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On the Genetics of Prelingual Deafness

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Summary

In view of the many discordant findings in previous studies regarding the genetics of prelingual deafness, family data (133 nuclear families and 25 pedigrees) were gathered from India. Analysis of these data has revealed that the defect is primarily genetic, which is in agreement with earlier findings. Segregation analysis was performed to compare various autosomal diallelic one-locus and multilocus models. Our analysis revealed that the most parsimonious model for prelingual deafness is that it is controlled by recessive genes at a pair of unlinked diallelic autosomal loci. Individuals are affected if and only if they are recessive homozygous at both loci. The likelihood of the present data under this two-locus multiple recessive homozygosis model is at least 10^8 times higher than that of the one-locus models that were examined in previous studies. This model is also the best-fitting model among other plausible two-locus models.

Introduction

Because of the complexity of the hearing mechanism in man, deafness can arise in a variety of ways. All forms of deafness can be broadly classified as conductive or perceptive (also sometimes referred to as sensorineural or neural. In conductive deafness the abnormality lies in the middle or external ear, while in the perceptive type there is dysfunction somewhere between the receptors in the inner ear and the auditory regions of the brain (Beighton 1983). Deafness can also be of a "mixed" type. Individuals who are born deaf or lose their hearing before 3 years of age are said to be "prelingually deaf" (Schein 1980). (The term "prelingual deafness" replaces the older term "deaf-mutism.") Prelingual deafness may be either inherited or acquired. The more common etiological agents which lead to hearing loss are prenatal infection (rubella), maternal drug therapy during pregnancy (e.g., quinine or thalidomide), perinatal trauma, postnatal meningitis, middle-ear disease, etc. (For a more complete list of etiological agents, see Konigsmark and Gorlin 1976.) Deafness is also associated with many genetic syndromes, e.g., Waardenburg, Usher, etc. (Konigsmark and Gorlin 1976). The estimates of the proportion of inherited deafness vary from 20% (Fraser 1964, 1976) to 70% (Chung and Brown 1970). In the class of hereditary deafness, there seems to be extensive heterogeneity in the pattern of inheritance. Nance and McConnell (1973) estimated that the autosomal dominant pattern of inheritance accounts for 20%–30% of nonsyndromic prelingual hereditary deafness, the autosomal recessive pattern accounts for about 60%–70%, and the X-linked recessive pattern accounts for about 2%. Parental consanguinity has frequently been found among the prelingual deaf, as is expected for a defect that is primarily recessive. Previous segregation analyses of data on prelingual deafness have only been conducted on nuclear families; pedigree information was used to classify the nuclear family of the proband to either of two classes: positive family history and negative family history (Stevenson and Cheeseman 1956; Chung et al. 1959; Chung and Brown 1970; Nance 1980). These analyses revealed certain uniform as well as discordant patterns. In most studies it was found that in nuclear families in which there was parental consanguinity, deafness segregated as a one-locus autosomal recessive trait with no sporadic cases (Stevenson and Cheeseman 1956; Chung et al. 1959; Chung and Brown 1970; Nance 1980). However, in nonconsanguineous nuclear fami-

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lies, conflicting patterns of inheritance and/or grossly different estimates of the sporadic proportion were found. In nonconsanguineous nuclear families without positive family history, Chung et al. (1959) and Chung and Brown (1970) inferred that deafness segregated as a recessive defect with about 26%–27% sporadics. In such families, while accepting a recessive mode of inheritance, Nance (1980) estimated the percentage of sporadics to be 65%, which is about 2.5-fold higher than the previous estimates. In nonconsanguineous nuclear families with positive family history, the discordance in inference was even more striking. While Chung and Brown (1970) inferred that in such families deafness was due to an autosomal dominant gene with about 80% penetrance and a sporadic frequency of 12.8%, Nance (1980) found that in such families in his data set deafness segregated as an autosomal recessive defect with 20% sporadics. The number of recessive genes involved in deafness has also been estimated by an analysis of the frequency of consanguinity in relation to prevalence of deafness in the population and by the use of the theory of detrimental equivalents (Chung et al. 1959; Chung and Brown 1970). The estimates of this number vary widely. Chung et al. (1959) gave an estimate of 36 recessive genes for deafness. Chung and Brown (1970) estimated this number to be five; while Sank (1963) proposed a broad range of 45–6,800. It is also unclear from these analyses whether the genes are recessive mutant alleles at the same locus, or whether deafness is controlled by several autosomal loci. Chung et al. (1959) have stated that "it seems much more likely that there are many loci."

In view of these discordant findings regarding the genetics of deafness, we undertook a family study on prelingual deafness in India. We have performed segregation analyses of data on both nuclear families and pedigrees and have considered both one-locus and multilocus genetic models. The present paper reports the results of these analyses.

Prevalence of Prelingual Deafness

The generally accepted incidence of profound prelingual deafness is 1 in 1,000 births (Fraser 1964). There is, however, a wide variation in prevalence. From Brown's (1967) compilation, the range of variation is seen to be from 45 (in Denmark and Northern Ireland) to 160 (among Chicago school children) per 100,000. In India, a census of the physically handicapped was conducted in 1980, and it yielded an overall prevalence of 42/100,000 inhabitants (Census of India 1981). There is, however, a good deal of variation in the prevalence even among the different states of India. The prevalence in the State of Tamil Nadu (south India), from which all the probands and families in the present study were drawn, was 58/100,000 inhabitants. We shall, for the purpose of the present study, accept a prevalence of .0006 in the general population from which the families under study were drawn.

The Family Data

The data used in the present study comprise phenotypic information on members of 133 nuclear families and 25 pedigrees. Each nuclear family and pedigree was ascertained through a sensorineural deaf proband. The probands were selected from four schools for the deaf (St. Louis Institute for the Deaf and the Blind, C.S.I. School for the Deaf, Little Flower Convent School for the Deaf, and Bala Vidyalaya School for the Deaf) and from the Institute of Basic Medical Sciences, all located in the city of Madras. The only criteria used for selecting the probands were that all members of their nuclear families (parents and sibs) had to be resident in the city of Madras and family members had to be willing to cooperate. The data on the hearing status of every person included in this study were gathered by one of us (D.C.) through repeated household visits. Apart from phenotypic information on deafness, data on age at onset of deafness and on other conditions (rubella, premature birth, drug use during pregnancy, perinatal trauma, ear disease, meningitis, etc.) were also collected from most of the family members. Biological relationship between spouses was ascertained through extensive questioning and, whenever possible, by verification from elderly members of the household. Nuclear families were extended to pedigrees if several other family members were resident in Madras and vicinity and were available for study. The proportion of males among the probands is 62%. This high proportion is not due to any selection bias but is a reflection of the fact that in India the proportion of males among schoolchildren—including those in schools for the deaf, from which the probands were drawn—is generally higher than that of females. The proband in every nuclear family was an offspring. Only two of the 25 pedigrees had two independently ascertained probands each. The ascertainment probability is therefore small, approximating a single-selection ascertainment scheme. Syndromic conditions were observed in only two pedigrees. In one pedigree, two members (including the proband) were deaf and mute, three members had postlingual

deafness, and three members had a speech defect (stammering). In another pedigree, the proband was deaf and mute, one member had postlingual deafness, and two members were mentally retarded. In this analysis, both these pedigrees have been analyzed using information only on prelingual deafness; other conditions (including postlingual deafness) have been ignored (scored as "unaffected"). No syndromic or other associated conditions were observed in the remaining families (nuclear and pedigree).

The nuclear families were of two types: (1) parents unrelated (nonconsanguineous) and (2) parents related (consanguineous). Among the consanguineous families, two kinds of relationship were observed between the parents—uncle-niece and first cousins. It may be reiterated that consanguinity is common in south India —about 25% of Hindu marriages are consanguineous (Roychoudhury 1976). In the state of Tamil Nadu (of which Madras is the capital city) the two most frequent forms of consanguineous marriages are between a pair of first cousins and between an uncle-niece pair (Roychoudhury 1980). In the present set of 133 families, the parents were unrelated in 83 families (62.4%), and in 50 families (37.6%) the parents were related. Thus, compared with the inbreeding level in the general population, there is about a 13% higher frequency of consanguinity among parents of affected individuals. This observation of increased parental consanguinity is consistent with all previous studies on deafness. Among the 50 consanguineous nuclear families, in 31 families the parents were a pair of first cousins, and in 19 families they were an uncle-niece pair. Similarly, in the set of the 25 pedigrees, no consanguineous marriage was observed in 13 pedigrees; in the remaining 12 pedigrees one or more consanguineous marriages were noted. None of the parents in any nuclear family was found to be deaf; that is, all nuclear families were normal × normal mating type. The average sibship sizes in nonconsanguineous and consanguineous nuclear families are 3.61 (SD = 1.48) and 3.44 (SD = 1.40), respectively. Data on the nuclear families are summarized in table 1, from which it is seen that 10 of the nonconsan-

Table 1

Description of Prelingual Deafness in 133 Nuclear Families

Family Type and Sibship Size (s)	No. of Families	No. of Affected Offspring (r)		
		1	2	3
Nonconsanguineous:				
2	21	21	0	0
3	24	22	2	0
4	21	16	5	0
5	6	5	1	0
6	7	5	1	1
7	2	2	0	0
8	2	2	0	0
Total	83	73	9	1
Consanguineous—uncle-niece:				
2	7	6	1	0
3	8	5	3	0
4	2	0	1	1
5	1	0	0	1
7	1	0	1	0
Total	19	11	6	2
Consanguineous—first cousins:				
2	7	7	0	0
3	10	8	2	0
4	10	4	5	1
5	2	2	0	0
6	1	1	0	0
7	1	1	0	0
Total	31	23	7	1

guineous families are multiplex and the remaining 73 are simplex. Among the consanguineous uncle-niece families, eight are multiplex and 11 are simplex; the corresponding figures for the consanguineous first-cousin families are eight and 23. Among the 25 pedigrees, seven are 2-generational, 13 are 3-generational, and five are 4-generational. Only one of the pedigrees had no affected relative of the proband. In the pedigrees, most of the matings producing affected offspring are normal × normal; one affected × affected mating produced all affected offspring, three matings in which one parent is affected and the other parent was not examined (affected × "unknown" mating) produced all normal offspring, two affected × "unknown" matings produced all affected offspring, and one normal × affected mating produced two offspring of whom one was normal and the other affected.

Segregation Analysis of Nuclear Family Data

Segregation analysis has been performed separately for the three types of families—nonconsanguineous (n = 83), consanguineous uncle-niece (n = 19), and consanguineous first-cousin (n = 31). Before testing any genetic model, we computed the likelihoods of the three sets of families under the nongenetic model (that is, assuming that deafness is solely due to environmental causes). The likelihood function under the nongenetic model is $\binom{S-1}{R-1}\,\delta^{R-1}\,(1-\delta)^{S-R}$, where S and R denote, respectively, the total number of offspring and the total number of affected offspring in all families, and where δ denotes the prevalence. For the prevalence of .0006, the $\log_{10}$ likelihood values were −30.20, −28.81, and −25.55, respectively, for the three types of nuclear families. The joint $\log_{10}$ likelihood for all the 133 families is, therefore, −84.56.

We have compared several genetic models. The present choice of models was guided by those considered in earlier studies. Recessive models have been considered primarily because of the higher frequency of consanguineous unions among parents of affected individuals than in the general population—a phenomenon that has been consistently observed in all previous studies as well as in the present study. The genetic models that have been fitted to the data are (1) one-locus recessive, (2) one-locus recessive with sporadics, (3) one-locus dominant with incomplete penetrance, (4) two-locus recessive, and (5) three-locus recessive. In all the models, it is assumed that the loci are autosomal diallelic and unlinked. In the multilocus models it is assumed that only the multiple recessive homozygotes are affected; individuals of the remaining genotypes are normal. The general derivation of the likelihood function for a normal × normal family is given in appendix A. The details of the models compared in the present study are given in appendix B. Since the probabilities of various genotypic matings are dependent on the biological relationship between the parents, the likelihood functions for the different types of nuclear families are different under the various genetic models. The likelihood functions are given in appendixes B and C.

Table 2 presents the individual $\log_{10}$ likelihood values for the three types of families, as well as the joint $\log_{10}$ likelihood values under the various genetic models that were considered. In all the likelihood computations, we assumed a fixed prevalence of deafness δ = .0006. (It may be noted that for each model the parameters are functionally related to the prevalence of the disorder. Unconstrained maximization of the likelihood functions under the various models to obtain maximum likelihood estimates of the parameters often resulted in grossly differing estimates of the prevalence, thereby making the comparison of the various genetic models difficult. Estimation of parameters, therefore, needed to be done through a constrained maximization of the likelihood functions, which we were unable to do. For this reason, we have not attempted to estimate parameters under the various models but have instead computed values of the likelihood functions at fixed values of the parameters: the values of the parameters were so chosen that the "prevalence constraint" was satisfied in each case. This procedure ensured comparability of the models.) Fixing the prevalence and values of other parameters in the models resulted in constraints on the gene frequency (frequencies). These constraints are given in appendix B. From the values of the $\log_{10}$ likelihood presented in table 2, it is clear that the nongenetic model can be rejected: the nongenetic model is about 10^6 times (84.56 − 78.21 = 6.35 ≈ 6) less likely than even the worst-fitting genetic model. Turning to the comparison of the various genetic models considered, we first note that for all the models the likelihoods of the various types of families are fairly insensitive to the ascertainment probability π. For brevity in table 2 we have presented the $\log_{10}$ likelihood values for only two values of π, .001 and .1. For reasons given in the previous section, the ascertainment probability in the present case is close to zero and approximates a single-selection situation. We shall therefore limit our discussion to the case of π = .001, although the relative performances of the models (that is, relative trends of the likelihood values)

Table 2

Values of the $\log_{10}$ Likelihood Function for Nonconsanguineous (NC) and Consanguineous (C) (Uncle-Niece [UN] and First Cousins [FC]) Nuclear Family Data under Various Genetic Models

Model	Ascertainment Probability (π)									
	.001					.1				
		C					C			
	NC	UN	FC	Joint UN + FC	Joint NC + C	NC	UN	FC	Joint UN + FC	Joint NC + C
1. One-locus recessive	−27.06	−6.23	−10.32	−16.55	−43.61	−26.14	−6.24	−10.11	−16.35	−42.49
2. One-locus recessive with sporadics:										
ψ = .00001; χ = .0166	−25.80	−6.21	−10.29	−16.50	−42.30	−25.54	−6.24	−10.10	−16.34	−41.88
ψ = .0001; χ = .1666	−23.08	−6.31	−10.25	−16.56	−39.64	−21.19	−6.28	−10.01	−16.29	−37.48
ψ = .0003; χ = .4998	−15.74	−6.36	−9.93	−16.29	−32.03	−15.52	−6.40	−9.74	−16.14	−31.66
ψ = .0005; χ = .8332	−13.06	−6.59	−9.29	−15.88	−28.94	−14.54	−6.77	−9.24	−16.01	−30.55
3. One-locus dominance with incomplete penetrance										
τ = 0.9	−52.01	−8.31	−17.89	−26.20	−78.21	−50.14	−8.11	−17.31	−25.42	−75.56
τ = 0.7	−38.27	−7.09	−13.92	−21.01	−59.28	−36.87	−6.97	−13.50	−20.47	−57.34
τ = 0.5	−27.08	−6.45	−10.97	−17.42	−44.50	−26.16	−6.41	−10.71	−17.12	−43.28
τ = 0.3	−18.36	−6.43	−9.11	−15.54	−33.90	−17.89	−6.46	−9.00	−15.46	−33.35
4. Two-locus recessive	−15.09	−7.50	−8.55	−16.05	−31.14	−14.86	−7.63	−8.57	−16.20	−31.06
5. Three-locus recessive	−13.71	−8.73	−9.06	−17.79	−31.50	−13.66	−8.89	−9.15	−18.04	−31.70

Note.—Abbreviations: ψ = sporadic rate; χ = proportion of sporadics among affected persons; τ = penetrance probability.

are exactly the same even for π = .1. It is seen from table 2 that the best value (−28.94) of the joint $\log_{10}$ likelihood function corresponds to the one-locus recessive model with sporadics. However, this value (which, incidentally, is the maximum value of the $\log_{10}$ likelihood function under this model for the present data set) corresponds to a sporadic proportion of about 83%. This sporadic proportion is unrealistically high. It may also be noted that for the nonconsanguineous families and the consanguineous first-cousin families, the value of the likelihood function increases with increase in the sporadic proportion. However, the trend is the reverse for consanguineous uncle-niece families; the reason for this is unclear. For a more reasonable range of values (.01 − .20) of the sporadic proportion, the joint $\log_{10}$ likelihood value ranges between −43 and −39. Among the other one-locus models considered, the one-locus dominance model is rejected in favor of a recessive model, unless one assumes a very low (<50%) penetrance of the dominant gene in the heterozygotes. From table 2 it is also seen that the joint likelihoods are of a similar magnitude for both the two- and three-locus recessive models. Compared with a one-locus recessive model and even allowing for a reasonable proportion of sporadics, the joint likelihood under the multilocus recessive model is between 10^8 and 10^{10} times higher. Since the two- and three-locus models yield similar likelihood values, we think that the most reasonable and parsimonious explanation of the nuclear family data on deafness is that the defect is genetic and is due to recessive genes at two unlinked autosomal diallelic loci.

From table 2 it is also seen that when the sets of nonconsanguineous and consanguineous families are considered separately, for the consanguineous set there is hardly any difference (actually a slight increase) in the likelihood values between the one-locus recessive ($\log_{10}$ likelihood = −16.55) and the two-locus recessive ($\log_{10}$ likelihood = −16.05) models. For this set of families, the three-locus model is about 55 times less likely than the two-locus model. However, for the nonconsanguineous set, the likelihood of the families increases monotonically with an increase in the number of loci from one to three. The rate of increase is, however, not uniform. While the two-locus recessive model is about 10^{12} times more likely than the one-locus recessive model, the three-locus recessive is only about

24 times more likely than the two-locus recessive model. To check whether this monotonicity of increase in likelihood persists beyond three loci, we have computed the likelihood of the families under the four-locus and five-locus recessive models by using an algorithm presented in Majumder et al. (1988). The $\log_{10}$ likelihood values under the four-locus and five-locus models turned out to be −13.62 and −13.75, respectively. Thus, for the nonconsanguineous set of families, the four-locus multiple recessive homozygosis model is about eight times more likely than the three-locus model, and the five-locus model is actually less likely than the four-locus model. It may further be pointed out that a plausible reason that the improvement in likelihood for the two-locus model over the one-locus model is small for the consanguineous set of families is that, because of inbreeding and consequent increase in the probability of sharing alleles that are identical by descent, many biologically related spouses are homozygous for the same allele at one of the two loci. The joint two-locus segregation pattern therefore mimics a one-locus segregation pattern. (The slight decrease in likelihood for the uncle-niece set when the two-locus model is compared with the one-locus model may be due to sampling fluctuations.) For the nonconsanguineous set of families the probability of such homozygosity is small, and hence the two-locus model turns out to be much more likely than the one-locus model. In any case, as mentioned earlier, the two-locus multiple recessive homozygosis model is the most parsimonius when both consanguineous and nonconsanguineous families are considered jointly.

Segregation Analysis of Pedigree Data

Segregation analysis of data on the 25 pedigrees has been performed using PAP (Hasstedt and Cartwright 1981). PAP uses the "peeling algorithm" (Cannings et al. 1976)—a generalization of the Elston-Stewart algorithm—to compute likelihoods of pedigrees. Ascertainment-bias correction in PAP is done by dividing the likelihood of the pedigree by the likelihood of the proband(s). The $\log_{10}$ likelihood values, corrected for bias of ascertainment, were computed separately for each pedigree under the nongenetic and various genetic models. Under the nongenetic model, the frequency of the allele causing the disorder was set at 1.0, so that all individuals were of the same genotype, and the penetrance value—conditional probability of affection, given the genotype—was set at the prevalence of .0006. Under each genetic model, the gene frequencies were set at the values computed by using the "prevalence constraint" at the given values of the other parameters. In all cases, Mendelian transmission and

Table 3

Results of Segregation Analysis of 13 Nonconsanguineous Pedigrees: $\log_{10}$ Likelihood Values under Nongenetic and Genetic Models

		Genetic Model					
			One-Locus Recessive with Sporadics		One-Locus Dominant with Incomplete Pentrance		
Pedigree No.	Nongenetic Model	One-Locus Recessive	ψ = .00001, χ = .0166	ψ = .0001, χ = .1666	τ = .9	τ = .7	Two-Locus Recessive
1	−12.89	−6.39	−6.41	−6.55	−10.45	−8.40	−4.26
2	−12.89	−2.51	−2.52	−2.63	−1.39	−1.82	−1.73
3	−.002	−.16	−.16	−.13	−1.97	−1.23	−.36
4	−3.22	−2.57	−2.58	−2.66	−1.90	−1.58	−1.97
5	−16.11	−4.97	−4.98	−5.08	−5.11	−4.60	−4.31
6	−6.44	−1.36	−1.37	−1.44	−2.40	−1.96	−1.55
7	−6.44	−3.35	−3.36	−3.39	−3.03	−2.48	−2.77
8	−3.22	−3.14	−3.14	−3.20	−3.98	−2.96	−2.62
9	−3.22	−2.64	−2.64	−2.72	−4.51	−3.23	−2.13
10	−3.22	−2.74	−2.75	−2.82	−4.76	−3.41	−2.12
11	−3.22	−2.74	−2.75	−2.82	−4.75	−3.41	−2.09
12	−6.45	−3.61	−3.62	−3.71	−5.14	−4.37	−2.84
13	−3.22	−3.81	−3.79	−3.66	−9.14	−6.27	−3.21
All	−80.542	−39.99	−40.07	−40.81	−58.53	−45.72	−31.96

Table 4

Results of Segregation Analysis of 12 Consanguineous Pedigrees: Log_{10} Likelihood Values under Nongenetic and Genetic Models

		Genetic Model					
			One-Locus Recessive with Sporadics		One-Locus Dominant with Incomplete Penetrance		
Pedigree No.	Nongenetic Model	One-Locus Recessive	ψ = .00001, χ = .1666	ψ = .0166, χ = .1666	τ = .9	τ = .7	Two-Locus Recessive
1	−6.45	−2.83	−2.84	−2.91	−3.83	−3.08	−2.77
2	−6.45	−2.74	−2.73	−2.73	−3.57	−2.89	−2.80
3	−3.22	−1.87	−1.87	−1.94	−2.70	−2.07	−1.84
4	−3.23	−1.29	−1.29	−1.35	−3.98	−2.93	−1.12
5	−3.23	−2.13	−2.13	−2.20	−4.52	−3.27	−2.03
6	−3.23	−2.38	−2.39	−2.43	−4.78	−3.46	−2.28
7	−.003	−.44	−.43	−.43	−2.83	−1.88	−.47
8	−6.45	−2.45	−2.46	−2.52	−4.36	−3.48	−2.59
9	−3.23	−1.37	−1.38	−1.44	−4.22	−3.03	−1.60
10	−6.45	−3.65	−3.66	−3.74	−5.11	−3.87	−3.00
11	−3.23	−2.19	−2.19	−2.23	−7.15	−5.30	−2.28
12	−3.23	−1.78	−1.79	−1.85	−4.17	−2.98	−1.95
All	−48.403	−25.08	−25.16	−25.77	−51.22	−38.24	−24.73

equality of gene frequencies in both sexes were assumed. For the two-locus models, we further assumed the frequencies of the alleles jointly responsible for causing the disorder are equal at both loci. The two loci were, of course, assumed to be unlinked. The results are given separately for the sets of nonconsanguineous and consanguineous pedigrees in tables 3 and 4. As in the case of the nuclear family data, for each model, the likelihoods of the pedigrees have been computed under the constraint that the prevalence of the defect in the population is .0006. We begin our discussion by considering the joint likelihoods of all the 25 pedigrees (consanguineous and nonconsanguineous). The joint $\log_{10}$ likelihood value under the nongenetic model is $-(80.542 + 48.403) = -128.945$. In contrast, the $\log_{10}$ likelihood values under the genetic models vary between −109.75 (one-locus dominant model with penetrance probability [τ] = 0.9) and −56.69 (two-locus recessive model). Thus, the genetic models considered are between 10^{19} and 10^{72} times more likely than the nongenetic model. We therefore reject the nongenetic model in favor of a genetic model. The $\log_{10}$ likelihood values of the pedigrees under various genetic models are presented for a set of reasonable parameter values of each model in tables 3 and 4. It is seen that the joint $\log_{10}$ likelihood values under the one-locus recessive and the two-locus recessive models, respectively, are, $-(39.99+25.08) = -65.07$ and $-(31.96+24.73) = -56.69$. It is also seen that when sporadics are included in the one-locus recessive model, the joint likelihood decreases monotonically with an increase in the sporadic rate. Thus, the likelihood under the two-locus recessive model is found to be about 10^8 times higher than that under the one-locus recessive model. It is also seen that the one-locus recessive model fits the data much better than the one-locus dominant model with incomplete penetrance for reasonable values of the penetrance probability. Thus, we conclude that the two-locus multiple recessive homozygosis model yields the best fit to the data and is the most likely genetic model for deafness.

When the likelihood values for the individual pedigrees are examined, we find more or less the same trends as described above, with three notable exceptions. For nonconsanguineous pedigree 3 and for consanguineous pedigree 7, the nongenetic model is the best-fitting model. For nonconsanguineous pedigree 13, the likelihoods under the nongenetic and the two-locus models are virtually equal. It therefore seems that the affected individuals in these three pedigrees are sporadic cases. It may further be noted that for most of the consanguineous pedigrees the improvement in the likelihood value for the two-locus recessive model is small in comparison with that for the one-locus recessive

model; the improvement is, however, fairly large for most of the nonconsanguineous pedigrees. A reason for this, as mentioned in the previous section, may be inbreeding and consequent homozygosity at one of the two loci, for biologically related spouses.

Discussion

The population genetics of the multiple recessive homozygosis model has been worked out in detail by Li (1953, 1987). In a recent study (Majumder et al. 1988), the model has been further investigated in the context of family data and has been found to provide an adequate fit to a data set on a dermatological disorder. It is becoming increasingly clear that many complex traits/disorders may indeed be due to the action of genes controlled by several loci (see, e.g., Quevedo et al. 1987; Prochazka et al. 1987). In the context of prelingual deafness, although a variety of single-locus models have been tested (see, e.g., Chung et al. 1959), multilocus models have not received any attention, although Chung et al. (1959) had mentioned this as a possibility. Because of the complexity of the hearing mechanism it is very likely that prelingual deafness may indeed be a multilocus defect. We have considered the multiple recessive homozygosis model for prelingual deafness primarily because previous studies suggested involvement of recessive genes and because the nonconsanguineous family data seemed to satisfy one of the properties of this model, in that the vast majority of families are simplex (Li 1987). It may also be noted that when a single-locus recessive model is fitted to a data set in which a large proportion of families is simplex, the estimate of the sporadic proportion usually turns out to be high. Indeed, in previous studies on deafness (Chung and Brown 1970; Nance 1980), the estimate of the proportion of sporadics varied from 26% to 65% in nonconsanguineous families "with negative family history." The present study shows that the two-locus multiple recessive homozygosis model gives a much better fit to family data on prelingual deafness than does a one-locus recessive model, even when a reasonable proportion of sporadics is allowed for in the model. (What a "reasonable" sporadic proportion may be can, of course, be debated. Our computations show that even when allowance is made for 50% of affected individuals to be sporadic in the one-locus model, the two-locus model still has a higher likelihood.) The patterns of likelihood values for nonconsanguineous and consanguineous families (both nuclear and pedigree) are also in accordance with expectations. If two recessive loci are involved in the causation of a defect, many spouses in consanguineous families will both be homozygous for the defect-causing allele at one of the two loci because of the increased joint probability of being of identical genotypes by descent. For such matings, the two-locus segregation pattern will mimic the pattern of segregation of a recessive gene at one locus. This will, however, not be true in matings between unrelated individuals. Thus, if indeed one is studying a defect caused by recessive alleles at two unlinked loci, one would expect that in consanguineous families the likelihoods under one- and two-locus models will be virtually the same, while in nonconsanguineous families the likelihood under the two-locus model will be higher than that under the one-locus model. That such a pattern in likelihood values is observed in the present set of families is obvious from tables 2, 3, and 4. In computing the likelihoods under the multilocus models, we have assumed equality of allele frequencies at the various loci controlling the disorder. While it may be argued that this assumption is arbitrary, it was made for algebraic convenience and because, given the lack of information, any other assumption regarding allele frequencies would have been equally arbitrary.

We would further like to mention that, for a dichotomous (affected/normal) trait, Hartl and Maruyama (1968) enumerated the number of possible diallelic autosomal two-locus models and found the number of distinct "phenograms" (phenotype-genotype relationships) to be 50. Defrise-Gussenhoven (1962) and Elston and Namboodiri (1977) suggested that six of these two-locus phenograms deserve special attention. Of these six phenograms, one is the two-locus multiple recessive phenogram that we have considered. We have also investigated whether any of the remaining five phenograms fit the present family data set. Our analyses revealed that none of these five phenograms can be a possible model for prelingual deafness; the likelihood of the family data under each of these phenograms turned out to be zero; in other words, the data are not compatible with any of these five phenograms. We also considered the "images" of these six phenograms, obtained by interchanging the labels "affected" and "normal" (see Elston and Namboodiri 1977, fig. 1). Among the six "image" phenograms, three were found to be incompatible, two yielded minimum prevalence values for the disorder which turned out to be at least an order higher than the observed prevalence of prelingual deafness, and the remaining one yielded likelihood values that were at least an order lower for most pedigrees than were the likelihood values obtained un-

der the two-locus recessive model. It may be noted that Chung et al. (1959) hypothesized that there are many loci controlling deafness, homozygosity for any one of which is sufficient to produce the affected phenotype. The likelihood of the pedigrees under this model turned out to be zero, thereby disproving Chung et al.'s hypothesis. Thus, it seems that the multiple recessive homozygosis model is the only valid model for deafness among the plausible two-locus autosomal diallelic models.

We therefore conclude that the best model for prelingual deafness is an autosomal diallelic multilocus recessive model which postulates that an individual is affected if and only if the individual is homozygous for the recessive defect-causing allele at all the loci. Our best estimate of the number of loci involved is two, although we note that the actual number of loci may be as high as four, because the likelihood of the nonconsanguineous nuclear family data set is slightly higher under the three- or four-locus multiple recessive homozygosis model. Because of the complexity of computations, we have not been able to fit three- or four-locus models to our pedigree data. In any case, whether prelingual deafness is actually caused by recessive genes acting together at multiple autosomal loci cannot be confirmed through statistical studies. We have, however, shown that the empirical observations on segregation of deafness in nuclear and extended families agree with the findings expected under the postulated model. We also do not rule out the possible occurrence of some sporadic cases, as has been observed in three of the pedigrees included in this study. It is also possible that other models may yield better fits to the data. Such models are, of course, not immediately pointed to by the present data. We have not entertained a multifactorial liability threshold model because under this model one would not expect, among parents of affected individuals, a frequency of consanguineous unions that is higher than that in the general population. Further, the multifactorial model assumes additive gene action at several loci—each gene having a very small effect—and normality of the liability distribution. The present two-locus model is more concrete and has fewer underlying assumptions.

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Appendix A

Likelihood of a Nuclear Family with Normal Parents, Ascertained through an Affected Offspring

Under any genetic model, since the family is ascertained through an affected offspring, each normal parent can be one of several possible genotypes, the number of which is less than the number of genotypes that a randomly drawn individual of normal phenotype can be. Suppose the number of possible genotypes for a parent is g. Thus, the number of possible genotypic parental mating types is $G = g^2$. For a given genotypic mating type i ($i = 1, 2, \ldots, G$), let θ_i be the probability that this mating type produces an affected offspring. Let m_i be the mating frequency of the ith genotypic mating type. Let $T = \sum_{i=1}^{G} m_i$. Then the conditional frequency of the ith genotypic mating type in the set of possible normal × normal matings is $M_i = m_i/T$. Following Elandt-Johnson (1971), we can easily write the likelihood of a sibship of size s comprising r affected and $s - r$ normal sibs. Let π = ascertainment probability = Prob (an individual is a proband given that she/he is affected). Then Prob (a family with r affected offspring will have at least one proband) $= 1 - (1 - \pi)^r$. Now, Prob (a family of parental genotypic mating type i with s offspring will have r affected offspring) $= \binom{s}{r} \theta_i^r (1-\theta_i)^{s-r}$, where $r = 1,2, \ldots, s$. Hence, the probability that such a family will be ascertained is

$$\varphi_{ir} = \binom{s}{r} \theta_i^r (1-\theta_i)^{s-r} [1-(1-\pi)^r] , \qquad \text{(A1)}$$

where $r = 1,2, \ldots, s$. Therefore, the probability that a family of parental genotypic mating type i with s offspring will have at least one affected child and that such a family will be ascertained as

$$\Phi_i = \sum_{r=1}^{s} \varphi_{ir} = 1 - (1-\pi\theta_i)^s . \qquad \text{(A2)}$$

The likelihood, L, of a normal × normal family ascertained through an affected offspring is, therefore,

$$L = \frac{\sum_{i=1}^{G} M_i \varphi_{ir}}{\sum_{i=1}^{G} M_i \Phi_i} . \qquad \text{(A3)}$$

Table A1

Parental Genotypic Mating Classes, Segregation Probabilities, and Mating Frequencies for the Two-Locus Recessive Model When Parents are Unrelated

Class (c)	Parental Genotypic Mating	Probability of Affected Offspring (θ)	Unconditional Mating Frequency for Class (m_i)	Conditional Mating Frequency for Class ($M_i = m_i/T$)
1	AaBb × AaBb	1/16	$16p^4q^4$	p^2
2	AaBb × aaBb AaBb × Aabb	1/8	$32p^3q^5$	$2pq$
3	aaBb × aaBb aaBb × Aabb Aabb × Aabb	1/4	$16p^2q^6$	q^2
Total			$T = 16p^2q^4$	1

It may be noted that since many genotypic matings will have the same value of θ_i, the number of terms in the numerator and denominator of the likelihood function L can be reduced to the number of distinct values (say, c) of θ by pooling the matings corresponding to a particular value of θ and adding their mating frequencies. This is exemplified in appendix B.

Appendix B

Likelihood Functions of a Normal × Nuclear Family Ascertained through an Affected Offspring When the Parents are Unrelated, under the Various Genetic Models Considered

1. *One-Locus Recessive Model*

In this model we assume that the defect is caused by a recessive gene at an autosomal diallelic locus with alleles A and a. Thus, an individual of genotype aa is affected and an individual of either genotype AA or Aa is normal. Since the family is ascertained through an affected offspring, each phenotypically normal parent is of genotype Aa. The value of θ corresponding to this Aa × Aa mating is 1/4. Hence,

$$L = \frac{\binom{s}{r}(1/4)^r(3/4)^{s-r}[1-(1-\pi)^r]}{1-(1-\pi/4)^s}. \qquad \text{(B1)}$$

2. *One-Locus Recessive Model with Sporadics*

This model is the same as the previous one except that we further assume that a fraction ψ of individuals of Aa or AA genotypes may be sporadically affected. Hence, the parents may be (1) both Aa, (2) one Aa and the other AA, or, (3) both AA. For an Aa × Aa mating, the probability of producing an affected offspring is $\theta_1 = 1/4 + 3\psi/4$, while the value for both AA × Aa and AA × AA matings is $\theta_2 = \psi$. Therefore, the mating types AA × Aa and AA × AA may be pooled, and hence the number of classes $c = 2$, corresponding to the two distinct values of θ. The unconditional mating frequencies for these two classes are $m_1 = 4p^2q^2$ and $m_2 = 4p^3q + p^4$, where p and $q = 1 - p$ denote, respectively, the frequencies of alleles A and a in the population. Therefore, $T = \sum_{i=1}^{c} m_i = p^2(1+q)^2$. The conditional mating frequencies are then $M_1 = 4q^2/(1+q)^2$ and $M_2 = p(1+3q)/(1+q)^2$. Hence, from equation (A1) of appendix A,

$$\varphi_{1r} = \binom{s}{r}[1/4 + 3\psi/4]^r[3(1-\psi)/4]^{s-r},$$
$$\text{and} \qquad \varphi_{2r} = \binom{s}{r}\psi^r(1-\psi)^{s-r}, \qquad \text{(B2)}$$

where $r = 1,2,\ldots,s$. From equation (A2) of appendix A, we get

$$\Phi_1 = 1 - [1-\pi(1/4+3\psi)/4)]^s,$$
$$\text{and} \qquad \Phi_2 = 1 - [1-\pi\psi]^s. \qquad \text{(B3)}$$

Thus,

$$L = \frac{M_1\varphi_{1r} + M_2\varphi_{2r}}{M_1\Phi_1 + M_2\Phi_2}. \qquad \text{(B4)}$$

Under this model, if δ denotes the frequency of deafness in the population, then $\delta = q^2 + (1-q^2)\psi$. Hence, for given values of δ and ψ,

$$q = \sqrt{(\delta - \psi)/(1 - \psi)} . \quad \text{(B5)}$$

The proportion of sporadic cases among all affected persons is, therefore,

$$\chi = (1 - q^2)\psi/\delta . \quad \text{(B6)}$$

For example, for $\delta = .0006$, the proportions of sporadics corresponding to $\psi = .00001$ and $\psi = .0005$, respectively, are 1.6% and 83.3%.

3. *One-Locus Dominant Model with Incomplete Penetrance in Heterozygotes*

In this model, we assume that the disease is caused by a dominant gene A at an autosomal diallelic locus. Individuals of genotype AA are always affected, and individuals of genotype aa are always normal. The heterozygote (Aa) individuals may be either affected or normal with probabilities τ and $1 - \tau$, respectively. (Thus, τ is the penetrance parameter.) The genotypic mating types of the parents are either Aa × aa or Aa × Aa. Thus, in this case, $c = 2$, $\theta_1 = \tau/2$, $\theta_2 = 1/4 + \tau/2$, $M_1 = q$, and $M_2 = p$. The likelihood can be easily written by using the above values and equation (A3) of appendix A. Under this model, the frequency δ of the defect in the population is $p^2 + \tau\, 2p(1-p)$; that is,

$$p = \frac{\sqrt{\tau^2 + \delta(1-2\tau)} - \tau}{1 - 2\tau} \text{ if } \tau \neq 0.5 ,$$
$$p = \delta \qquad \text{if } \tau = 0.5 . \quad \text{(B7)}$$

Table B1

Parental Genotypic Mating Classes, Segregation Probabilities, and Unconditional Mating Frequencies for the Three-Locus Recessive Model

Class (c)	Parental Genotypic Mating	Probability of Affected Offspring (θ)	Unconditional Mating Frequency (m_i): Unrelated Parents	Unconditional Mating Frequency (m_i): Related Parents
1	AaBbCc × AaBbCc	1/64	$64p^6q^6$	α^3H^3
2	AaBbCc × AaBbcc	1/32	$192p^5q^7$	$6\alpha^2\beta H^3$
	AaBbCc × AabbCc			
	AaBbCc × aaBbCc			
3	AaBbCc × Aabbcc	1/16	$240p^4q^8$	$6\alpha\beta^2H^3 + H^2R(3\alpha^2\varepsilon + 6\alpha\beta\nu)$
	AaBbCc × aaBbcc			
	AaBbCc × aabbCc			
	AaBbcc × AaBbcc			
	AaBbcc × AabbCc			
	AaBbcc × aaBbCc			
	AabbCc × AabbCc			
	AabbCc × aaBbCc			
	aaBbCc × aaBbCc			
4	AaBbcc × Aabbcc	1/8	$144p^3q^9$	$6H^2R(\beta^2\nu + 2\alpha\beta\varepsilon)$
	AaBbcc × aaBbcc			
	AaBbcc × aabbCc			
	AabbCc × Aabbcc			
	AabbCc × aaBbcc			
	AabbCc × aabbCc			
	aaBbCc × Aabbcc			
	aaBbCc × aaBbcc			
	aaBbCc × aabbCc			
5	Aabbcc × Aabbcc	1/4	$36p^2q^{10}$	$H^2R(3\alpha\varepsilon^2 + 2\beta\nu\varepsilon + 2\beta\varepsilon^2)$
	Aabbcc × aaBbcc			
	Aabbcc × aabbCc			
	aaBbcc × aaBbcc			
	aaBbcc × aabbCc			
	aabbCc × aabbCc			

NOTE.—For an uncle-niece pair: $\alpha = (\frac{1}{2} + 2pq)/2$, $\beta = q(\frac{1}{2} + q)/2$, $\nu = p(1 + 2q)/2$, $\varepsilon = q(1 + q)/2$, $H = 2pq$, $R = q^2$. For a pair of first cousins: $\alpha = (\frac{1}{2} + 6pq)/4$, $\beta = q(\frac{1}{2} + 3q)/4$, $\nu = p(1 + 6q)/4$, $\varepsilon = q(1 + 3q)/4$, $H = 2pq$, $R = q^2$.

4. *Two-Locus Recessive Model:*

In this model we assume that the defect is caused by the action of recessive genes at two unlinked autosomal diallelic loci. Thus, if (A,a) and (B,b) denote the pairs of alleles at the two loci, then we postulate that individuals of genotype aabb are affected; individuals of all other genotypes are normal. Since the nuclear family is ascertained through an affected (aabb) offspring, the possible classes of genotypic matings of the normal × normal parents and other relevant probabilities necessary for computing the likelihood are given in table A1. The mating probabilities given in table A1 are based on the assumption that the frequencies of the alleles a and b are both equal to q (=1−p). The likelihood equation is obtained by plugging into equations (A1), (A2), and (A3) of appendix A the probabilities given in table A1. The frequency of the defect $\delta = q^4$; that is,

$$q = \delta^{1/4} . \qquad (B8)$$

5. *Three-Locus Recessive Model*

This is a straightforward extension of the two-locus recessive model. In this model, we postulate that the defect is controlled by recessive genes at three unlinked autosomal diallelic loci designated (A,a), (B,b), and (C,c); individuals of genotype aabbcc are affected; individuals of all other genotypes are normal. Each normal parent in a nuclear family ascertained through an affected offspring may be of any one of seven genotypes: AaBbCc, AaBbcc, AabbCc, aaBbCc, Aabbcc, aaBbcc, or aabbCc. Table B1 presents the various classes of parental genotypic matings and their corresponding unconditional mating frequencies, assuming that the frequencies of the recessive alleles at all three loci are equal to $q = \delta^{1/6}$. The likelihood equation is obtained from equation (A3) of appendix A.

Appendix C

Likelihood Functions of a Normal × Normal Nuclear Family Ascertained Through an Affected Offspring When the Parents are Biologically Related

The models considered in this appendix are exactly the same as those considered in appendix B. The likelihood functions are algebraically similar. The only changes are the frequencies of parental matings. Since the parents are genetically related, the probabilities of the matings are different from those of a pair of unrelated parents because the parents, at any locus, may share alleles identical by descent. The mating probabilities under the genetic models considered can easily be obtained by using the ITO method developed by Li and Sacks (1954) and extended by Campbell and Elston (1971). To recapitulate the relevant portions of this method briefly, we note that the conditional genotypic probability matrix for a parent-offspring pair is

$$\mathbf{T} = \begin{array}{c} \\ \text{Parent} \end{array} \begin{array}{c} \overbrace{\text{AA} \quad \text{Aa} \quad \text{aa}}^{\text{Offspring}} \\ \begin{matrix} \text{AA} \\ \text{Aa} \\ \text{aa} \end{matrix} \end{array} \begin{bmatrix} p & q & 0 \\ p/2 & 1/2 & q/2 \\ 0 & p & q \end{bmatrix} . \qquad (C1)$$

Similarly, the conditional genotypic matrix for a pair of unrelated individuals is

$$\mathbf{O} = \begin{bmatrix} p^2 & 2pq & q^2 \\ p^2 & 2pq & q^2 \\ p^2 & 2pq & q^2 \end{bmatrix} . \qquad (C2)$$

With these matrices, the conditional genotypic matrix for an uncle-niece pair is given by

$$\mathbf{T}^2 = (1/2)\mathbf{T} + (1/2)\mathbf{O} , \qquad (C3)$$

and the matrix for a pair of first cousins is given by

$$\mathbf{T}^3 = (1/4)\mathbf{T} + (3/4)\mathbf{O} . \qquad (C4)$$

The joint genotype probabilities for an uncle-niece pair or a first-cousin pair are obtained by multiplying the first, second, and third rows of the corresponding conditional genotypic probability matrix by p^2, $2pq$, and q^2, respectively. When two unlinked loci are considered, the joint probabilities of genotypes are the products of the joint probabilities of genotypes at individual loci. For example, the joint probability that an uncle is of genotype AaBb and his niece is of genotype aaBb is Prob (uncle is Aa and niece is aa) × Prob (uncle is Bb and niece is Bb). The joint probabilities of genotypes at three unlinked loci can be obtained similarly, or one can use the Kronecker product technique given by Campbell and Elston (1971).

1. *One-Locus Recessive Model*

The likelihood function is given by equation (B1) for

both the cases—i.e., when the parents are an uncle-niece pair or when they are a pair of first cousins.

2. *One-Locus Recessive Model with Sporadics*

For this model, the two genotypic parental mating classes are class 1 = Aa × Aa and class 2 = {Aa × AA and AA × AA}. For these two classes, $\theta_1 = 1/4 + 3\psi/4$ and $\theta_2 = \psi$, $M_1 = m_1/(m_1+m_2)$ and $M_2 = m_2/(m_1+m_2)$, where $m_1 = pq(1/2+2pq)$ and $m_2 = p^2[q(1+2p) + p(1+p)/2]$ for an uncle-niece pair and where $m_1 = pq(1+12pq)/4$ and $m_2 = p^2[q(1+6p)/2+p(1+3p)/4]$ for a pair of first cousins. The likelihood functions are given by equation (A3).

3. *One-Locus Dominant Model with Incomplete Penetrance in Heterozygotes*

Here, the two genotypic mating classes are class 1 = {Aa × aa and aa × Aa} and class 2 = Aa × Aa. The probabilities of producing an affected offspring are, for these two classes, $\theta_1 = \tau/2$ and $\theta_2 = 1/4 + \tau/2$. The values of m_1 and m_2 for an uncle-niece pair are $pq^2(1+2q)$ and $pq(1/2+2pq)$, respectively. For a pair of first cousins, these values are $pq^2(1+6q)/2$ and $pq(1+6pq)/2$, respectively. The likelihood functions are easily derived from equation (A3).

4. *Two-Locus Recessive Model*

In this model, as in the case of unrelated parents, there are three parental genotypic mating classes, which are given in table A1. For an uncle-niece pair, the unconditional mating frequencies for these classes are $m_1 = p^2q^2(1/2+2pq)^2$, $m_2 = p^2q^3(1+4pq)(1+2q)$, and $m_3 = 2pq^4\{[(1+q)(1+4pq)+p(1+2q)^2]/4\}$. For a pair of first cousins, these values are $m_1 = 1/16 + 3p^3q^3(1/2+3pq)$, $m_2 = p^2q^3[1/4+3q/2 + 3pq(1+6q)]$, and $m_3 = pq^4[(1+q)+12pq(1+3q)]/4$. The values of θ_1, θ_2, and θ_3 are given in table A1. The likelihood functions are obtained by plugging these values into equation (A3).

5. *Three-Locus Recessive Model*

The model is described in section 5 of appendix B. The mating classes and their corresponding frequencies are given in table B1. The likelihood equations are obtained from equation (A3).

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