THE CONFIDENCE INTERVAL OF ALLELIC ODDS RATIOS UNDER THE HARDY-WEINBERG DISEQUILIBRIUM

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The modern molecular biology has made it reasonably affordable to identify a genotype at any particular genetic locus for a large number of individuals. In genetic association studies, the phenotype at interest associated with an allele or genotype is typically represented using a 2×2 or 3×2 contingency table, respectively, for biallelic markers such as single nucleotide polymorphisms (SNP). The allelic odds ratio and its confidence interval (CI) are usually used to evaluate the association between disease and alleles at each SNP. The usual formula for calculating the CI of allelic odds ratio is based on the assumption of the Hardy-Weinberg equilibrium (HWE). However, it may lead to errors beyond control assured by the nominal confidence level, if HWE is not true.

Here we present a generalized formula for CI that does not require HWE assumption. According to this generalized formula, the CIs are likely to be wider than those by the usual method, if Hardy-Weinberg disequilibrium (HWD) is toward a relative deficiency of the heterozygotes (fixation index greater than 0), whereas they are likely to be narrower, if HWD is toward a relative excess of the heterozygotes (fixation index less than 0). A simulation experiment to examine the influence of the generalization was performed for various distributions of the fixation index. It revealed that the observed positive predictive value and sensitivity were different between the two formulas when the CI was used for judgment of association between disease and alleles.