of p-values smaller than α under the null hypothesis based on $10,000$ simulated datasets.

Table S2. Observed Number of Variants within Randomly Selected 3 kb Regions in the Power Simulation

Total sample size	% of causal variants	% of protective variants	All	case	control
200	10%	0%	20.69	17.03	14.33
		20%	20.05	16.38	14.14
		50%	19.23	15.41	14.11
	20%	0%	21.71	18.37	14.11
		20%	21.03	17.44	14.11
		50%	19.91	15.90	14.29
	50%	0%	22.36	19.42	14.13
		20%	21.15	17.87	14.08
		50%	19.53	15.68	14.19
500	10%	0%	28.04	22.64	19.52
		20%	27.40	21.95	19.39
		50%	26.83	20.95	19.72
	20%	0%	29.58	24.71	19.35
		20%	28.98	23.80	19.31
		50%	27.17	21.40	19.50
	50%	0%	31.18	27.03	19.41
		20%	29.78	24.98	19.56
		50%	27.41	21.67	19.59
1000	10%	0%	34.97	28.16	25.24
		20%	34.73	27.62	25.43
		50%	33.63	26.17	25.23
	20%	0%	36.74	30.56	25.06
		20%	35.84	29.40	25.03
		50%	34.58	26.99	25.41
	50%	0%	39.16	34.19	25.14
		20%	37.88	32.01	25.50
		50%	34.46	27.10	25.21

Each entry represents the average number of observed variants in the simulated datasets. “all” represents the number of variants observed among all samples. “case” and “control” represent the number of observed variants among cases and controls, respectively.

Table S3. Observed Number of Causal Variants within Randomly Selected 3 kb Regions in the Power Simulation

Total sample size	% of protective variants	observed causal			observed harmful			observed protective		
		all	Case	control	all	case	control	all	case	control
	10% variants were causal (average number of causal variants = 4.9)									
200	0%	3.38	3.38	0.00	3.33	3.33	0.00	0.70	0.70	0.00
	20%	3.02	2.90	0.12	2.89	2.87	0.02	0.72	0.60	0.12
	50%	2.31	1.94	0.37	2.00	1.91	0.09	0.78	0.43	0.36
500	0%	4.39	4.39	0.00	4.37	4.37	0.00	1.16	1.16	0.00
	20%	3.95	3.78	0.17	3.81	3.77	0.05	1.12	0.95	0.17
	50%	3.02	2.43	0.59	2.58	2.42	0.16	1.20	0.63	0.57
1000	0%	4.74	4.74	0.00	4.74	4.74	0.00	1.56	1.56	0.00
	20%	4.33	4.07	0.27	4.12	4.05	0.06	1.62	1.36	0.26
	50%	3.43	2.62	0.81	2.82	2.62	0.20	1.66	0.87	0.80
	20% variants were causal (average number of causal variants = 10.2)									
200	0%	5.85	5.85	0.00	5.68	5.68	0.00	1.49	1.49	0.00
	20%	5.33	5.02	0.31	4.94	4.85	0.09	1.62	1.33	0.29
	50%	4.05	3.20	0.84	3.34	3.11	0.23	1.59	0.79	0.80
500	0%	8.15	8.15	0.00	8.01	8.01	0.00	2.49	2.49	0.00
	20%	7.42	6.93	0.48	6.96	6.82	0.14	2.51	2.05	0.46
	50%	5.67	4.34	1.33	4.70	4.27	0.42	2.60	1.32	1.28
1000	0%	9.41	9.41	0.00	9.33	9.33	0.00	3.47	3.47	0.00
	20%	8.55	7.88	0.67	8.03	7.81	0.22	3.58	2.94	0.64
	50%	6.96	5.03	1.94	5.56	4.98	0.58	3.70	1.84	1.86
	50% variants were causal (average number of causal variants = 26.3)									
200	0%	10.14	10.14	0.00	9.08	9.08	0.00	4.10	4.10	0.00
	20%	9.23	8.31	0.92	7.84	7.39	0.45	4.23	3.44	0.79
	50%	7.47	5.17	2.30	5.64	4.61	1.04	4.08	2.11	1.97
500	0%	15.45	15.45	0.00	14.27	14.27	0.00	6.75	6.75	0.00
	20%	13.97	12.56	1.41	12.20	11.56	0.64	6.75	5.48	1.26
	50%	11.67	7.82	3.86	8.94	7.20	1.74	6.86	3.39	3.47
1000	0%	19.80	19.80	0.00	18.63	18.63	0.00	9.53	9.53	0.00
	20%	18.23	16.20	2.03	16.13	15.20	0.93	9.60	7.78	1.82
	50%	15.14	10.00	5.14	11.64	9.43	2.21	9.54	4.80	4.73

Each entry represents the average number of observed causal variants (harmful + protective), observed harmful variants, and observed protective variants in the simulated datasets. “all” represents the number of causal variants observed among all samples. “case” and “control” represent the number of observed causal variants among cases and controls, respectively. Harmful variants increase the chance to be a case ($\beta > 0$) and protective variants reduce the chance to be a case ($\beta < 0$).

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ISGS and SWISS:

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[1]Anthropometry Project Team, [2]Blood Count/Hematology Project Team, [3]Blood Pressure Project Team, [4]Data Flow Working Group, [5]Early MI Project Team, [6]ELSI Working Group, [7]Executive Committee, [8]Family Study Project Team, [9]Lipids Project Team, [10]Lung Project Team, [11]Personal Genomics Project Team, [12]Phenotype and Harmonization Working Group, [13]Population Genetics and Statistical Analysis Working Group, [14]Publications and Presentations Working Group, [15]Quantitative Analysis Ad Hoc Task Group, [16]Sequencing and Genotyping Working Group, [17]Steering Committee, [18]Stroke Project Team, [19]Structural Variation Working Group, [20]Subclinical/Quantitative Project Team

ESP Cohorts:

[21]Acute Lung Injury (ALI), [22]Atherosclerosis Risk in Communities (ARIC), [23]Cardiovascular Health Study (CHS), [24]Chronic Obstructive Pulmonary Disease (COPDGene), [25]Coronary Artery Risk Development in Young Adults (CARDIA), [26]Cystic Fibrosis (CF), [27]Early Pseudomonas Infection Control (EPIC), [28]Framingham Heart Study (FHS), [29]Jackson Heart Study (JHS), [30]Lung Health Study (LHS), [31]Multi-Ethnic Study of Atherosclerosis (MESA), [32]Pulmonary Arterial Hypertension (PAH), [33]Severe Asthma Research Program (SARP), [34]Women's Health Initiative (WHI)