



Excess relatedness is the major source of inflation in the association test statistic

We investigated the source of score inflation in our association test using the observed (not modified/spiked) BMI phenotype. Using PLINK/QFAM-Total with permutation testing, the sibships-without-parents dataset produced genome-wide association results for BMI with a genomic control inflation factor (λ) of 1.41 (Figure S2). To determine the impact of genotyping artifact on the score distribution, we analyzed a subset of 88,431 common SNPs with 100% genotyping completeness. Score inflation was unchanged from the larger marker set, suggesting that genotyping artifact is not a major cause of score inflation (data not shown). This observation is consistent with the null score distribution observed for the within-family test of association using the full marker set.

To examine the impact of excess relatedness on the score distribution, we filtered individuals to reduce relatedness between family units. Removing sibships containing parents of another sibship substantially reduced score inflation ($\lambda = 1.10$) as compared to using all sibships ($\lambda=1.41$) (Figure S2). A set of “unrelated” individuals ($n=133$; related less than first cousins)

produced a score distribution with $\lambda=1.10$. We note that residual relatedness between the reduced set of sibships or between “unrelated” individuals is roughly comparable to first-degree and higher-order cousins, and this residual relatedness is reflected in the genomic control inflation factor $\lambda=1.10$. Since minimizing relatedness in the cohort also reduces inflation of the association test statistic, we conclude that excess relatedness is the major source of score inflation in our association study.