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Supplemental Data

Meta-analysis of Gene-Level Associations

for Rare Variants Based on Single-Variant Statistics

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Figure S1. Power of T5 at the nominal significance level α of 0.001 for binary traits with an internal reference. Ratio is the case-control ratio for Study 2 and Study 3. SV-score, SV-LR and SV-Wald mean that single-variant *p*-values are based on the score, LR and Wald tests, respectively. Each power estimate is based on 10,000 replicates.



Figure S2. Power of T5 at the nominal significance level α of 0.001 for binary traits with an external reference. Ratio is the case-control ratio for Study 2 and Study 3. SV-score, SV-LR and SV-Wald mean that single-variant *p*-values are based on the score, LR and Wald tests, respectively. Each power estimate is based on 10,000 replicates.



Figure S3. Power of SKAT for the proposed and Fisher's methods at the nominal significance level α of 0.001. For quantitative traits, the error variances in Study 2 and Study 3 are 1. For binary traits, the case-control ratios in Study 2 and Study 3 are 1. For SV-I and SV-E, single-variant *p*-values are based on the score test. Each power estimate is based on 10,000 replicates.



Figure S4. Power of T5 for *LDLRAD1* at the nominal significance level α of 0.001: SV-E and SV-E' pertain to correct and incorrect specifications of the external panel. For quantitative traits, σ^2 is the error variance of Study 2 and Study 3. For binary traits, "Ratio" is the case-control ratio of Study 2 and Study 3. Singlevariant *p*-values are based on the score test. Each power estimate is based on 10,000 replicates.

			SV-I		SV-E		naive	
Gene	Test	σ^2	score	LR	score	LR	score	LR
OR2T29	T5	0.5	0.98	0.99	0.96	0.97	75.67	75.90
		1.0	1.00	1.01	0.97	0.98	75.54	75.77
	VT	0.5	1.00	1.01	0.97	0.98	53.53	53.75
		1.0	1.00	1.00	1.01	1.02	53.34	53.53
	SKAT	0.5	0.95	0.97	0.94	0.96	19.19	19.33
		1.0	1.01	1.01	0.98	1.00	19.13	19.24
LDLRAD1	T5	0.5	0.98	0.99	0.97	0.98	2.87	2.90
		1.0	0.98	0.98	0.97	0.98	2.81	2.85
	VT	0.5	1.04	1.04	1.02	1.03	2.92	2.95
		1.0	1.05	1.06	1.01	1.02	2.98	3.00
	SKAT	0.5	1.02	1.03	1.01	1.03	2.39	2.44
		1.0	1.00	1.01	1.03	1.05	2.38	2.41
Note: The su	immary st	tatistics	do not ind	lude the	standard	error esti	mates T	he

 Table S1. Type I error (divided by the nominal significance level)

 for quantitative traits

Note: The summary statistics do not include the standard error estimates. The nominal significance level $\alpha = 0.001$. σ^2 pertains to the error variance in Study 2 and Study 3. Each entry is based on 1,000,000 replicates.

			SV-I		SV-E		naive		
Gene	Test	Ratio	score	LR	score	LR	score	LR	
OR2T29	T5	1.0	0.88	0.94	0.86	0.92	73.13	74.75	
		2.0	0.99	1.00	0.93	0.97	73.60	73.93	
	VT	1.0	0.89	0.95	0.83	0.92	51.10	52.54	
		2.0	1.02	1.01	0.98	0.98	51.91	52.14	
	SKAT	1.0	0.90	0.96	0.84	0.92	17.65	18.64	
		2.0	0.98	0.98	0.92	0.95	18.16	18.45	
LDLRAD1	T5	1.0	0.83	0.89	0.76	0.86	2.18	2.46	
		2.0	1.06	1.00	0.99	0.96	3.12	2.81	
	VT	1.0	0.76	0.85	0.64	0.77	2.04	2.46	
		2.0	1.07	0.98	0.88	0.83	3.20	2.82	
	SKAT	1.0	0.83	0.96	0.70	0.85	1.58	1.92	
		2.0	0.93	0.94	0.75	0.82	1.95	1.98	

Table S2. Type I error (divided by the nominal significance level)for binary traits

Note: The summary statistics do not include the standard error estimates. The nominal significance level $\alpha = 0.001$. Ratio is the case-control ratio in Study 2 and Study 3. Each entry is based on 1,000,000 replicates.

Table S3. C	Correlation ma	atrix of the Li	DLRAD1 geno	otypes in ESP	' HeartGO da	ta		
	rs143619888	rs150468103	rs141759859	rs149768061	rs147345740	rs145889899	rs142900519	rs149114405
rs143619888	1	0	0.003	0.014	0	0.011	0	0
rs150468103		1	0	0	0	0	0	0
rs141759859			1	0.004	0	0.003	0.001	0
rs149768061				1	0	0.780	0.004	0
rs147345740					1	0	0	0
rs145889899						1	0.003	0
rs142900519							1	0
rs149114405								1

Table S4.	Type I error	(divided by the	nominal significance
level) of S	V-E' for testi	ng <i>LDLRAD1</i>	

	Qu	Quantitative traits				Binary traits			
Test	σ^2	score	LR	Wald	Ratio	score	LR	Wald	
T5	1.0	0.74	0.74	0.75	1.0	0.52	0.60	0.39	
	0.5	0.72	0.72	0.74	2.0	0.64	0.63	0.50	
VT	1.0	0.90	0.91	0.92	1.0	0.48	0.57	0.32	
	0.5	0.89	0.90	0.90	2.0	0.71	0.67	0.48	
SKAT	1.0	0.90	0.91	0.92	1.0	0.64	0.74	0.46	
	0.5	0.89	0.90	0.91	2.0	0.60	0.68	0.45	

Note: The nominal significance level $\alpha = 0.001$. For quantitative traits, σ^2 is the error variance of Study 2 and Study 3. For binary traits, "Ratio" is the case-control ratio of Study 2 and Study 3. Each entry is based on 1,000,000 replicates.