

Haplotyping and Identity-by-Descent Matrix Calculation Methods for QTL Mapping in Pedigrees

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Abstract:

Haplotyping and Identity-by-descent (IBD) matrix calculation in pedigrees are two important steps for the fine mapping of Quantitative Trait Loci (QTL) or complex disease genes. To reconstruct haplotypes efficiently for large pedigrees with large numbers of linked loci, we develop two algorithms based on conditional probabilities and likelihood computations. The first algorithm (the conditional probability method) produces a single, approximately optimal haplotype configuration. The other algorithm (the conditional enumeration method) identifies a set of haplotype configurations with high probabilities conditional on the observed genotype data for a pedigree. The algorithms are tested on published and simulated data sets. The new haplotyping methods are much faster and provide more information than several existing stochastic and rule-based methods. The accuracies of the new methods are equivalent to or better than those of these existing methods. Based on the reconstruction of haplotype configurations, we propose an approximation IBD calculation method for large pedigrees with large numbers of loci. The proposed method uses a subset of haplotype configurations with high likelihoods identified by the conditional enumeration haplotyping method. The new IBD calculation method is compared with a Markov Chain Monte Carlo (MCMC) method (Loki) in terms of QTL mapping performance on simulated pedigrees. Both methods yield almost identical results for the estimation of QTL positions and variance parameters, while the new method is much more computationally efficient than the MCMC approach for large pedigrees and large numbers of loci. The new method can be used for fine mapping with joint linkage disequilibrium and linkage analysis, which improves the power and accuracy of QTL mapping.