SUPPLEMENTARY DATA

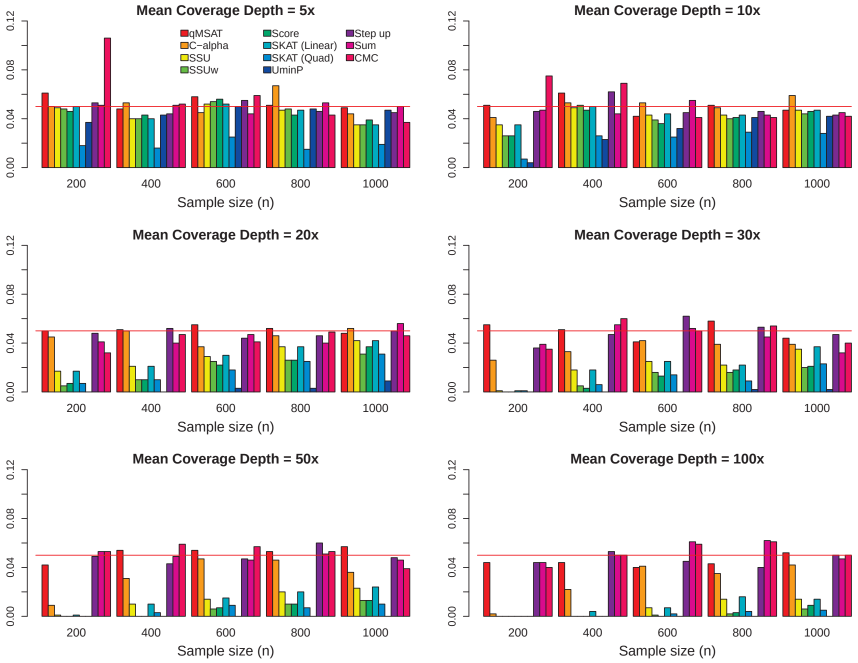

Figure S1. Type I errors over varying coverage depths and sample sizes at MAF=0.1%. There are $n/2$ numbers of cases and controls each. Twenty noncausal rare variants ($d = 20$) are considered with odds ratios at 1 for all variants. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

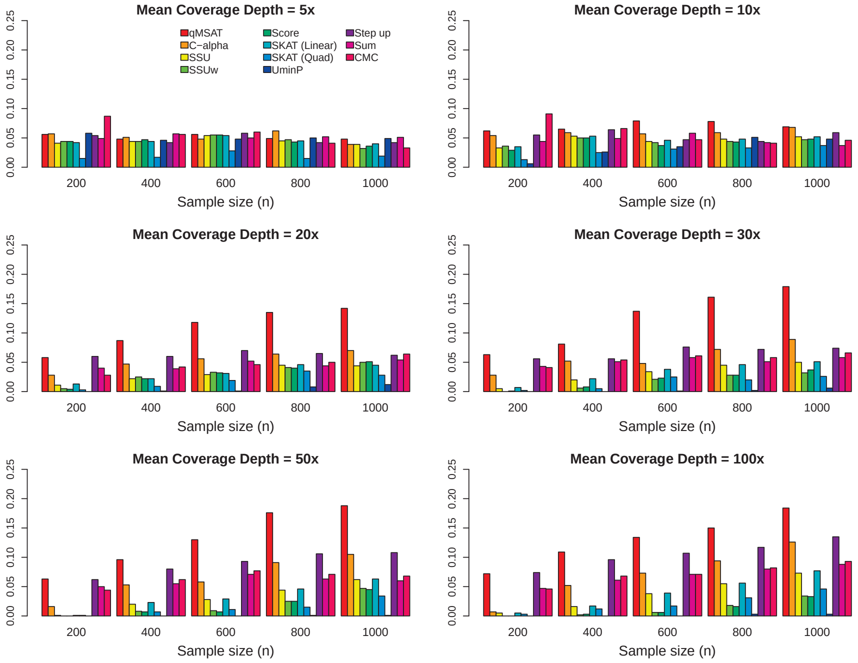

Figure S2. Power evaluation of the effects of coverage depths and sample sizes at MAF=0.1%. There are $n/2$ numbers of cases and controls each. Twenty rare variants ($d = 20$) are considered, of which five are causal with odds ratios at 2, 3, 4, 0.5, and 0.5. No LD is assumed among the variants.

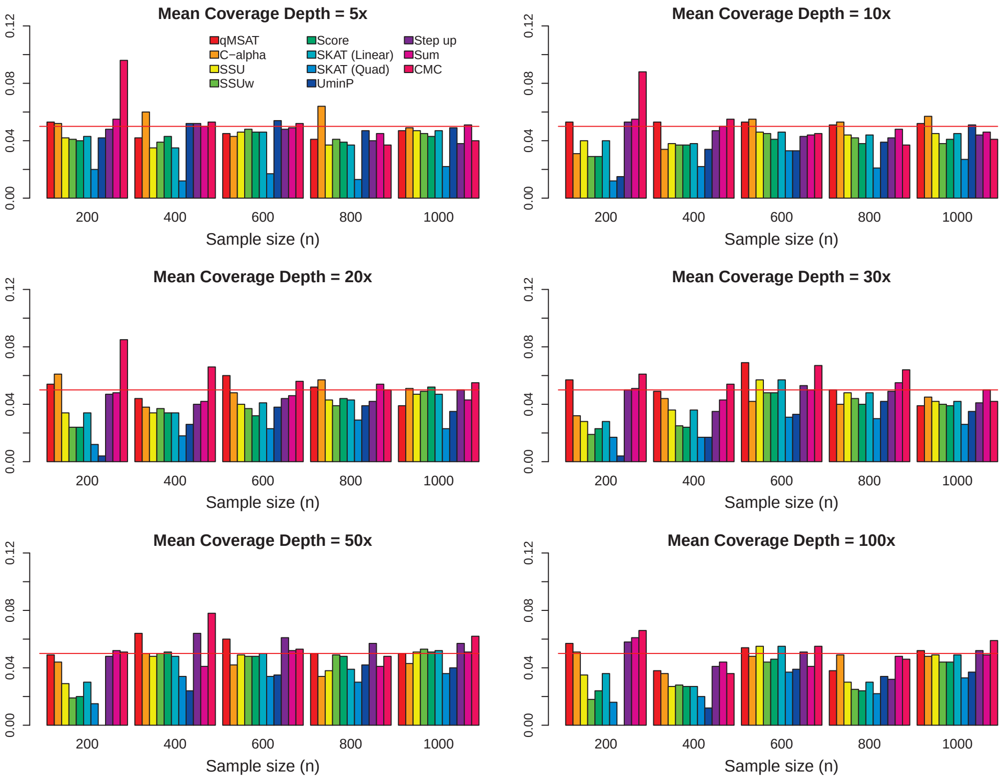

Figure S3. Type I errors over varying coverage depths and sample sizes at MAF=1%. There are $n/2$ numbers of cases and controls each. Twenty noncausal rare variants ($d = 20$) are considered with odds ratios at 1 for all variants. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

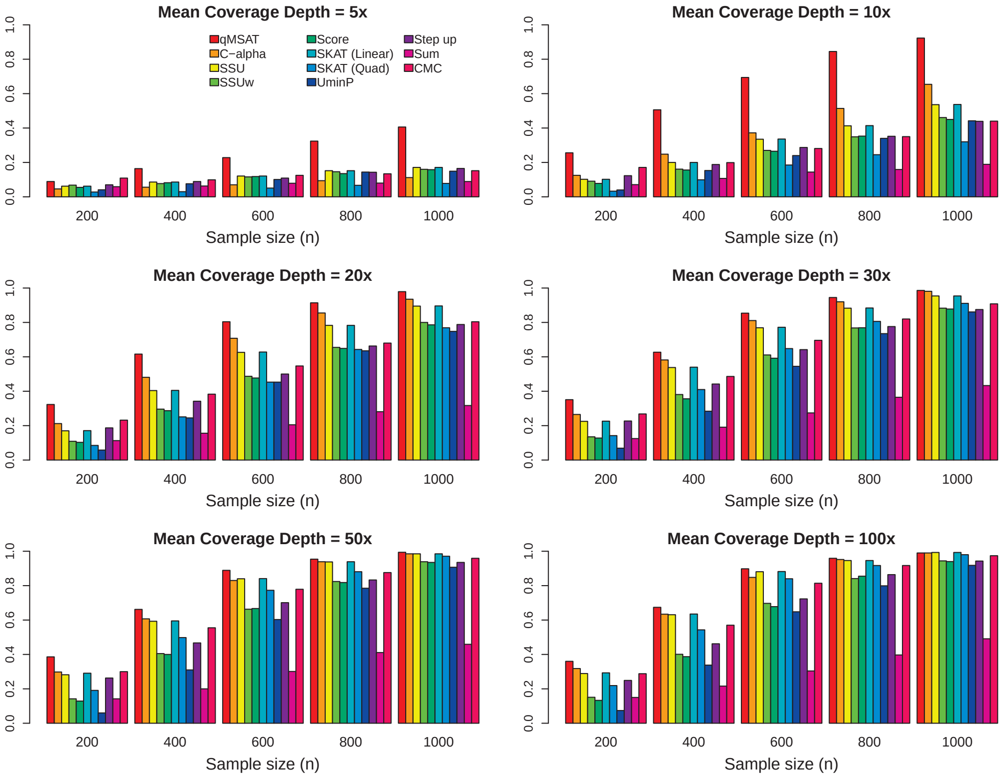

Figure S4. Power evaluation of the effects of coverage depths and sample sizes at MAF=1%. There are $n/2$ numbers of cases and controls each. Twenty rare variants ($d = 20$) are considered, of which five are causal with odds ratios at 2, 3, 4, 0.5, and 0.5. No LD is assumed among the variants.

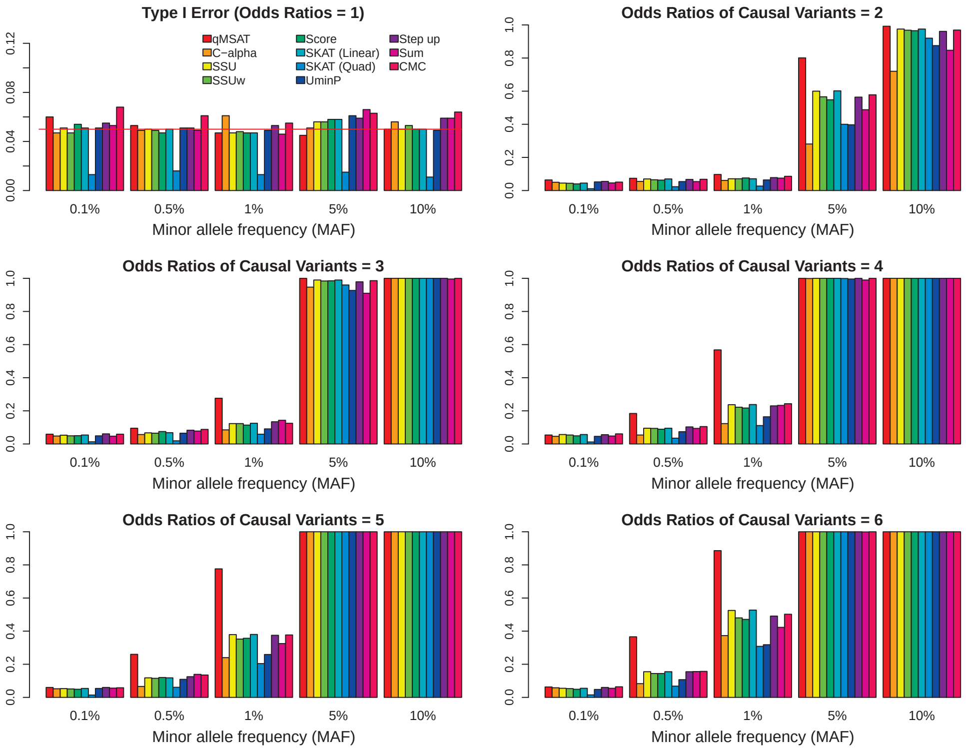

Figure S5. Effects of MAFs and odds ratios at a mean coverage depth of 5x. Empirical powers and type I errors are presented at a mean coverage depth of 5x with varying MAFs and odds ratios for five variants amongst twenty ($d = 20$) considered altogether. We use $n = 500$ observations, where there are $n/2 = 250$ numbers of cases and controls each. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

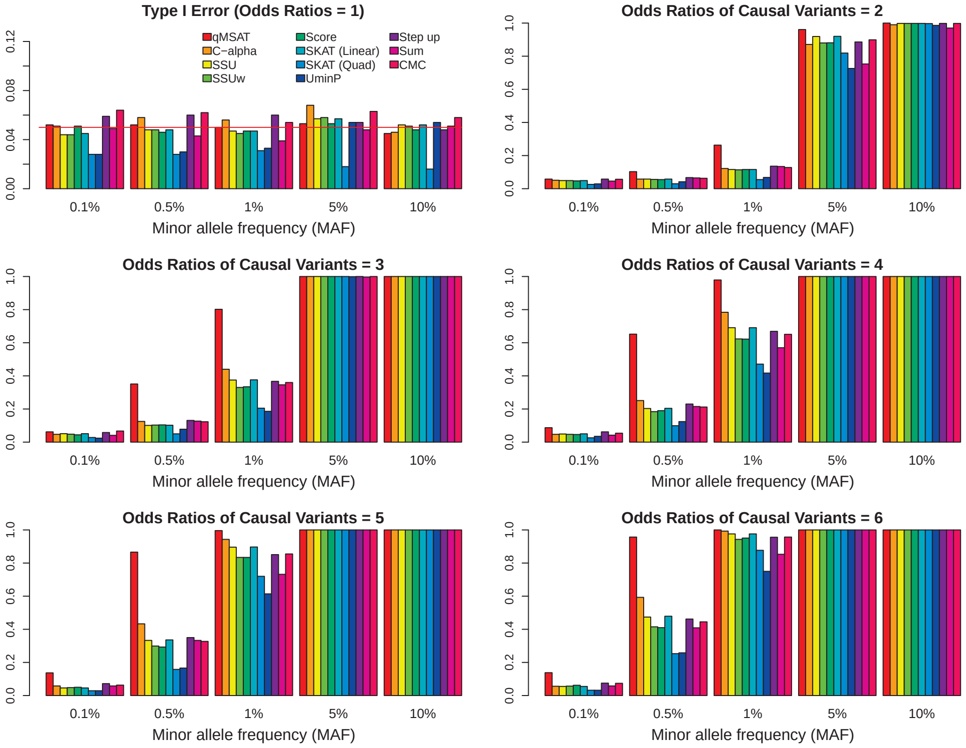

Figure S6. Effects of MAFs and odds ratios at a mean coverage depth of 10x. Empirical powers and type I errors are presented at a mean coverage depth of 10x with varying MAFs and odds ratios for five variants amongst twenty ($d = 20$) considered altogether. We use $n = 500$ observations, where there are $n/2 = 250$ numbers of cases and controls each. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

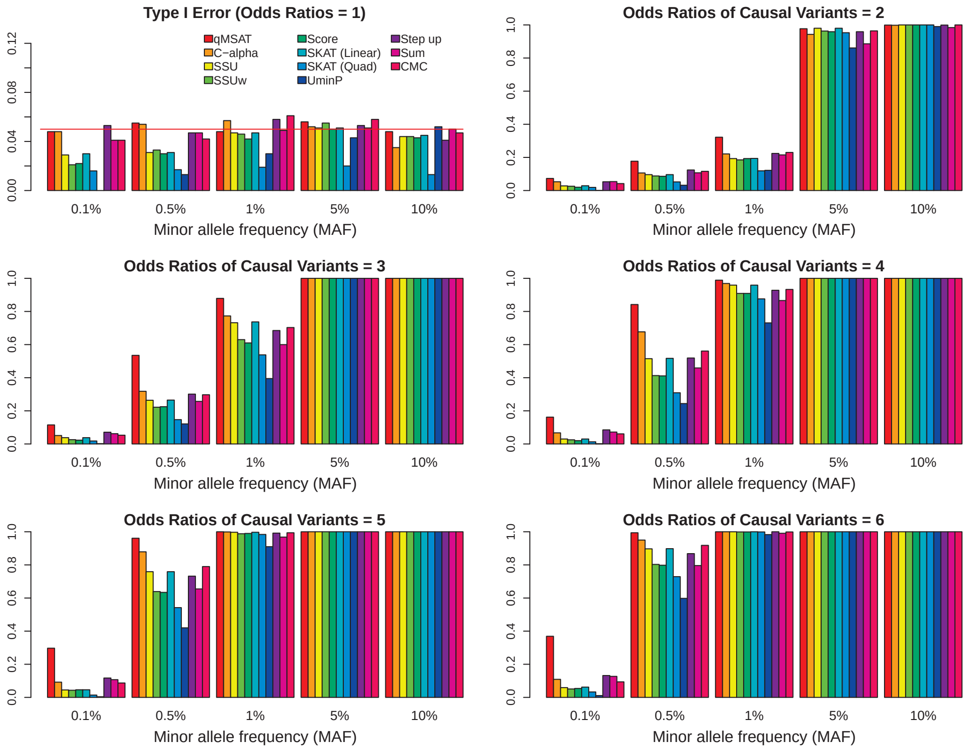

Figure S7. Effects of MAFs and odds ratios at a mean coverage depth of 20x. Empirical powers and type I errors are presented at a mean coverage depth of 20x with varying MAFs and odds ratios for five variants amongst twenty ($d = 20$) considered altogether. We use $n = 500$ observations, where there are $n/2 = 250$ numbers of cases and controls each. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

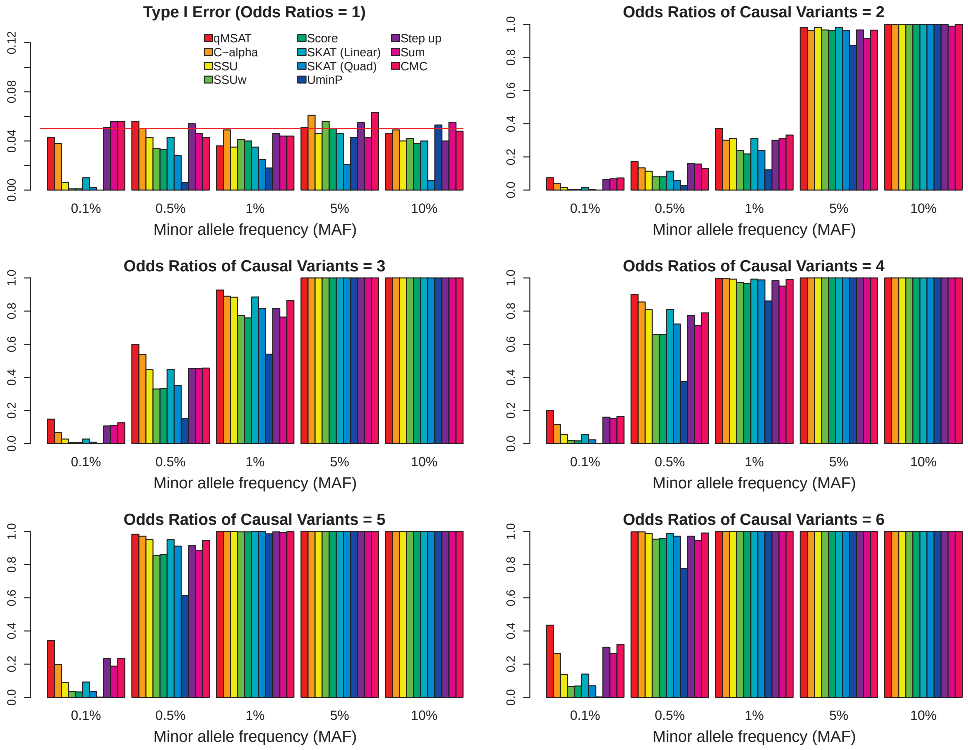

Figure S8. Effects of MAFs and odds ratios at a mean coverage depth of 50x. Empirical powers and type I errors are presented at a mean coverage depth of 50x with varying MAFs and odds ratios for five variants amongst twenty ($d = 20$) considered altogether. We use $n = 500$ observations, where there are $n/2 = 250$ numbers of cases and controls each. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

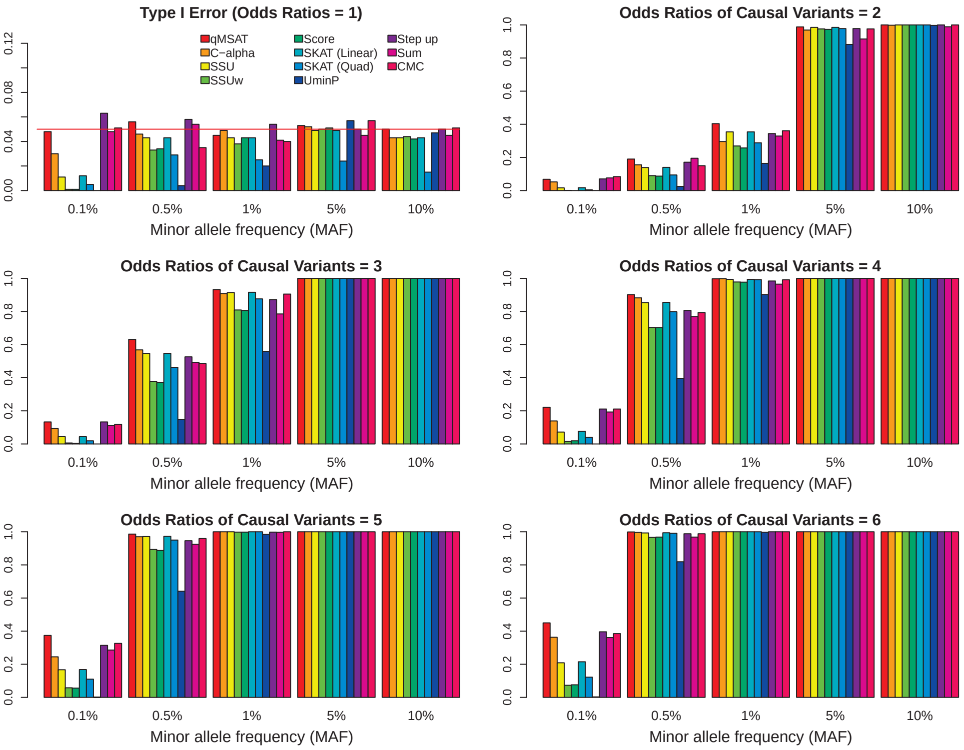

Figure S9. Effects of MAFs and odds ratios at a mean coverage depth of 100x. Empirical powers and type I errors are presented at a mean coverage depth of 100x with varying MAFs and odds ratios for five variants amongst twenty ($d = 20$) considered altogether. We use $n = 500$ observations, where there are $n/2 = 250$ numbers of cases and controls each. No LD is assumed among the variants. Reference lines (in red) are drawn at the 0.05 error rate.

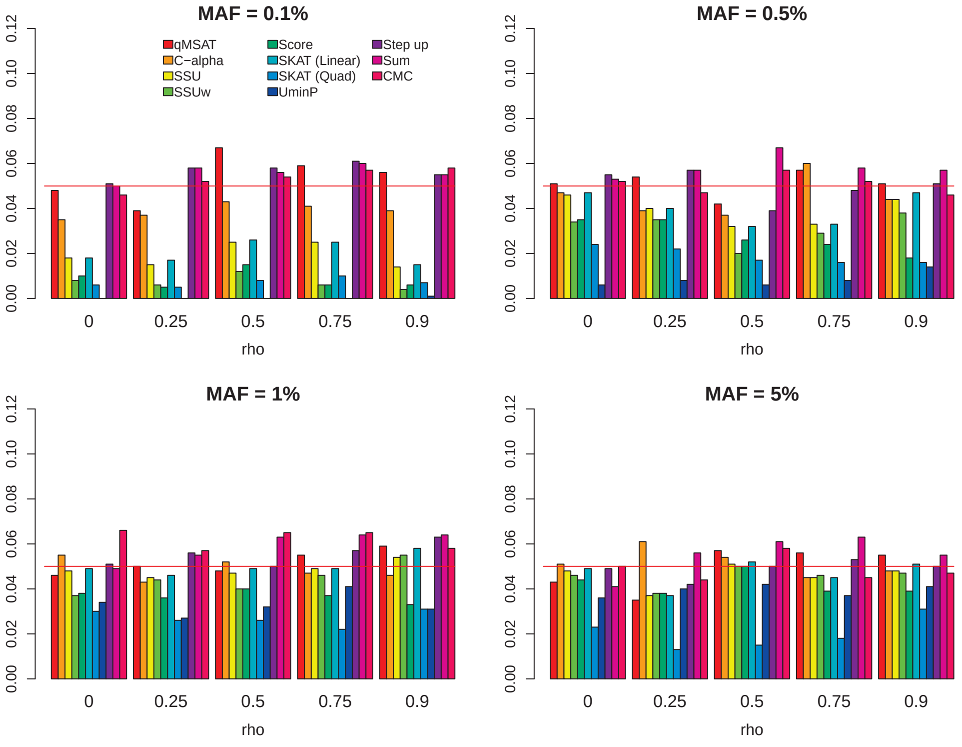

Figure S10. Type I errors over varying linkage disequilibrium structures. Type I errors are presented at a mean coverage depth of 30x and sample sizes $n = 500$ with equal numbers of cases and controls for a spectrum of LD structures generated from latent variables having autoregressive covariance matrices $\mathbf{\Sigma} = \rho^{|i-j|}$. Variants generated with $\rho = 0$ have no LD, whereas variants generated with large values of ρ are in high LD. Twenty noncausal variants ($d = 20$) are considered with odds ratios at 1 for all variants. Reference lines (in red) are drawn at the 0.05 error rate.

Table S1. Multiple rare variants association analysis of UCSD obesity data over regions with p-values $>$ 0.05.

	FAAH exons (d=2)	FAAH intron 1 (d=18)	FAAH intron 2 (d=2)	FAAH intron 3 (d=10)	MGLL exons (d=3)	MGLL intron 1 (d=11)	MGLL intron 2 (d=54)	MGLL intron 3 (d=182)	MGLL intron 4 (d=94)
qMSAT	0.610	0.318	0.069	0.212	0.330	0.180	0.657	0.212	0.213
C-alpha	1.000	0.795	0.244	0.160	0.94	0.505	0.452	0.294	0.795
SSU	0.367	0.125	0.181	0.156	0.212	0.196	0.673	0.420	0.221
SSUw	0.367	0.241	0.219	0.284	0.264	0.293	0.441	0.564	0.387
Score	0.368	0.233	0.220	0.277	0.264	0.300	0.404	0.377	0.358
SKAT (Linear)	0.367	0.123	0.181	0.152	0.213	0.194	0.709	0.435	0.217
SKAT (Quad)	0.367	0.346	0.184	0.169	0.218	0.229	0.996	0.485	0.165
UminP	0.526	0.749	0.280	0.550	0.408	0.853	0.972	0.999	0.957
Step up	0.747	0.089	0.299	0.247	0.379	0.202	0.334	0.282	0.180
Sum	0.988	0.363	0.550	0.973	0.324	0.492	0.331	0.825	0.095
CMC	0.988	0.297	0.551	0.786	0.325	0.346	0.185	0.064	0.136

P-values are provided for association tests performed over d multiple rare variants. FAAH exons, three FAAH disjoint intron regions, MGLL exons, and four MGLL disjoint intron regions exhibit no significant association of multiple rare variants with extreme BMI at the 0.05 level by all methods.

Table S2. Marginal rare variants association analysis of the UCSD obesity data.

	CHR	Position		MAF		P-value	OR	Direction
			Cases	Controls	Overall			
FAAH promoter	1	46848783	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
(d=17)	1	46850416	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
	1	46851533	0.0000	0.0068	0.0035	0.0984	4.79e-07	protective
	1	46851558	0.0070	0.0000	0.0035	0.0918	2.21e06	deleterious
	1	46851599	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46851601	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46851679	0.0634	0.0308	0.0469	0.0561	2.21	deleterious
	1	46852006	0.0000	0.0068	0.0035	0.101	4.89e-07	protective
	1	46852118	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46852929	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46853232	0.0035	0.0000	0.0017	0.233	2.21e06	deleterious
	1	46853789	0.0071	0.0000	0.0035	0.091	2.22e06	deleterious
	1	46853835	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46854645	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46856075	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	1	46857019	0.0357	0.0240	0.0297	0.400	1.53	deleterious
	1	46858932	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
MGLL promoter	3	127543931	0.0282	0.0753	0.0521	**0.0097**	0.357	protective
(d=25)	3	127544033	0.0035	0.0034	0.0035	0.984	1.03	deleterious
	3	127544943	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
	3	127545675	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	3	127545878	0.0000	0.0034	0.0017	0.243	4.82e-07	protective
	3	127545923	0.0070	0.0068	0.0069	0.978	1.03	deleterious
	3	127546057	0.0317	0.0171	0.0243	0.309	1.65	deleterious
	3	127546365	0.0035	0.0034	0.0035	0.984	1.03	deleterious
	3	127546515	0.0493	0.0479	0.0486	0.938	1.03	deleterious
	3	127547523	0.0176	0.0068	0.0122	0.229	2.63	deleterious
	3	127547753	0.0000	0.0034	0.0017	0.243	4.82e-07	protective
	3	127549097	0.0000	0.0068	0.0035	0.0984	4.79e-07	protective
	3	127549174	0.0106	0.0000	0.0052	**0.0392**	6.01e06	deleterious
	3	127549868	0.0000	0.0034	0.0017	0.243	4.82e-07	protective
	3	127550666	0.0000	0.0034	0.0017	0.242	4.79e-07	protective
	3	127551249	0.0000	0.0068	0.0035	0.0984	4.79e-07	protective
	3	127551357	0.0000	0.0034	0.0017	0.243	4.82e-07	protective
	3	127551569	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	3	127552842	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	3	127553213	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	3	127553586	0.0070	0.0034	0.0052	0.542	2.07	deleterious
	3	127553769	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
	3	127553858	0.0000	0.0034	0.0017	0.241	4.75e-07	protective
	3	127553864	0.0000	0.0034	0.0017	0.242	4.79e-07	protective
	3	127554251	0.0035	0.0000	0.0017	0.234	2.19e06	deleterious
MGLL 3' UTR	3	127408552	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
(d=6)	3	127408973	0.0070	0.0000	0.0035	0.0926	2.19e06	deleterious
	3	127409079	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
	3	127409415	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious
	3	127410539	0.0000	0.0034	0.0017	0.242	4.79e-07	protective
	3	127411029	0.0035	0.0000	0.0017	0.235	2.18e06	deleterious

The chromosome ID (CHR), positions, minor allele frequencies (MAFs), Chi-square p-values, effect sizes (or ORs), and direction of effects are provided for each variant. Cases represent individuals with BMI > 40 kg/m^2, whereas controls represent those having BMI ≤ 30 kg/m^2. FAAH promoter, MGLL promoter, and MGLL 3' UTR are regions exhibiting significant association of multiple rare variants with extreme BMI at the 0.05 level by one or more multivariate methods. P-values significant at the 0.05 level are boldfaced.