Letter to the Editor

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Reply to Dudbridge

To the Editor:

The standard permutation approach cannot be applied to two-stage association studies, because a marker that was not originally selected for the second stage of the study may be selected after permutation. To get around this difficulty, Frank Dudbridge proposes[1] (in this issue) to simulate a two-stage design by using only the first-stage subjects. This is a very clever idea and seems to be in a spirit similar to my Monte Carlo method,[2] in that both methods use only the data from the first-stage subjects to estimate the correlations of the test statistics. I believe that Dudbridge's permutation method (implicitly) requires that the same design (in terms of the proportion of subjects used in the first stage) be adopted in the permutation process as in the original study; otherwise, the joint distribution between the two stages obtained by permutation will not properly reflect the true joint distribution.

I wish to respond briefly to Dudbridge's comment that my Monte Carlo method "is limited to analysis based on efficient score functions and does not use permutation."[1] As mentioned in my report,[2] all test statistics can be represented by efficient score functions. Thus, the use of efficient score functions in generating the null distribution of the test statistics does not, in any way, limit the scope of application. As discussed in an earlier article,[3] the Monte Carlo approach has important advantages over the permutation approach. First, the permutation approach requires repeated calculations of the test statistics for each permuted data set, which can be prohibitively time consuming if the calculation of each test statistic is nontrivial, as will be the case if proper statistical methods are employed to test haplotype-disease associations,[4] whereas the Monte Carlo approach involves simulation of normal random variables only and is thus very efficient. Second, the permutation method can be used only to test the global null hypothesis that the variable being permuted is independent of all other variables and cannot be used to test, for example, gene-environment interactions, whereas the Monte Carlo approach can be used to test any kind of hypothesis.

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References

1. Dudbridge F (2006) A note on permutation tests in multistage association scans. Am J Hum Genet 78:1094–1095 (in this issue)
2. Lin DY (2006) Evaluating statistical significance in two-stage genomewide association studies. Am J Hum Genet 78:505–509
3. Lin DY (2005) An efficient Monte Carlo approach to assessing statistical significance in genomic studies. Bioinformatics 21:781–787
4. Lin DY, Zeng D, Millikan R (2005) Maximum likelihood estimation of haplotype effects and haplotype-environment interactions in association studies. Genet Epidemiol 29:299–312

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