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Supplemental Data

A Statistical Approach for Rare-Variant Association Testing in Affected Sibships

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Pairwise IBD Sharing of Affected Pairs Across Candidate Genes

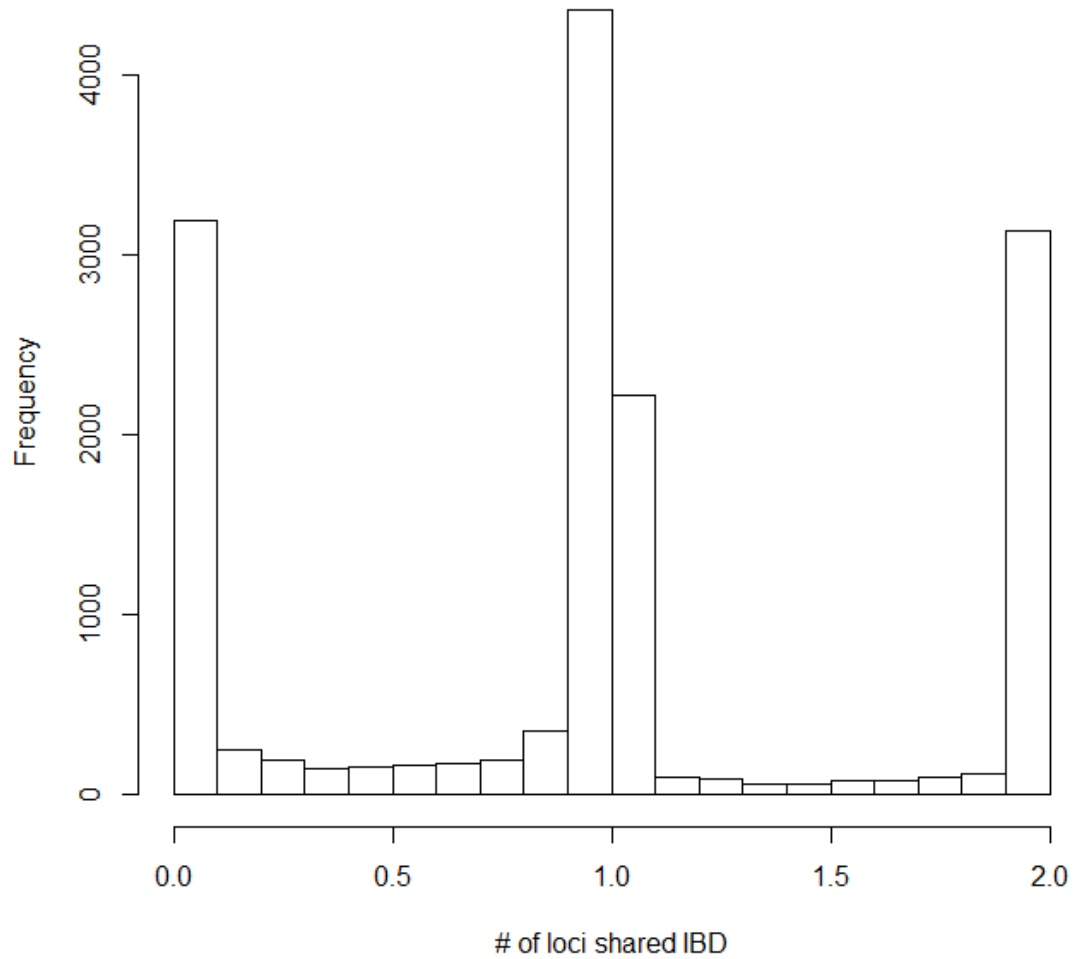


Figure S1. Histogram of pairwise IBD estimates between GENOA affected sibling pairs for candidate genes listed in Table 3. IBD was estimated from MERLIN using 4448 common SNPs on the Illumina HumanExome Beadchip.

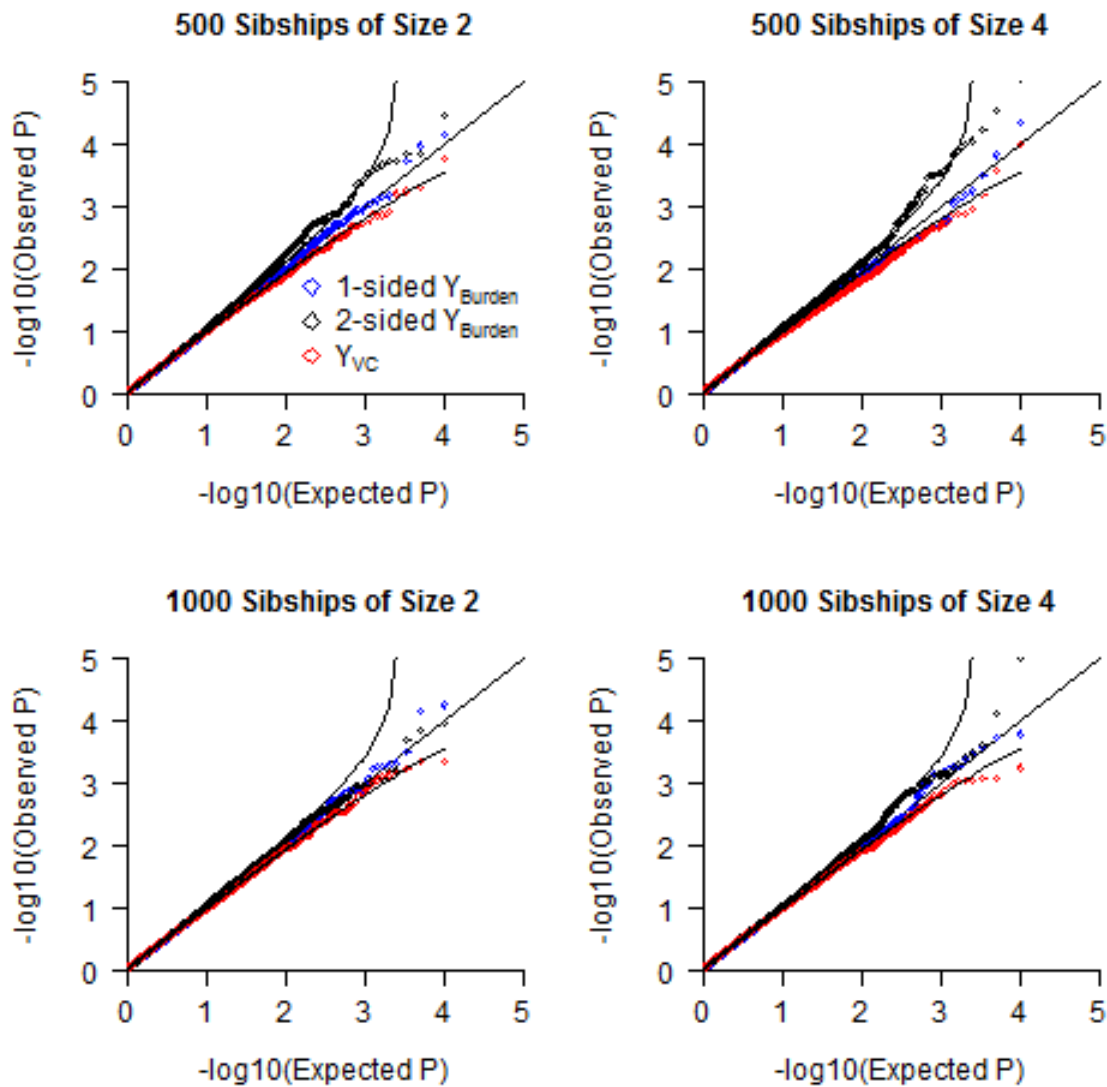


Figure S2. Quantile-quantile (QQ) plots of observed p-values versus expected p-values (on $-\log_{10}$ scale) for the Y_{Burden} and Y_{VC} tests under the null hypothesis using samples of European ancestry. QQ plots are shown for 500 sibships of size 2 (upper left panel), 500 sibships of size 4 (upper right panel), 1000 sibships of size 2 (lower left panel), and 1000 sibships of size 4 (lower right panel). Each set of results based on 10,000 replications with $\lambda_C = 8$.

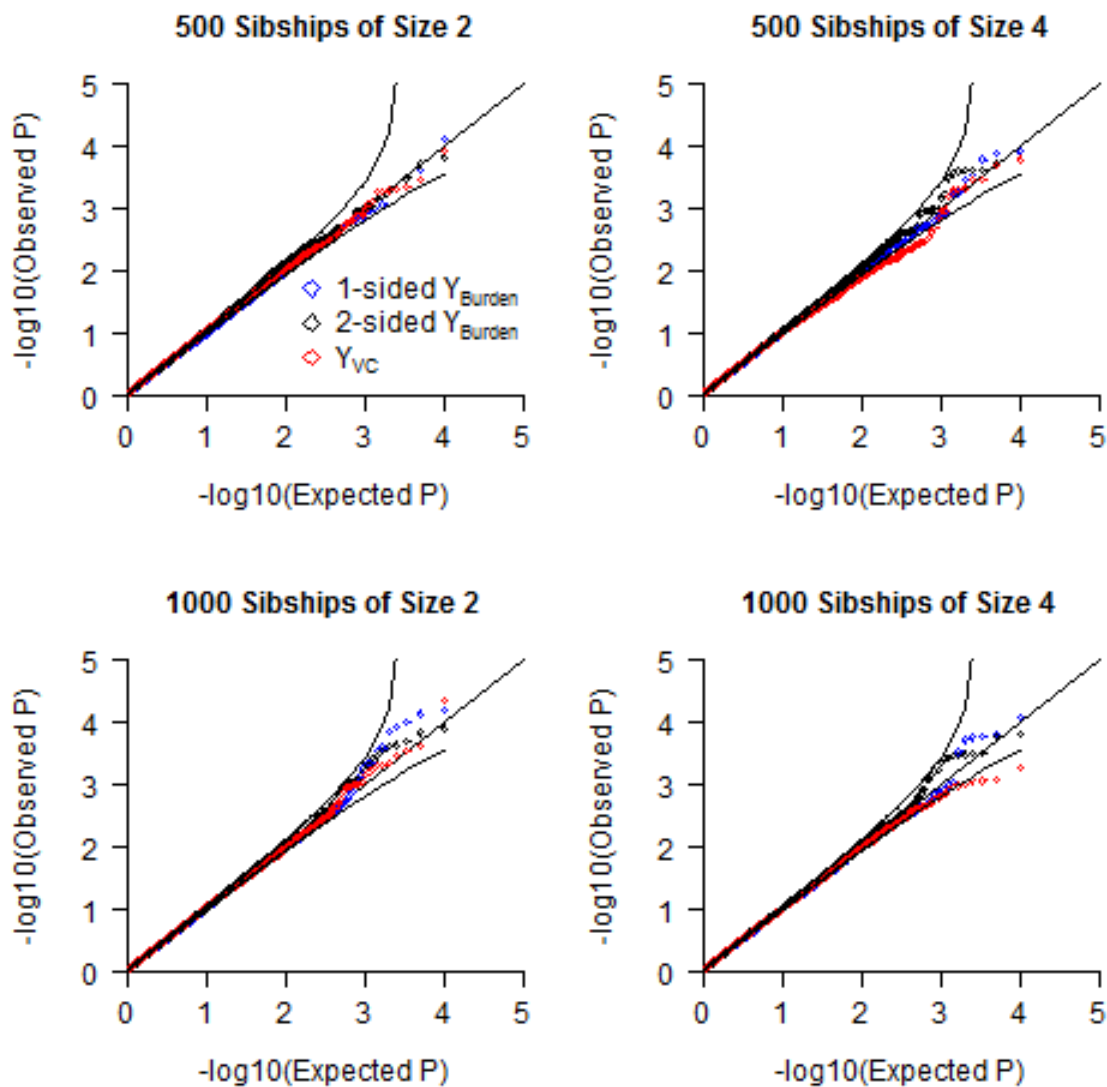


Figure S3. Quantile-quantile (QQ) plots of observed p-values versus expected p-values (on $-\log_{10}$ scale) for the Y_{Burden} and Y_{VC} tests under the null hypothesis using samples of both African and European ancestry. Odds ratio of disease for African versus European ancestry is 4. QQ plots are shown for 500 sibships of size 2 (upper left panel), 500 sibships of size 4 (upper right panel), 1000 sibships of size 2 (lower left panel), and 1000 sibships of size 4 (lower right panel). Each set of results based on 10,000 replications with $\lambda_C = 8$.

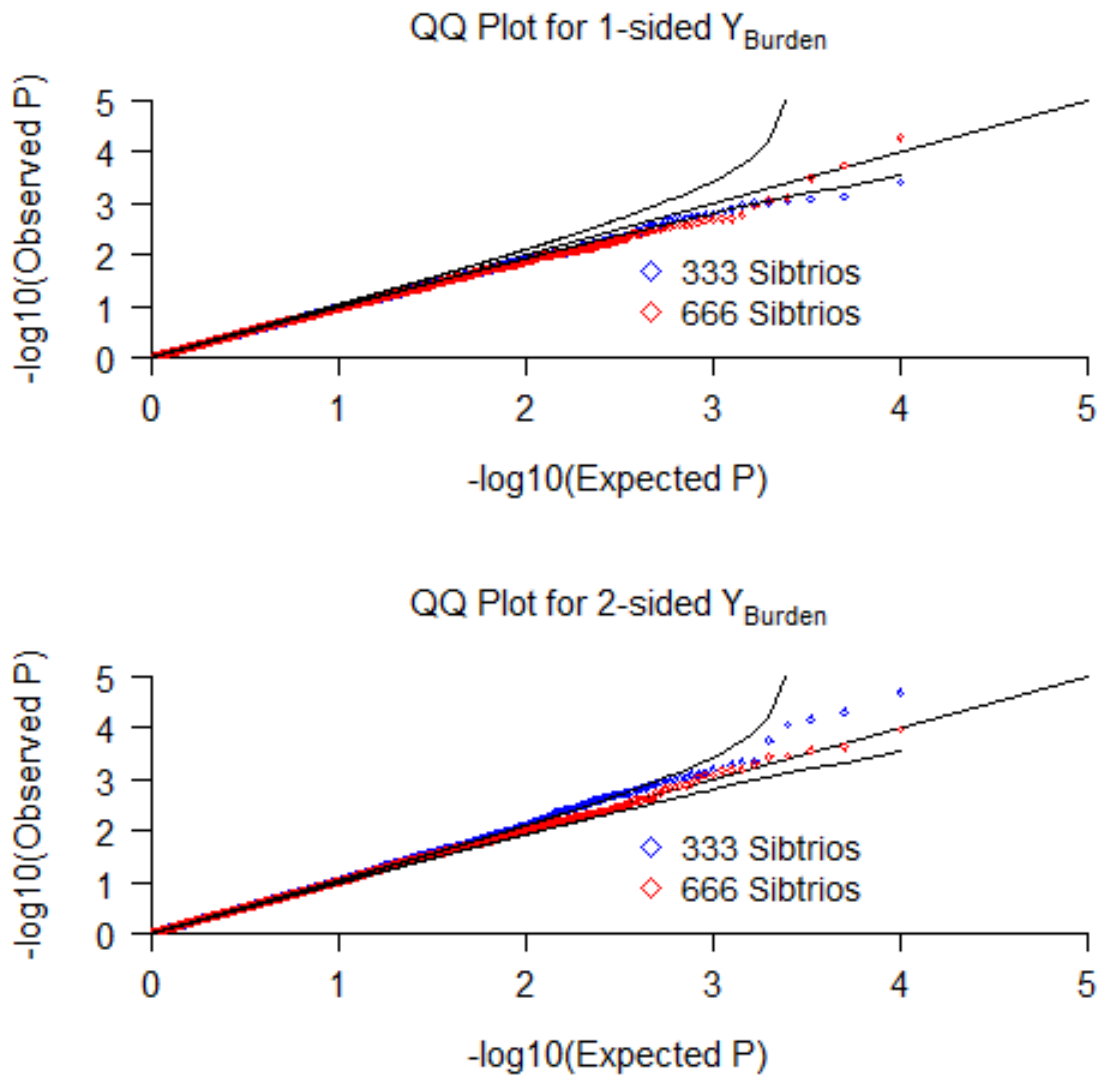


Figure S4. Quantile-quantile (QQ) plots of observed p-values versus expected p-values (on $-\log_{10}$ scale) for the Y_{Burden} test under the null hypothesis for 333 (blue) or 666 (red) sibtrios comprised of 3 affected siblings. Top panel shows the result of the 1-sided Y_{Burden} test. Bottom panel shows the result of the 2-sided Y_{Burden} test. Each set of results based on 10,000 replications with $\lambda_C = 4$.

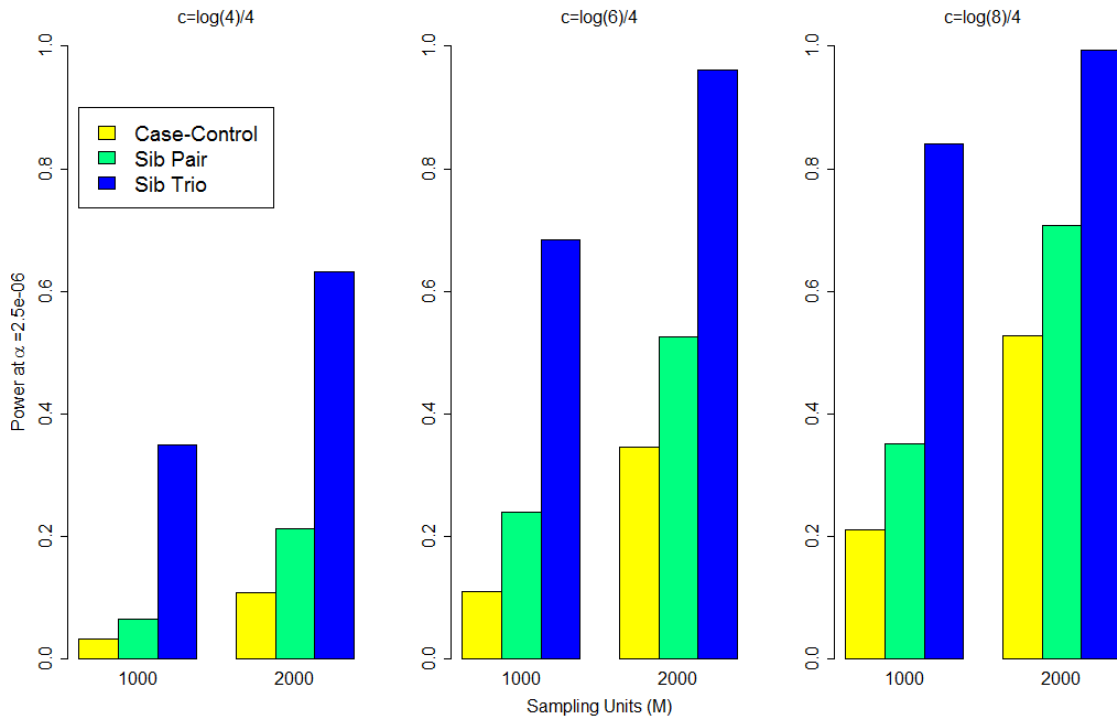


Figure S5. Power at $\alpha = 2.5 \times 10^{-6}$ to detect rare susceptibility variants under different sampling designs assuming a fixed number of M sampling units. Yellow bar denotes power using $M/2$ cases and $M/2$ controls using logistic-regression burden test. Green bar denotes power for $M/2$ affected sib pairs using 1-sided Y_{Burden} test. Blue bar denotes power for $M/3$ affected sibtrios using 1-sided Y_{Burden} test. Results are shown for $c = \log(4)/4$ (left panel), $c = \log(6)/4$ (middle panel), and $c = \log(8)/4$ (right panel). Each set of results based on 1,000 replications assuming $\lambda_C = 4$ and 15% of rare variants are causal with 100% of causal variants increasing risk. For 1-sided Y_{Burden} test, we induced uncertainty in IBD sharing based on the observed information in Figure S1 as described in the Discussion