The Hierarchical Structure of Multi-Locus Linkage Disequilibrium Testing

David N. Stivers, Ranajit Chakraborty
Human Genetics Center, School of Public Health, the University of Texas, PO Box 20334, Houston, Texas 77225

The issue of independence of alleles within and across loci in DNA typing population databases had been a major point of controversy in statistical interpretation of the strength of DNA evidence in courtroom discussions of DNA forensics. Some critics (e.g., Mueller, State of Washington vs. Robert Parker, No. 96-1-07511-2SEA) argue that recently compiled population data on PCR-based loci show statistically significant departure from the independence assumption. Specifically, such conclusions were reached by a combination exact and likelihood ratio tests performed by pooling data from a number of laboratories and by performing the tests for all possible combinations of loci.

For example, with data on 5 polymarkers (LDLR, GYPA, HBGG, D7S8 and GC), HLA-DQA1 and three STR loci (CSF1PO, TPOX and TH01) in three major population groups in the continental US (US Caucasians, African-Americans and Hispanics), there are 27 intra-locus tests of allelic independence and 502 possible tests for mutual independence of alleles across loci. While the dependence of such test results are generally acknowledged, arguments such as "the European-Americans do not meet the independence assumption" were made by simply noting that 51 of the possible 502 tests yielded p-values below the nominal level of significance.

In this presentation we show that such conclusions are statistically flawed. First, we show that the tests performed in such analyses are nested due to the hierarchical structure of taking all possible combinations of loci in a database. Consequently, the test results are interdependent for each population analyzed. Second, through random permutation of alleles within and across loci, we determined the number of times departures from the independence assumption can be expected by chance alone in such hierarchical tests. Applications of such permutation tests to the same data show that the observed number of significant deviations is well below the nominal level of significance, more so when rare alleles are merged with adjacent common alleles. (Supported by NIH grants GM 58545, AR 44888-01, GM 45861 and GM 41399, and NIJ grant 98 LB VX-0010)