GENETIC EFFECT ESTIMATION VIA RESAMPLING IN LINKAGE ANALYSIS OF QUANTITATIVE TRAIT LOCI

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Bias occurs in locus-specific effect-size estimation in genome-wide linkage analysis of quantitative trait loci (QTL) when the original data are used for both hypothesis testing and parameter estimation. Maximization of the test statistic over the genome leads to upward bias in the effect-size estimates. The upward bias is further increased by adoption of a stringent level of statistical significance to control genome-wide type I error. Sun and Bull (2005) proposed three bootstrap estimators for genetic effect estimation at a single locus. In this report we extend their approach to multi-loci estimation and examine the performance of both single and multi-loci estimators of heritability in QTL linkage analysis. In our simulation studies the bootstrap locus-specific QTL-heritability estimates had substantially reduced bias and smaller mean squared error compared to the naïve estimate. We applied the multi-loci estimators to a phenotype derived from longitudinal systolic blood pressure measurements in extended pedigrees from the Framingham Heart Study. Genome-wide linkage analysis detected two statistically significant chromosomal regions on chromosomes 8 and 17 respectively, with naïve locus-specific heritabilities of 0.55 and 0.46. The bootstrap procedure yielded estimates as much as 70% smaller than the naïve estimates.