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Further Comments on the Genetics of Prelingual Deafness

To the Editor:

Majumder et al. (1989*a*) recently published the results of genetic analysis of 133 nuclear families and 25 extended pedigrees, ascertained through sensorineural deaf probands from four schools for the deaf in Madras, India. Kimberling et al. (1989) commented on the analysis, to which Majumder et al. (1989*b*) responded. This study represents a laudable attempt to investigate the genetics of prelingual deafness. However, the authors exhibit insensitivity to the deaf community through use of the nomenclature "affected" versus "normal"—"deaf" versus "hearing" more accurately reflects the perceptions of the deaf community. Furthermore, we agree with Kimberling et al. (1989, p. 158) that "the report by Majumder et al. does not present convincing evidence in favor of the two-locus multiple homozygosis model for the genetics of prelingual deafness." We have several comments to add to those of Kimberling et al. (1989).

First, in no case was a statistical test of significance possible, because Majumder et al. (1989*a*) were unable to estimate the parameters of the models investigated—they supplied parameter values, calculated likelihoods, and compared the magnitudes of the likelihoods between the hypotheses. This procedure is reasonable when there is a great difference in the likelihoods between hypotheses; for example, we agree that hypotheses postulating that the recurrence risk is the same as the population frequency could be rejected (the likelihoods of those hypotheses were about 10^6 times less likely than hypotheses postulating familial transmission). However, as Kimberling et al. (1989) point out, the likelihood surface comparing the various genetic models is very flat, and the lack of a formal significance test makes interpretations problematical.

Second, even if the above scheme of comparing the magnitudes of likelihoods is allowed, the authors end up rejecting the most likely model for the nuclear-family data in favor of a two-locus model. The most likely model consisted of a single-locus recessive with 83.32% sporadics and was about 100 times more likely than the two-locus model. The authors rejected this model on the grounds that "this sporadic proportion is unrealistically high" (Majumder et al. 1989*a*, p. 90). The authors enumerate some of the many recognized environmental causes for deafness, including prematurity, ototoxic drugs, and infections, at least some of which can be epidemic in nature (e.g., congenital rubella). Thus, there is no a priori reason why the frequency of sporadic cases could not be 83% or even higher.

In their response to Kimberling et al. (1989), Majumder et al. (1989*b*) state that the number of probands in their data who are deaf due to known nongenetic causes is zero. This does not preclude the possibility of undetected nongenetic causes among the probands. Majumder et al. (1989*b*) claim that they have allowed for this possibility by testing a single-locus recessive model with sporadics as an alternative—however, as discussed in the first point above, they did not estimate the parameters (e.g., proportion of sporadic cases) in their data. As discussed in the second point above, the only single-locus recessive models with sporadics that could be rejected were those with very small proportions (15% or less) of sporadics.

Bieber (1981) estimated the proportions of familial and sporadic cases both among probands born in the United States during the rubella epidemic years of 1963–64 and also among probands born at other times. During the epidemic years the estimated proportion of sporadic cases was 85%, in close agreement with the

result of Majumder et al. (1989*a*) that the most likely model was a recessive with 83.32% sporadics. Furthermore, Bieber (1981) found that the estimated proportion of familial cases was almost twice as large for "non-epidemic" probands. Following the reasoning of Majumder et al. (1989*a*), one would interpret such secular trends in the incidence of sporadic deafness as reflecting temporal fluctuations in the number of recessive loci required to produce deafness!

Third, the authors conclude that analysis of the 25 extended pedigrees was also consistent with a two-locus model—again, the parameters were not estimated. The only "recessive plus sporadics" hypotheses presented specified very small values for the proportion of sporadic cases; the likelihoods may well have been greater than the likelihoods of the two-locus model if a higher proportion of sporadics had also been tested.

Finally, a two-locus model is not consistent with the attributes of deafness in families worldwide. A very important prediction of the two-locus model that Majumder et al. (1989*a*) propose is that all deaf × deaf matings will produce all deaf children. This was true in Majumder et al.'s data set; however, there was only one deaf × deaf mating (in one of the extended kindreds).

In other data sets, such as those analyzed by Rose (1975), hundreds upon hundreds of deaf × deaf matings have been observed which have produced either all hearing offspring or both hearing and deaf offspring. In a very large data set of nuclear families ascertained through deaf offspring (Rose 1975), the estimated proportion of nonsegregating sibships was only 36%. In the Fay data set (Rose 1975), among 65 deaf × deaf matings that were selected because both marriage partners appeared to have a recessive phenotype, the estimated proportion who could have only deaf children was 8%. Taken together, these data provide compelling evidence for multilocal genetic heterogeneity rather than a model of multilocus recessive epistasis as proposed by Majumder et al. (1989*a*, 1989*b*). In addition, deafness can be an inconsistent feature in known genetic syndromes—even for such well-recognized genetic entities as Waardenburg syndrome, only about 20% of individuals who inherit the gene exhibit bilateral deafness. Therefore, reduced penetrance, rather than the multilocus model that Majumder et al. (1989*a*) propose, could be another likely explanation for the low segregation ratio.

On November 13, 1883, at New Haven, CT, Alexander Graham Bell (Bell 1883) presented a paper to the National Academy of Science in which he speculated that the intensive degree of assortative mating that occurs among the deaf would ultimately lead to the formation of a "deaf variety of the human race." In the intervening century, masses of empiric data on the outcome of deaf × deaf marriages have provided compelling evidence that Bell's fears were unfounded, largely because of the extensive genetic heterogeneity that exists among the mutations at many different loci which can cause deafness. Regrettably, we find nothing in the inferences presented in Majumder et al. (1989*a*, 1989*b*) that would cause us to alter this view.

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More on the Genetics of Prelingual Deafness

To the Editor:

Marazita et al. (1989) have charged that we have exhibited insensitivity to the deaf community through use of the terms "affected" for "deaf" and "normal" for "hearing" in our recent paper (Majumder et al. 1989*a*). Nothing could be farther from the truth; it is difficult to be insensitive to the deaf community when one of us has a significant hearing impairment! The only reason why