

Letters to the Editor

CONSANGUINITY AND HETEROGENEITY: CYSTIC FIBROSIS NEED NOT BE HOMOGENEOUS IN ITALY

To the Editor: By studying the frequency of consanguinity among parents of children with cystic fibrosis (CF), Romeo et al. [1] conclude that "CF is homogeneously determined by mutations at a single gene in Italy," although the authors leave open the possibility of a very minor, second form. Such a conclusion would be of great importance if correct. Recent discoveries of linkage among CF, a DNA polymorphism [2], and an enzyme marker [3] do not yet distinguish between a single or several genes for CF in a statistically significant way. Thus, the report of Romeo et al. stands as the best current indication of homogeneity in cause of CF.

Unfortunately, we are obliged to point out that the conclusion of Romeo et al. is unjustified because of an error in their analysis of their data. Briefly, under the hypothesis that CF is caused by two equally frequent genes, the authors correctly calculate the expected frequency of first-cousin marriages among families segregating one of the genes. They then erroneously say that the expected *frequency* of first-cousin marriages would be twice as large for CF families overall compared to either class alone. What they undoubtedly meant was that the *number* of first-cousin marriages would be double. The error results in an overestimate of the number of consanguineous marriages expected among the Italian sample (42 instead of 21). Regrettably, while the erroneous number (42) is so much larger than the observed (14) that a simple statistical test allowed heterogeneity to be rejected, the correct expected number (21) is too close to distinguish statistically between one CF gene and two of roughly equal frequency.

Our objection is not to the consanguinity test for homogeneity [4], which is sound in principle given a large enough sample and accurate estimates of consanguinity. Nevertheless, since the expected frequency of consanguineous marriages depends (roughly linearly) on the square-root of the number of independent disease loci, the number of families required to distinguish between one, two, or three genes is quite large.

A further problem is that the expected frequency depends (again, roughly linearly) on the estimated frequency of consanguinity in the general population from which the disease families are drawn. In the present instance, Romeo et al. estimate the present rate of consanguinity by mathematical extrapolation to

the present from excellent data for the period before 1964. Even small errors here might so strongly influence the expected numbers that the results could be in doubt, regardless of the apparent statistical significance of the difference between expected and observed.

In conclusion, we believe that Romeo et al. have provided strong evidence that CF in Italy is not a highly heterogeneous disease, frequently caused by mutations at many independent loci. However, their analysis leaves open the possibility of two or three major genes, each of which can cause CF.

NOTE ADDED IN PROOF: Since this letter was written, enough linkage data to closely linked RFLP markers have accumulated to make very unlikely any heterogeneity at the 5% level.

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HOMOGENEITY VS. HETEROGENEITY OF CYSTIC FIBROSIS IN ITALY

To the Editor: In table 6 of our paper [1], which deals with estimates of incidence, genetic heterogeneity, and segregation ratios of cystic fibrosis (CF) in Italy, there is a mistake rightly pointed out by Lander and Botstein in the preceding letter [2].

According to hypothesis 2 of table 6, we subdivided the total population of 594 couples of CF parents into two subsets, each of 297 couples, giving birth to CF children affected with two genetically distinct forms of CF. Under this hypothesis, we calculated the expected frequency of first-cousin marriages in each subset but simply failed to realize that this relative value, which was hypothesized as identical for the two subsets, cannot be doubled.

If the correct value of relative frequency is used, the expected number of first-cousin marriages in each subset of CF couples is, therefore, 10.93, which is equal to a total of 21.85 for the total sample of 594 CF samples. The relative frequencies corresponding to 177 couples (last column) should be treated in a similar way. Accordingly, the last part of table 6 of our paper should be rewritten as follows: