SUPPORTING INFORMATION

FIGURES

Figure S1. Quantile-Quantile plots of MAGEE tests on quantitative and binary traits in 100,000 unrelated samples under the null model. (A) Main effect (MV and MF) tests on quantitative traits. (B) GEI (IV and IF) tests on quantitative traits. (C) Joint (JV, JF and JD) tests on quantitative traits. (D) Main effect (MV and MF) tests on binary traits. (E) GEI (IV and IF) tests on binary traits. (F) Joint (JV, JF and JD) tests on binary traits.

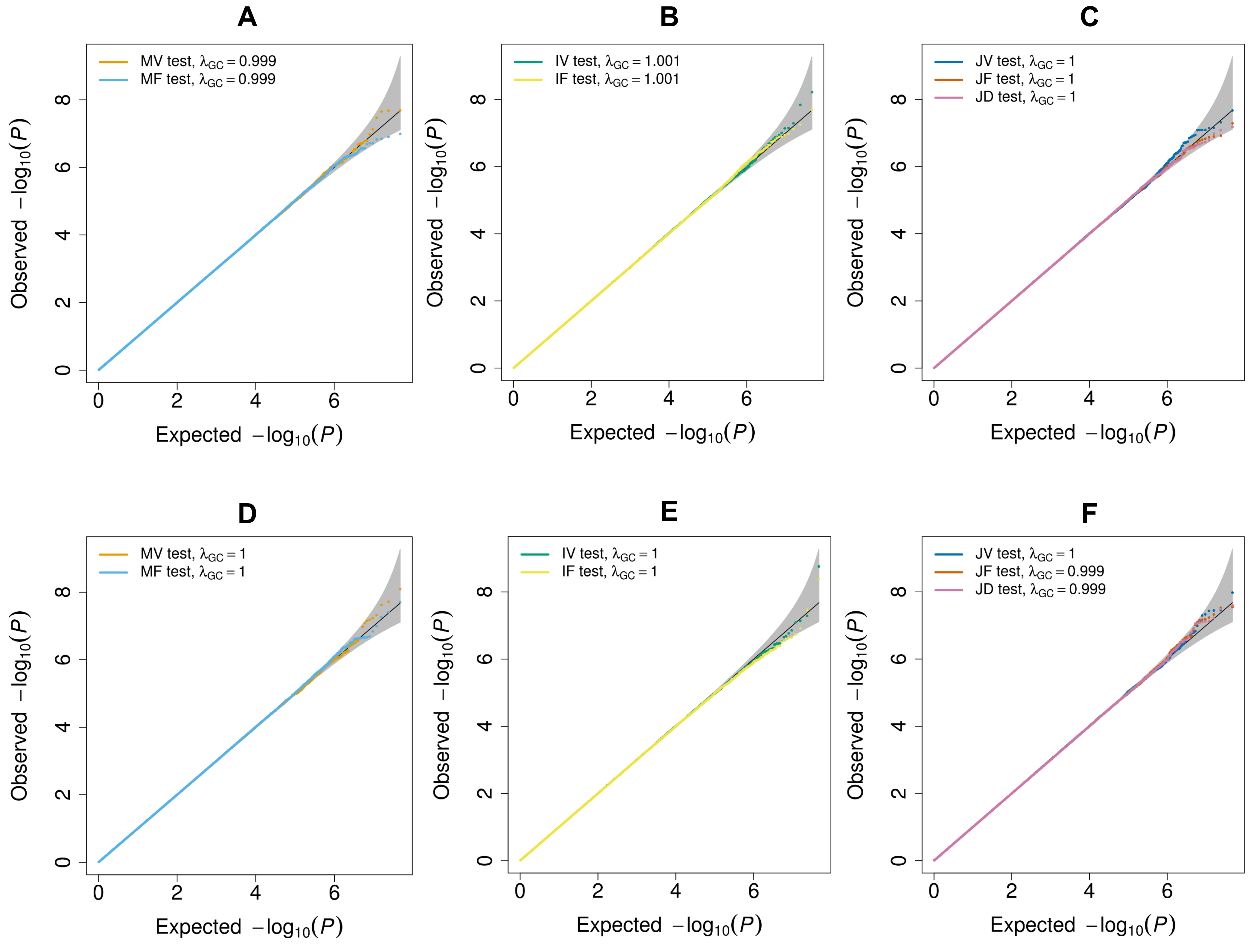


Figure S2. Quantile-Quantile plots of MAGEE tests on quantitative and binary traits in 100,000 related samples under the null model. (A) Main effect (MV and MF) tests on quantitative traits. (B) GEI (IV and IF) tests on quantitative traits. (C) Joint (JV, JF and JD) tests on quantitative traits. (D) Main effect (MV and MF) tests on binary traits. (E) GEI (IV and IF) tests on binary traits. (F) Joint (JV, JF and JD) tests on binary traits.

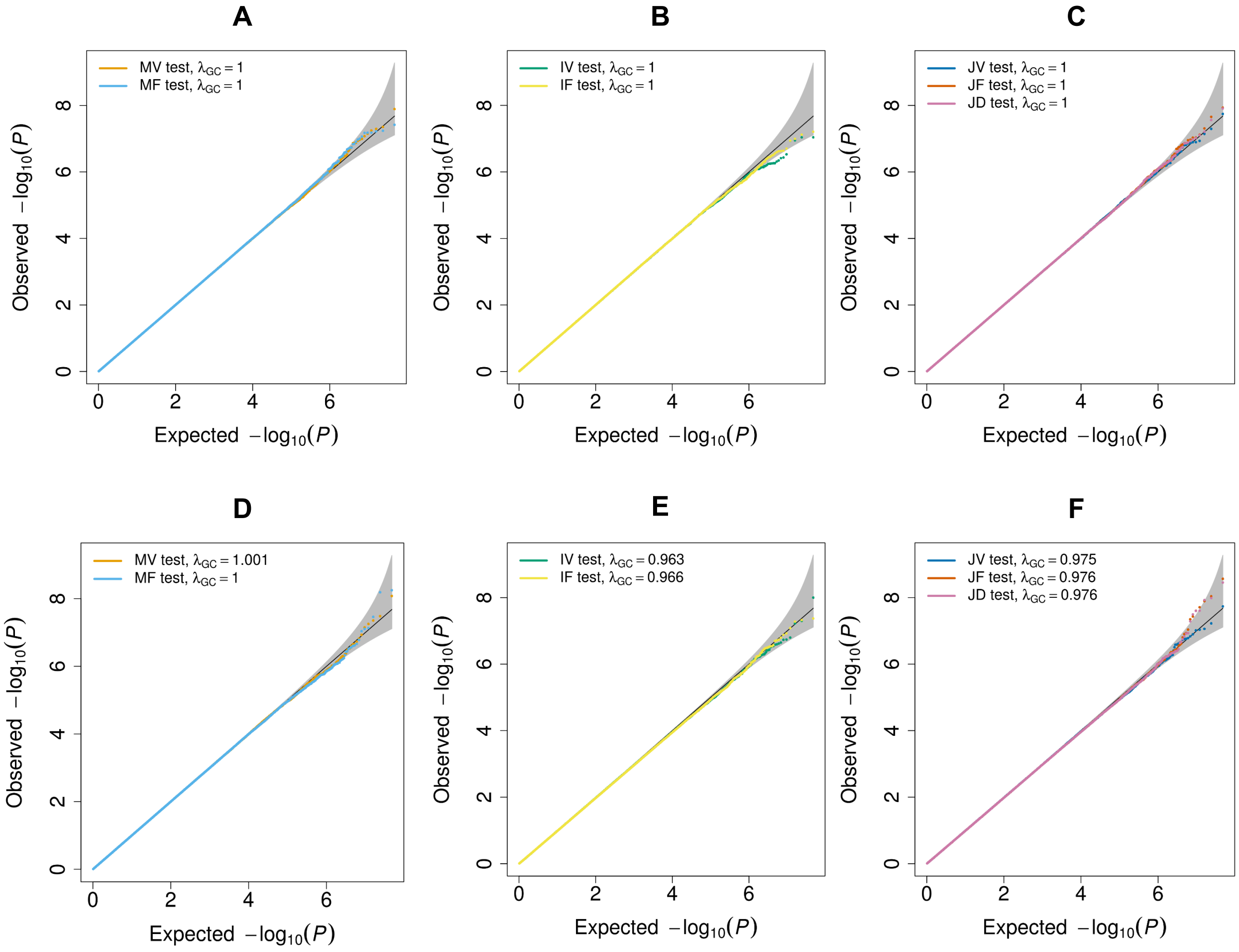


Figure S3. Comparison of *p* values from MAGEE versus rareGE and MiSTi tests on quantitative traits when only genetic effects but no GEI effects were present (scenario 2) in 2,000, 5,000, and 10,000 unrelated samples. (A) MAGEE IV vs. rareGE GEI tests. (B) MAGEE IF vs. MiSTi tests. (C) MAGEE JV vs. rareGE JOINT tests.

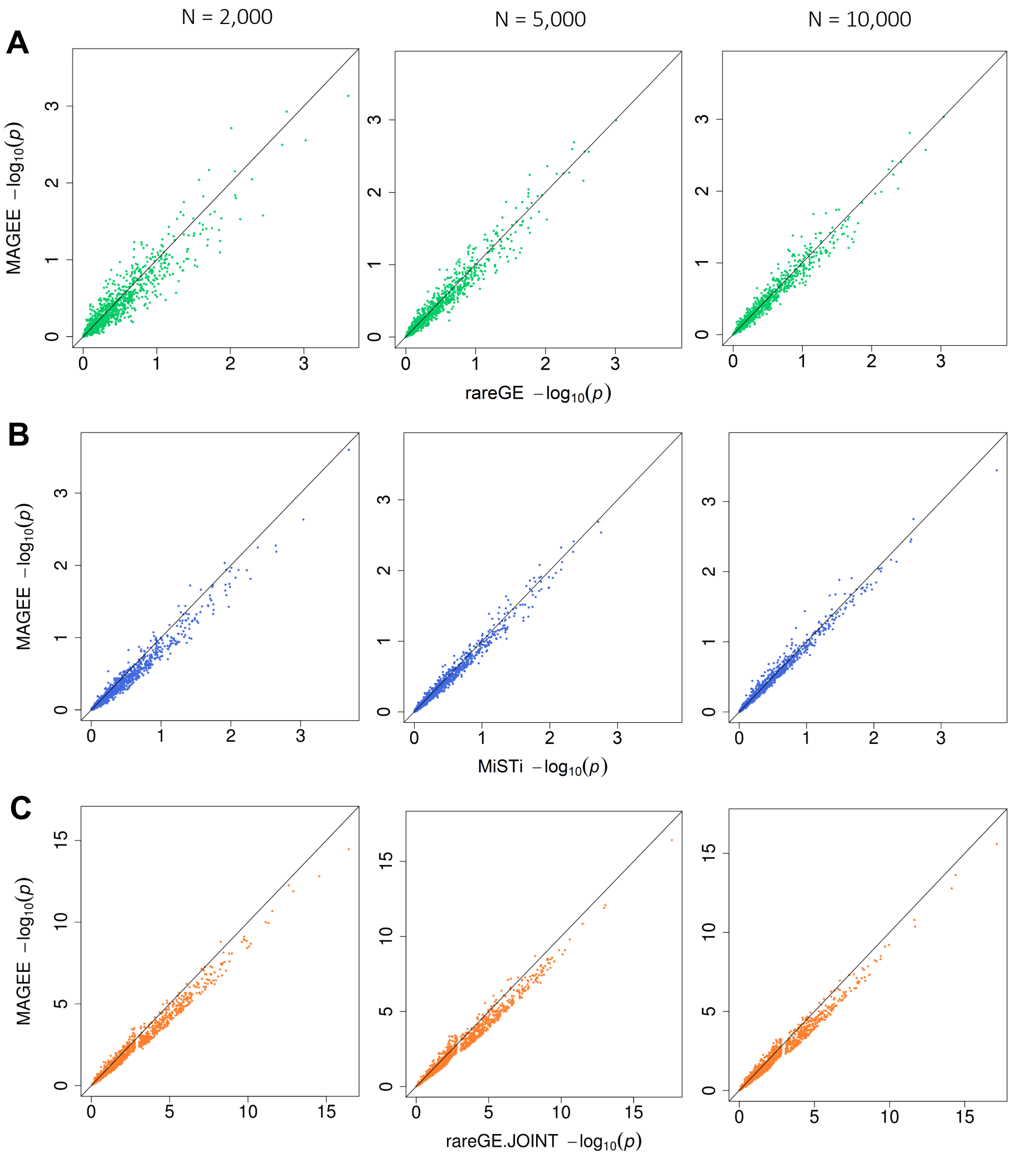


Figure S4. Comparison of *p* values from MAGEE versus rareGE and MiSTi tests on binary traits when both genetic and GEI effects were present (scenario 1) in 2,000, 5,000, and 10,000 unrelated samples. A) MAGEE IV vs. rareGE GEI tests. (B) MAGEE IF vs. MiSTi tests. (C) MAGEE JV vs. rareGE JOINT tests.

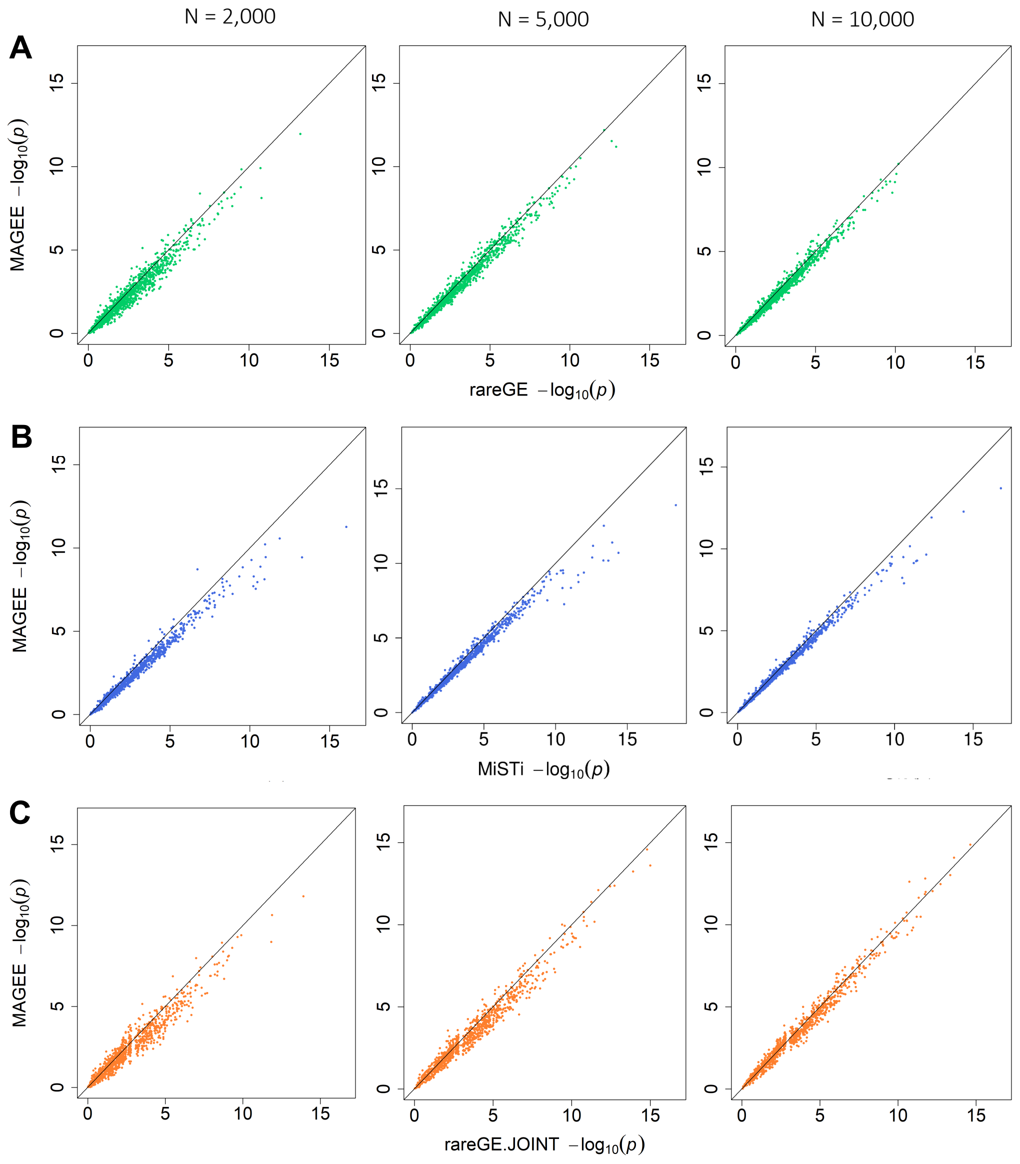


Figure S5. Comparison of *p* values from MAGEE versus rareGE and MiSTi tests on binary traits when only genetic effects but no GEI effects were present (scenario 2) in 2,000, 5,000, and 10,000 unrelated samples. (A) MAGEE IV vs. rareGE GEI tests. (B) MAGEE IF vs. MiSTi tests. (C) MAGEE JV vs. rareGE JOINT tests.

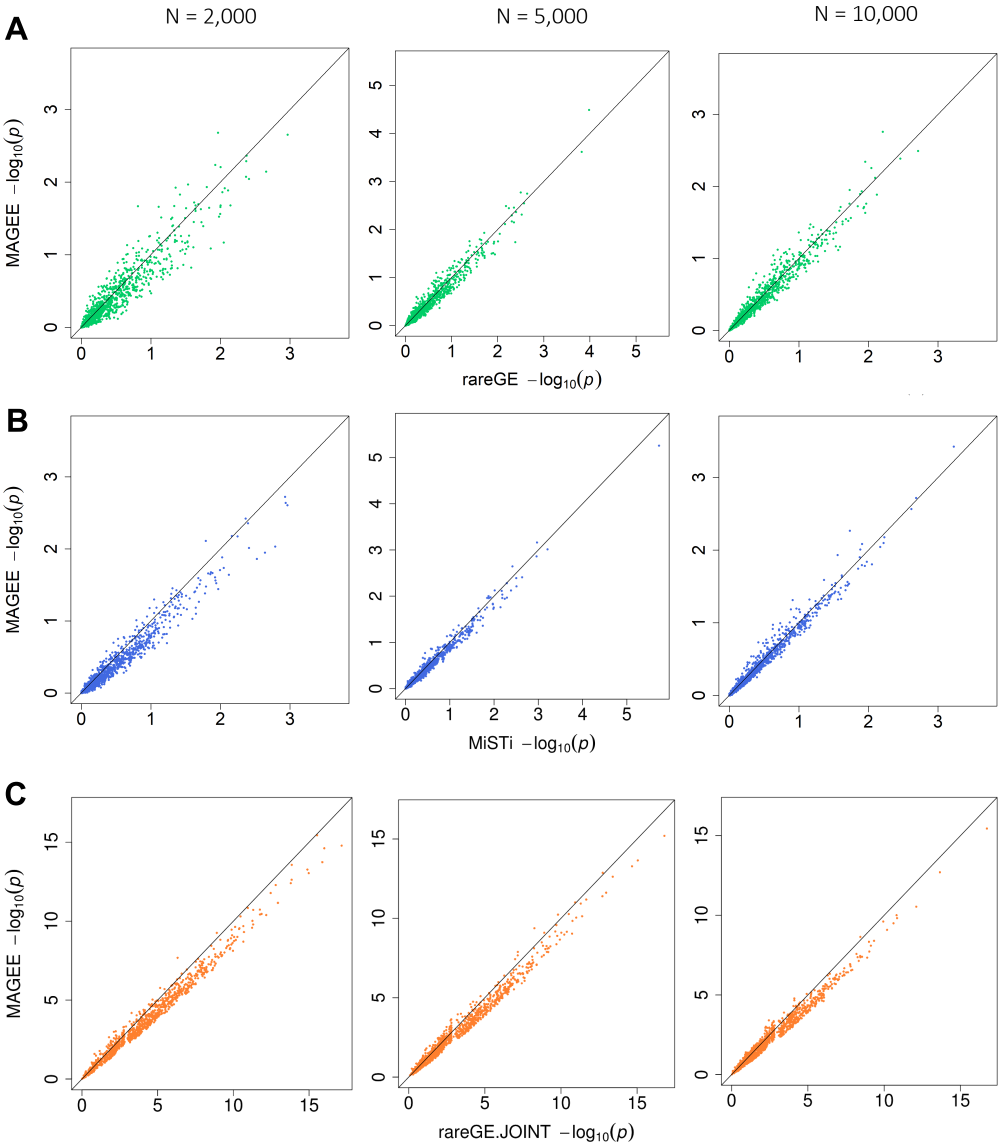


Figure S6. Empirical power of MAGEE IV, IF, and JV tests versus rareGE GEI test, MiSTi test, and rareGE JOINT test in 2,000, 5,000, and10,000 unrelated samples, respectively, in the presence of both strong genetic main effects and GEI effects. (A) Quantitative traits. (B) Binary traits.

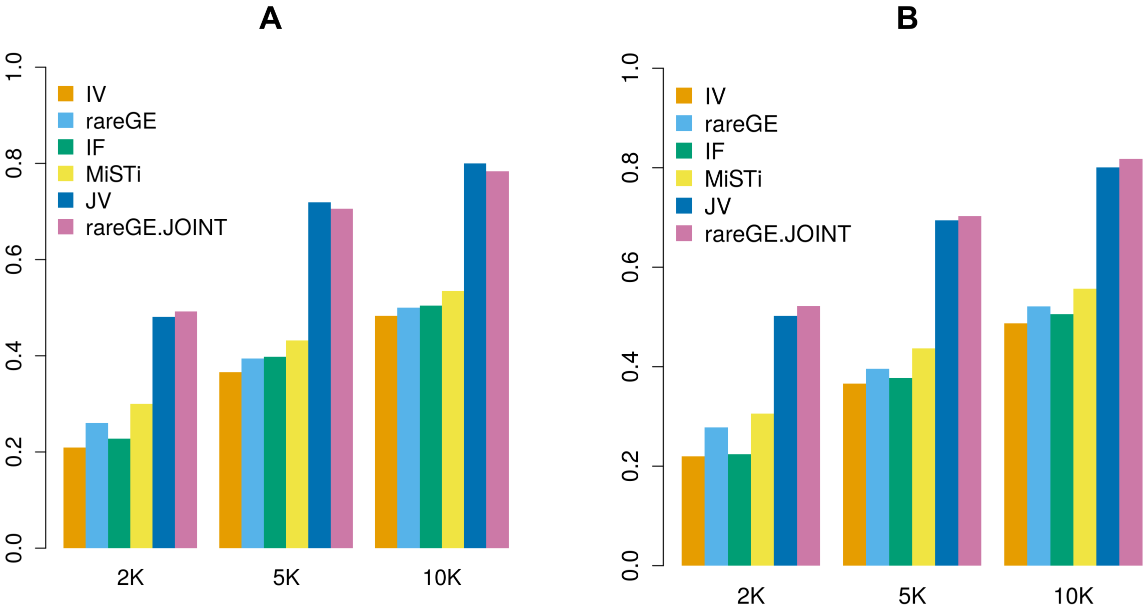


Figure S7. CPU time per *p* value of MAGEE, rareGE and MiSTi tests on binary traits in unrelated samples. (A) MAGEE, rareGE and MiSTi GEI tests. (B) MAGEE and rareGE joint tests.

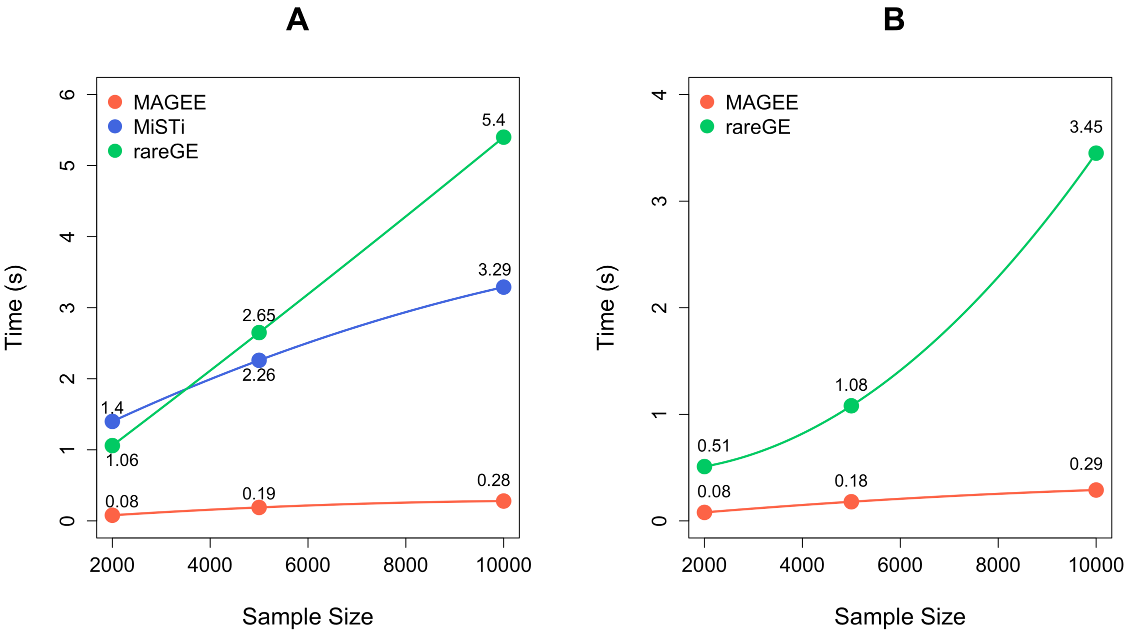
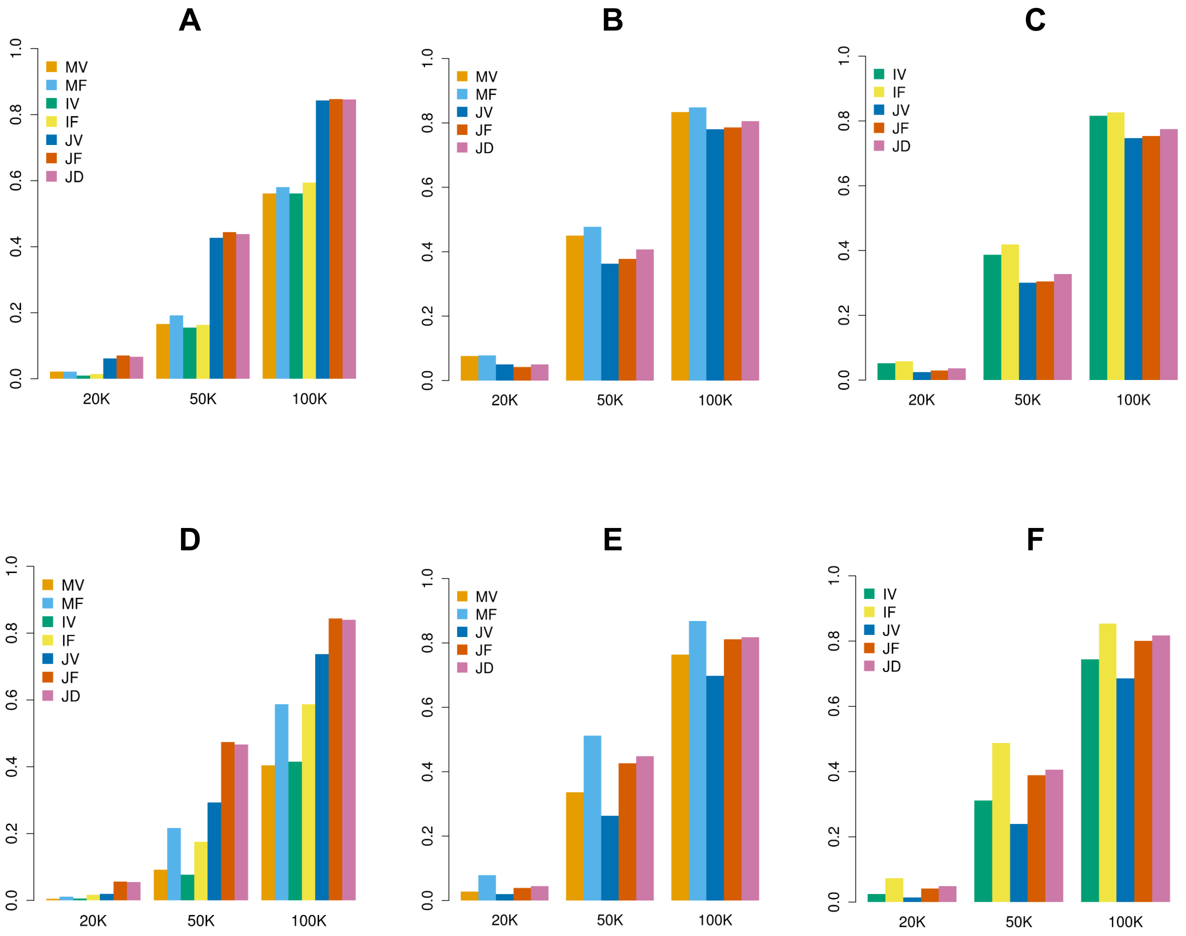


Figure S8. Empirical power of MAGEE tests on binary traits in 20,000, 50,000, and 100,000 related samples. (A) Scenario 1: 80% null variants, 10% causal variants with positive effects and 10% causal variants with negative effects for both genetic main effects and GEI effects. (B) Scenario 2: 80% null variants, 10% causal variants with positive effects and 10% causal variants with negative effects for genetic main effects only. (C) Scenario 3: 80% null variants, 10% causal variants with positive effects and 10% causal variants with negative effects for GEI effects only. (D) Scenario 4: 80% null variants, 16% causal variants with positive effects and 4% causal variants with negative effects for both genetic main effects and GEI effects. (E) Scenario 5: 80% null variants, 16% causal variants with positive effects and 4% causal variants with negative effects for genetic main effects only. (F) Scenario 6: 80% null variants, 16% causal variants with positive effects and 4% causal variants with negative effects for GEI effects only.


A
B
C
D
E
F
MV
MF
IV
IF
JV
JF
JD
0.0
0.2
0.4
0.6
0.8
1.0
20K
50K
100K

TABLES

Table S1. A summary of the test statistics and their distributions under the null hypothesis, and the combination methods of p values for the GEI and joint tests within the MAGEE framework.

Test statistic	Distribution	Combination Method
GEI tests		
1. Interaction variance component (IV) test		None
$T_\gamma = \tilde{\boldsymbol{S}}_{\boldsymbol{K}}^T \boldsymbol{W}_{\boldsymbol{K}} \boldsymbol{W}_{\boldsymbol{K}} \tilde{\boldsymbol{S}}_{\boldsymbol{K}}$	$\sum_{j=1}^{cq} \xi_{\gamma,j}\, \chi_{1,j}^2$, and $\xi_{\gamma,j}$ are the eigenvalues of $\boldsymbol{W}_{\boldsymbol{K}} \boldsymbol{\Lambda} \boldsymbol{W}_{\boldsymbol{K}}$	
2. Interaction hybrid test using Fisher's (IF) method		$p_{IF} = \mathrm{P}(\chi_4^2 > -2\log p_{\gamma_0} - 2\log p_\tau)$
$T_{\gamma_0} = \tilde{\boldsymbol{S}}_{\boldsymbol{KB}}^2$	$\xi_{\gamma_0}\chi_1^2$, and $\xi_{\gamma_0} = \boldsymbol{1}_{\boldsymbol{cq}}^T \boldsymbol{W}_{\boldsymbol{K}} \boldsymbol{\Lambda} \boldsymbol{W}_{\boldsymbol{K}} \boldsymbol{1}_{\boldsymbol{cq}}$	
$T_\tau = \tilde{\boldsymbol{S}}_{\boldsymbol{KV}}^T \boldsymbol{W}_{\boldsymbol{K}} \boldsymbol{W}_{\boldsymbol{K}} \tilde{\boldsymbol{S}}_{\boldsymbol{KV}}$	$\sum_{j=1}^{cq} \xi_{\tau,j}\, \chi_{1,j}^2$, and $\xi_{\tau,j}$ are eigenvalues for $\boldsymbol{W}_{\boldsymbol{K}} \boldsymbol{\Lambda}_{\boldsymbol{KV}} \boldsymbol{W}_{\boldsymbol{K}}$, $\boldsymbol{\Lambda}_{\boldsymbol{KV}} = \boldsymbol{\Lambda} - \boldsymbol{\Lambda} \mathbf{W}_{\mathbf{K}} \boldsymbol{1}_{\boldsymbol{cq}} \left(\boldsymbol{1}_{\boldsymbol{cq}}^T \mathbf{W}_{\mathbf{K}} \boldsymbol{\Lambda} \mathbf{W}_{\mathbf{K}} \boldsymbol{1}_{\boldsymbol{cq}}\right)^{-1} \boldsymbol{1}_{\boldsymbol{cq}}^T \mathbf{W}_{\mathbf{K}} \boldsymbol{\Lambda}$	
Joint tests		
1. Joint variance component (JV) test		$p_{JV} = \mathrm{P}(\chi_4^2 > -2\log p_{MV} - 2\log p_{IV})$
MV test p value p_{MV}	See variance component test SMMAT-S (Chen et al., 2019)	
IV test p value p_{IV}	See IV test above	
2. Joint hybrid test using Fisher's (JF) method		$p_{JF} = \mathrm{P}(\chi_8^2 > -2\log p_B - 2\log p_{AS} - 2\log p_{\gamma_0} - 2\log p_\tau)$
MF burden test p value p_B	See burden test in SMMAT-E (Chen et al., 2019)	
MF adjusted SKAT test p value p_{AS}	See adjusted SKAT in SMMAT-E (Chen et al., 2019)	
P value p_{γ_0} for T_{γ_0} in IF test	See T_{γ_0} in IF test above	
P value p_τ for T_τ in IF test	See T_τ in IF test above	
3. Joint hybrid test using double Fisher's (JD) procedures		Step 1: separately combine the p values for main effects and GEI effects: $p_{MF} = \mathrm{P}(\chi_4^2 > -2\log p_B - 2\log p_{AS})$; $p_{IF} = \mathrm{P}(\chi_4^2 > -2\log p_{\gamma_0} - 2\log p_\tau)$; Step 2: combine the main effects MF test p value p_{MF} and GEI effects IF test p value p_{IF}: $p_{JD} = \mathrm{P}(\chi_4^2 > -2\log p_{MF} - 2\log p_{IF})$.
p_B, p_{AS}, p_{γ_0} and p_τ in JF test	See JF test above	

Table S2. A summary of the simulation scenarios and values of constant c for p value comparison of MAGEE, rareGE, and MiSTi tests in unrelated samples.

		Quantitative trait		**Binary trait**	
		β_t	γ_t	β_t	γ_t
Scenario 1: +/0/-: 10%/80%/10% for both main and GEI effects					
Sample size	2,000	0.015	0.042	0.08	0.09
	5,000	0.015	0.026	0.06	0.065
	10,000	0.015	0.017	0.06	0.04
Scenario 2: +/0/-: 10%/80%/10% for main effects only					
Sample size	2,000	0.09	0	0.22	0
	5,000	0.06	0	0.13	0
	10,000	0.038	0	0.082	0

+/0/-: proportions of variants with positive, null and negative effects.

Table S3. A summary of the values of constant c in the type I error simulations for MAGEE GEI tests in 2,000, 5,000, and10,000 unrelated samples in the presence of strong genetic main effects.

		Quantitative trait		**Binary trait**	
		β_t	Variance explained[a]	β_t	Odds ratio[b]
+/0/-: 10%/80%/10% for main effects only					
Sample size	2,000	0.1	2.508%	0.21	12.6
	5,000	0.075	1.412%	0.16	7.38
	10,000	0.058	0.863%	0.12	4.69

+/0/-: proportions of variants with positive, null and negative effects.

[a] Phenotypic variance explained by a single variant set, averaged across 1,000 simulation replicates.

[b] Largest possible odds ratio explained by a single variant set, computed as the exponential of the maximum difference of the linear predictor (on the logit scale) in the simulated samples, averaged across 1,000 simulation replicates.

Table S4. A summary of the values of constant c in the power simulations for MAGEE IV, IF, and JV tests versus rareGE GEI test, MiSTi test, and rareGE JOINT test in 2,000, 5,000, and10,000 unrelated samples, respectively, in the presence of both strong genetic main effects and GEI effects.

		Quantitative trait		**Binary trait**	
		β_t	γ_t	β_t	γ_t
+/0/-: 10%/80%/10% for main effects only					
Sample size	2,000	0.1	0.054	0.21	0.135
	5,000	0.075	0.039	0.16	0.09
	10,000	0.058	0.029	0.12	0.066

+/0/-: proportions of variants with positive, null and negative effects.

Table S5. A summary of the simulation scenarios and values of constant c for power comparison of all the MAGEE tests in related samples.

	Quantitative trait		**Binary trait**	
	β_t	γ_t	β_t	γ_t
Scenario 1: +/0/-: 10%/80%/10% for both main and GEI effects				
	0.019	0.0094	0.019	0.0094
Scenario 2: +/0/-: 10%/80%/10% for main effects only				
	0.025	0	0.025	0
Scenario 3: +/0/-: 10%/80%/10% for GEI effects only				
	0	0.0116	0	0.0116
Scenario 4: +/0/-: 16%/80%/4% for both main and GEI effects				
	0.015	0.007	0.015	0.007
Scenario 5: +/0/-: 16%/80%/4% for main effects only				
	0.02	0	0.02	0
Scenario 6: +/0/-: 16%/80%/4% for GEI effects only				
	0	0.009	0	0.009

+/0/-: proportions of variants with positive, null and negative effects.

Table S6. Empirical type I error rates of MAGEE GEI tests (IV and IF) in 2,000, 5,000, and 10,000 unrelated samples under the null hypothesis of strong genetic main effects but no GEI effects, at significance levels of 0.05, 1.0×10^{-4}, and 2.5×10^{-6}.

		Quantitative trait			**Binary trait**		
		Significance Level			Significance Level		
Sample size	Test	0.05	1.0×10^{-4}	2.5×10^{-6}	0.05	1.0×10^{-4}	2.5×10^{-6}
2K	IV	0.044	7.35×10^{-5}	1.43×10^{-6}	0.041	5.31×10^{-5}	7.50×10^{-7}
	IF	0.044	7.02×10^{-5}	1.90×10^{-6}	0.041	5.37×10^{-5}	1.15×10^{-6}
5K	IV	0.047	8.49×10^{-5}	1.98×10^{-6}	0.045	7.22×10^{-5}	1.78×10^{-6}
	IF	0.046	8.49×10^{-5}	1.95×10^{-6}	0.045	7.17×10^{-5}	1.35×10^{-6}
10K	IV	0.048	9.15×10^{-5}	2.29×10^{-6}	0.047	8.52×10^{-5}	2.20×10^{-6}
	IF	0.048	8.95×10^{-5}	2.64×10^{-6}	0.047	8.40×10^{-5}	1.88×10^{-6}

REFERENCE

Chen, H., Huffman, J. E., Brody, J. A., Wang, C., Lee, S., Li, Z., . . . Lin, X. (2019). Efficient variant set mixed model association tests for continuous and binary traits in large-scale whole-genome sequencing studies. *The American Journal of Human Genetics, 104*(2), 260-274.