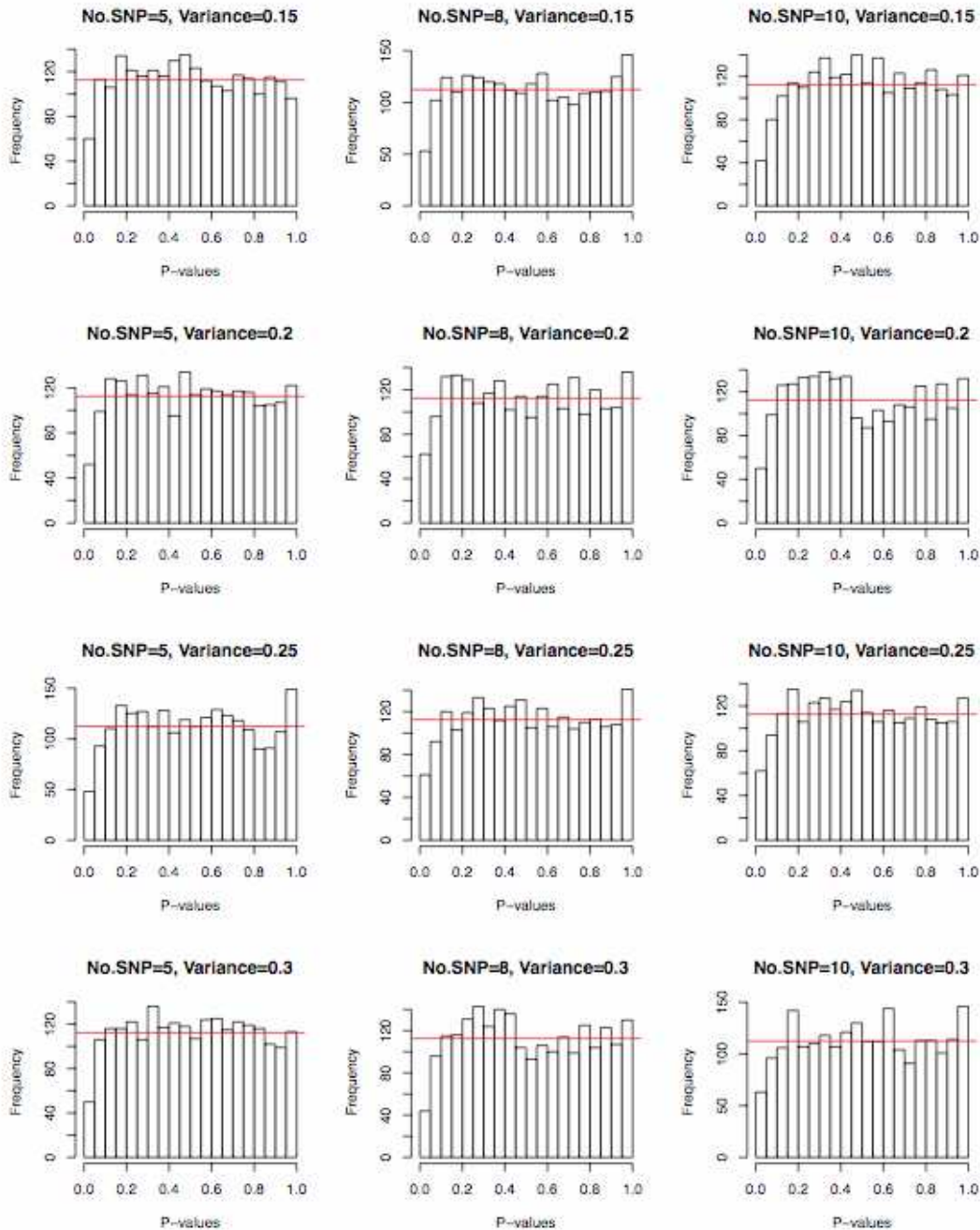
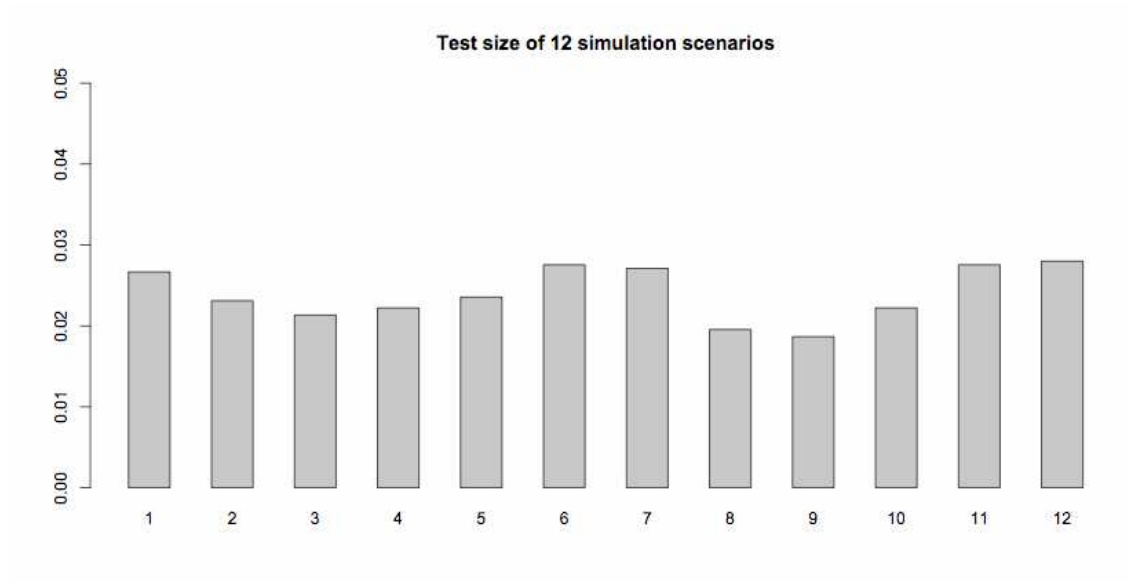


Supplementary Figure 1 Distribution of SPCA p-values for null gene sets where disease status were generated independently of genotype data, for each of the 12 simulation scenarios. Since there were 2250 null gene sets and 20 bins for each histogram, if p-values are uniformly distributed, one would expect each bin has a height of 112.5 ($= 2250/20$), indicated by the red lines. The first bin of the histogram corresponds to frequency of p-values less than 0.05 ($= 1.0/20$). Note that for all scenarios, an excess of small p values for the SPCA model is not observed, the height of the first bin is always below the red line, indicating fewer significant gene sets than expected at the 0.05 significance level.



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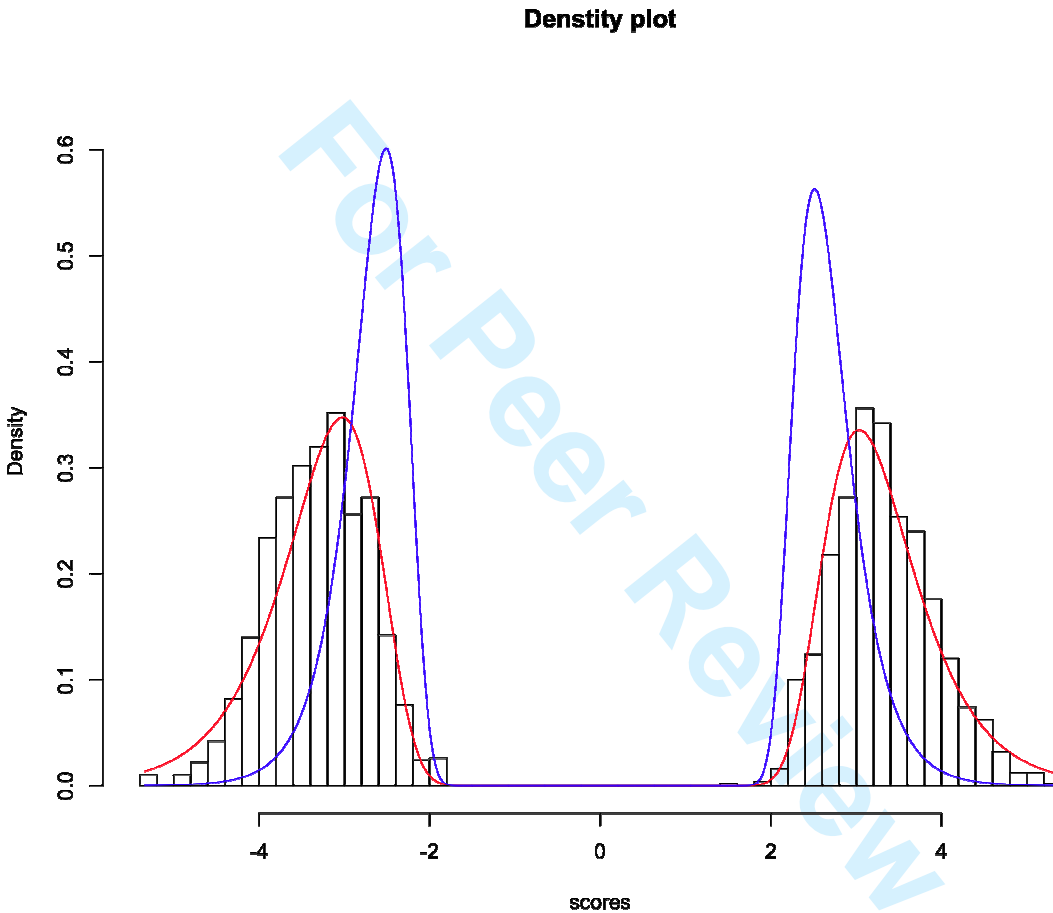
Supplementary Figure 2: Actual test sizes of SPCA model for each of 12 simulation scenarios.



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Supplementary Figure 3: Shown below are the histograms of the M_m statistic for a gene set with 1000 randomly generated outcomes. The red line was drawn using our estimated mixture distribution (parameter values $p=0.484$, $\gamma_1=0.523$, $\delta_1=0.596$, $\gamma_2=0.512$, $\delta_2=0.578$), which approximated the empirical null distribution well. The blue line is the mixture of extreme value distributions without addition parameters (i.e. $\gamma_1=\gamma_2=0$ and $\delta_1=\delta_2=1$), which provided a poor fit to the empirical null distribution.



Supplementary Table 1 Average p-values of SPCA model and sum statistic (SUMSTAT) for the 12 simulation scenarios.

Scene	N_SNP	Variance	Method	Gene set 1 (size=262)	Gene set 2 (size=254)	Gene set 3 (size=216)	Gene set 4 (size=145)	Gene set 5 (size=138)
1	5	0.15	SPCA	0.08	0.08	0.15	0.12	0.10
			SUMSTAT	0.31	0.25	0.42	0.15	0.25
2	5	0.20	SPCA	0.05	0.06	0.12	0.10	0.09
			SUMSTAT	0.16	0.24	0.27	0.12	0.14
3	5	0.25	SPCA	0.06	0.04	0.07	0.04	0.07
			SUMSTAT	0.12	0.11	0.16	0.28	0.10
4	5	0.30	SPCA	0.03	0.03	0.05	0.03	0.03
			SUMSTAT	0.16	0.08	0.12	0.04	0.07
5	8	0.15	SPCA	0.07	0.07	0.08	0.10	0.12
			SUMSTAT	0.27	0.22	0.23	0.11	0.17
6	8	0.20	SPCA	0.04	0.05	0.06	0.05	0.05
			SUMSTAT	0.15	0.10	0.17	0.04	0.06
7	8	0.25	SPCA	0.03	0.02	0.02	0.03	0.03
			SUMSTAT	0.05	0.04	0.07	0.02	0.05
8	8	0.30	SPCA	0.02	0.01	0.02	0.02	0.02
			SUMSTAT	0.06	0.04	0.05	0.01	0.02
9	10	0.15	SPCA	0.07	0.06	0.08	0.09	0.10
			SUMSTAT	0.24	0.10	0.19	0.08	0.17
10	10	0.20	SPCA	0.04	0.03	0.04	0.04	0.04
			SUMSTAT	0.07	0.08	0.15	0.04	0.09
11	10	0.25	SPCA	0.01	0.02	0.04	0.03	0.02
			SUMSTAT	0.03	0.03	0.07	0.03	0.04
12	10	0.30	SPCA	0.01	0.01	0.02	0.01	0.01
			SUMSTAT	0.01	0.01	0.06	0.01	0.01