"Skewness Correction in QTL Mapping Using Extended Pedigrees and Its Application to Gene Expression Linkage Analysis"

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Abstract:

Mapping quantitative trait loci (QTL) using expended pedigrees are more efficient than that based on sibling pairs. Likelihood ratio tests (LRT) and robust score tests are two popular approaches. The asymptotic distributions are usually used for approximating p-values when simulation is computationally intensive (e.g., very small p-values or thousands of traits). The dependence among Identity by Descent (IBD) of relative trios causes the score statistic skewed rightward and LRT skewed leftward. The p-values based on the asymptotic distributions are questionable in a typical QTL study with a small number of extended pedigrees. We will discuss methods of computing such skewness and correcting genome-wide p-values for skewness.

We applied our approach to a gene expression linkage analysis data (Morley et al., Nature, 2004). It contains genotypes of 2819 SNP markers across the genome of 14 three-generation CEPH families and 3354 gene expressions for each subject. The goal was to localize the genetic determinants of these gene expression traits. The original analysis detected significant linkages to the expression levels of 142 genes at a threshold LOD=5.3 with 3.5 false positives expected. Around 80% detected linkages were trans-linkages. We show that 110 out of 142 were expected to be false positives by appropriate statistical corrections. Controlling FDR at 10%, we detected linkages to the expression levels of 23 genes. Most of the detected linkages were cis-linkages. Our results were consistent with that from a larger gene expression linkage study (Goring et al., Nature Genetics, 2007).

The skewness effect in genome-wide association studies will be discussed briefly.