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Research Article

Recurrence risks for isolated cases of nonsyndromic deafness

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Abstract

We present, in this paper, general formulae developed so as to permit the calculation of the recurrence risks for isolated cases of nonsyndromic deafness in the offspring of nonconsanguineous and consanguineous couples. We included, in all analyzed situations, the following factors: (a) a generic degree of parental consanguinity; (b) a variable proportion of environmental (non-genetic) cases of the defect, so that the formulae can be easily applied to populations with any epidemiological profile; (c) a variable number of normal sibs of the propositus. Besides presenting the logic and the detailed derivation of all original formulae, we present tables for immediate use, with the numerical values of the recurrence risks as a function of the variables mentioned above.

Key words: nonsyndromic deafness; recurrence risks; genetic counseling.

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Introduction

Hearing loss is perhaps the sensorial defect more frequently found in humans, thus constituting a major public health problem, as it affects more than 1/1000 of the world population. Its importance among the congenital or acquired deficiencies is considerable, due to the consequences it brings about, not only to the affected infants, but also to the society as a whole.

Both incidence and prevalence of deafness vary in different regions, being closely and inversely related to their levels of medical, sanitary and economic development. In industrialized countries, approximately one in a thousand infants is born or becomes deaf before the acquisition of language (prelingual deafness), 50 to 60% of those cases being attributed to genetic causes (Marazita *et al*., 1993; Braga *et al*., 1999; Sundstrom *et al*., 1999; Kimberling, 2000). In developing countries, these figures are three to four times bigger than those detected in First-World countries, due to the higher prevalence of environmental factors causing deafness. In Brazil, for instance, the frequency of nonsyndromic congenital deafness ranges at four in 1000 births, 16% of which are of genetic etiology (Braga *et al*., 1999).

Nonsyndromic deafness is an astonishingly heterogeneous condition: it can be produced by genes belonging to different loci (gene heterogeneity), by different alleles at the same locus (allelic heterogeneity), transmitted by different patterns of inheritance, or caused by environmental factors (phenocopies).

Even in a country with a medical, sanitary and economic development profile like Brazil, where the environmental cases of the defect predominates (84%), the frequency of genetic cases (16%) is still significant (Braga, 1999); it is therefore important that the families of affected individuals receive counseling regarding the recurrence risks of deafness in sibs, children, and other close relatives.

The existence of several different causes of deafness makes it complicated to calculate the recurrence risks of the defect. In environmental cases, this risk is negligible. In a considerable proportion of cases, however, it is very difficult to find out if the defect is genetic or environmental in its origin; whenever this situation occurs, the deafness is classified as idiopathic. The vast majority of isolated cases, which unfortunately represent the most frequent situation in genetic counseling, fall into this category. Moreover, there are so many different categories of deafness that, even when environmental factors can be excluded, the calculation of risks is still complex.

Methods

In the calculations below, we employed standardized general methods detailed previously (Braga *et al*., 2000). Here, the recurrence risks for isolated cases of deafness

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were evaluated taking into account: the complete structure of the nuclear family, including the number of normal sibs of the propositus; in cases of parental consanguinity, a generic coefficient of inbreeding (F); and variable rates of environmental cases of the defect.

Numerical recurrence risk values were calculated for the offspring of nonconsanguineous couples and for nine different situations of parental consanguinity, without taking into account X-linked dominant and mitochondrial mechanisms, since their relative frequencies are negligible.

Results

The following symbols represent the variables used in our formulae:

K: penetrance value of a dominant condition;

μ_d, μ_x, μ_r: mutation rates for autosomal dominant, X-linked recessive, and autosomal recessive genes, respectively;

n_m, n_f, $n = n_m + n_f$: numbers of normal children within a sibship by gender (males, females, and both sexes, respectively);

p, q: mutually exclusive frequencies of a pair of alleles (one dominant and the other recessive) segregating at an autosomal locus;

P(dom), P(rec), P(Xlin), P(env) = ϕ_e: population frequencies of autosomal dominant, autosomal recessive, X-linked recessive, and environmental cases of a heterogeneous disorder;

R_{dom}, R_{rec}, R_{Xlin}, R_{env}: recurrence risks for each of the four possible mechanisms of inheritance, when there is no heterogeneity;

D, R, L, E: probabilities favoring, respectively, the four mechanisms mentioned above;

r(dom), r(rec), r(Xlin), r(env): recurrence risks for each mechanism, used jointly with the probabilities favoring each mechanism to evaluate the final recurrence risk (r) of a heterogeneous disorder;

F: inbreeding coefficient;

c: population frequency of consanguineous marriages of a given type (*e.g.*, between first cousins).

In the case of nonconsanguineous couples with one affected child and n_m normal sons and n_f normal daughters, if the affected individual is a boy, the situation can be explained by any of three possible mechanisms of inheritance: autosomal dominant, autosomal recessive, or X-linked recessive; besides, the deafness can be caused by environmental factors as well. If the affected child is a female, the possibility of an X-linked mechanism is excluded.

Assuming that the case is due to the autosomal dominant mechanism, the probability of any normal individual being a non-penetrant heterozygote depends on the probability of one of his/her parents also being a normal heterozygote who transmitted the gene to him/her, or on the probability of a non-penetrant mutation having occurred in any one of the two normal genes received from his/her parents:

$$P_{n+1}(Aa, nl) = [2 \times P_n(Aa, nl) \times \tfrac{1}{2} \times (1 - K)] + [2\mu_d \times (1 - K)]$$

At equilibrium, $P_{n+1}(Aa, nl) = P_n(Aa, nl) = P(Aa, nl)$, and

$$P(Aa, nl) = 2\mu_d(1 - K)/K$$

The births of the affected child and his or her $n = n_m + n_f$ normal sibs may have occurred under two distinct hypotheses (1: one of the parents is a heterozygote; 2: both parents are normal homozygotes).

	(1) father or mother heterozygote	(2) father and mother normal homozygotes
Prior probability	$4\mu_d(1 - K)/K$	$1 - 4\mu_d(1 - K)/K \approx 1$
Conditional probability		
1 affected and $n = n_m + n_f$ normal children	$K/2 \times [1/2 + (1 - K)/2]^n = K/2 \times [(2 - K)/2]^n$	$2\mu_d K$
Joint probability	$2\mu_d \times (1 - K) \times [(2 - K)/2]^n$	$2\mu_d K$

The probability of the father or the mother being a heterozygote, given that they have had one affected and $n = n_m + n_f$ normal children, will therefore be:

$$P(Aa) = \frac{(1-K)(2-K)^n}{(1-K)(2-K)^n + 2^n K}$$

and the risk for another child of the couple will be:

$$R_{dom} = P(Aa) \times \frac{K}{2} = \frac{K(1-K)(2-K)^n}{2\left[(1-K)(2-K)^n + 2^n K\right]}$$

Assuming now that the case is due to the X-linked recessive mechanism, the risk of deafness for another child of the couple depends on the probability of the mother being a heterozygote. In fact, since the affected individual is an isolated case, the gene that caused his/her affection is either the result of a new mutation or was transmitted to him/her only through his/her female ancestors, therefore behaving like a lethal gene.

Since, for lethal genes, the probability of any woman being a heterozygote depends on receiving the gene from her mother or on a mutation occurring in the X chromosome received either from her mother (probability μ) or from her father (probability ν), it follows that:

$$P_{n+1}(Aa, nl) = 1/2\ P_n(Aa, nl) + \mu + \nu;$$

At equilibrium, $P_{n+1}(Aa, nl) = P_n(Aa, nl) = P(Aa, nl)$ and

$$P(Aa, nl) = 2\mu + 2\nu;$$

If the mutation rate is the same for males and females ($\mu = \nu$), that value will be $P(Aa, nl) = 4\mu_x$.

The probabilities favoring the hypothesis of the mother being a heterozygote (1) or a normal homozygote (2) are calculated as before:

	(1) mother heterozygote	(2) mother homozygote
Prior probability	$4\mu_x$	$1 - 4\mu_x \approx 1$
Conditional probability (1 affected and n_m normal male children)	$(\frac{1}{2}) \times (\frac{1}{2})^{n_m}$	μ_x
Joint probability	$4\mu_x \times 1/2 \times (\frac{1}{2})^{n_m}$	μ_x

The probability of the mother being a heterozygote is therefore:

$$P(Aa) = \frac{4\mu_x \times \frac{1}{2} \times (\frac{1}{2})^{n_m}}{4\mu_x \times \frac{1}{2} \times (\frac{1}{2})^{n_m} + \mu_x} = \frac{4}{4 + 2^{n_m + 1}}$$

The risk of deafness for another child is given by:

$$R_{Xlin} = P(Aa) \times \frac{1}{4} = \frac{1}{4 + 2^{n_m + 1}}$$

If the defect is transmitted by the autosomal recessive mechanism, the occurrence of an affected individual is highly indicative of the parents being both heterozygotes. In fact, an isolated case can occur if: (1) both mother and father are AA homozygotes and a new mutation took place in both gametes which originated the child; (2) one parent is an AA homozygote, the other is a heterozygote, and a mutation occurred in the allele transmitted by the AA parent, while the heterozygote parent transmitted the allele a; (3) both parents are heterozygotes and both transmitted the allele a. The probabilities associated with the three situations described above are, respectively:

$$P(1) = \left[\frac{p^2}{p^2 + 2pq}\right]^2 \times \mu_r^2 = \left[\frac{\mu_r (1-q)}{1+q}\right]^2$$

$$P(2) = \frac{2\mu_r q(1-q)}{(1+q)^2}$$

and

$$P(3) = \frac{q}{(1+q)^2}.$$

These probabilities are, respectively, in the ratios

$$\frac{\mu_r^2 (1-q)^2}{(\mu_r (1-q) + q)^2}, \quad \frac{2\mu_r q(1-q)}{(\mu_r (1-q) + q)^2}, \text{ and } q^2.$$

Since the corresponding recurrence risks for another child are $r(1) = \mu_r^2$, $r(2) = \mu_r/2$, and $r(3) = 1/4$, the total risk is therefore given by:

$$R_{rec} = \left[\frac{\mu_r^2 (1-q) + \frac{q}{2}}{\mu_r (1-q) + q}\right]^2$$

an expression with a value of about $[(q/2)/q]^2 = 1/4$, since q is much larger than μ_r. For example, for $q = 0.01$ and $\mu_r = q^2 = 0.0001$, the exact value of r is $0.245 \approx 1/4$.

Since the probability of both parents being heterozygotes is practically 1, the number of normal sibs does not significantly influence the probability of the isolated case having been inherited.

If the case is due to environmental (non-genetic) factors, the recurrence risk is considered as negligible ($R_{env} \approx 0$).

Below, we describe in detail the logic we developed for an isolated case affected by a heterogeneous disease, with normal sibs.

The population frequencies of autosomal dominant, autosomal recessive, X-linked recessive, and environmental cases (which occur with a probability of ϕ_e) are, neglecting terms of the order of $\mu^2 \approx 0$ and similar:

$$P(dom) = \frac{4\mu_d (1-K)}{K} \times \frac{K}{2} + 2\mu_d \times K = 2\mu_d;$$

$$P(rec) = 2pq \times 2pq \times \frac{1}{4} = 4p^2 q^2 \times \frac{1}{4} \approx q^2 = \mu_r;$$

$$P(Xlin) = 4\mu_x \times \frac{1}{2} + \mu_x \times 1 = 3\mu_x;$$

$$P(env) = \phi_e.$$

The expressions above can be partitioned as follows:

P(mechanism)	=	P(mec., inher.)	+	P(mec., noninher.)
P(dom)	=	$2\mu_d = 2\mu_d(1 - K)$	+	$2\mu_d K$
P(rec)	=	$\mu_r = \mu_r$	+	0
P(Xlin)	=	$3\mu_x = 2\mu_x$	+	μ_x
P(env)	=	$\phi_e = 0$	+	ϕ_e

The partition above shows that the probabilities favoring the hypotheses of the isolated case having been inherited or not are in the ratios P(mec, inher) : P(mec, noninher), so that

$$P(\text{inher}|\text{mec}) = \frac{P(\text{mec, inher})}{P(\text{mec, inher}) + P(\text{mec, noninher})} = \frac{P(\text{mec, inher})}{P(\text{mec})}$$

and

$$P(\text{noninher}|\text{mec}) = \frac{P(\text{mec, noninher})}{P(\text{mec, inher}) + P(\text{mec, noninher})} = \frac{P(\text{mec, noninher})}{P(\text{mec})}.$$

Therefore, the probabilities of the affection being inherited or not are, respectively, for each mechanism:

P(mechanism)	=	P(inher|mec)	+	P(noninher|mec)
Aut. dominant		1 - K		K
Aut. recessive		1		0
X-linked recessive		2/3		1/3
Environmental		0		1

$P(\text{inher}|\text{mec})$ is also the probability of one of the parents (either the father or the mother in the case of an autosomal dominant mechanism; the mother in the case of

an X-linked recessive mechanism; both in the case of an autosomal recessive mechanism, and one or both in the case of environmental causes) being carriers of the genetic factor producing the deafness, given that they had an affected child.

The recurrence risks of the defect in another child are obtained for each case by multiplying P(inher|mec) by the corresponding risk (respectively K/2, 1/4, 1/4 and 0):

$$r(\text{dom}) = \frac{K(1-K)}{2}$$

$$r(\text{rec}) = \tfrac{1}{4}$$

$$r(\text{Xlin}) = \tfrac{1}{6}$$

$$r(\text{env}) = 0.$$

When an isolated case of deafness occurs in a family and there are no normal children, the probabilities favoring the four possible mechanisms are:

$$D = \frac{P(\text{dom})}{P(\text{dom})+P(\text{rec})+P(\text{Xlin})+P(\text{env})} = \frac{2\mu_d}{2\mu_d+\mu_r+3\mu_x+\phi_e} = \frac{D}{D+R+L+E}$$

$$R = \frac{P(\text{rec})}{P(\text{dom})+P(\text{rec})+P(\text{Xlin})+P(\text{env})} = \frac{\mu_r}{2\mu_d+\mu_r+3\mu_x+\phi_e} = \frac{R}{D+R+L+E}$$

$$L = \frac{P(\text{Xlin})}{P(\text{dom})+P(\text{rec})+P(\text{Xlin})+P(\text{env})} = \frac{3\mu_x}{2\mu_d+\mu_r+3\mu_x+\phi_e} = \frac{L}{D+R+L+E}$$

and

$$E = \frac{P(\text{env})}{P(\text{dom})+P(\text{rec})+P(\text{Xlin})+P(\text{env})} = \frac{\phi_e}{2\mu_d+\mu_r+3\mu_x+\phi_e} = \frac{E}{D+R+L+E}$$

In heterogeneous diseases or defects, the calculation of the recurrence risk takes into account the probability ($\mathbf{P}_i$) of occurrence favoring each mechanism of inheritance and the risks associated to each one of them ($\mathbf{R}_i$). The final risk is given by $\Sigma P_i R_i$. Therefore, the recurrence risk for an isolated case (one affected child with no sibs) is given by:

$$r = \frac{D\times r(\text{dom})+R\times r(\text{rec})+L\times r(\text{Xlin})+E\times r(\text{env})}{D+R+L+E} =$$

$$D\times r(\text{dom})+R\times r(\text{rec})+L\times r(\text{Xlin})+E\times r(\text{env}) =$$

$$D\times\frac{K(1-K)}{2}+\frac{R}{4}+\frac{L}{6}.$$

In case there already are n_m normal brothers and n_f normal sisters, the population frequency of isolated cases due, respectively, to autosomal dominant, autosomal recessive, X-linked recessive and environmental causes is given by:

$$P(\text{dom}) = 2\mu_d\left\{(1-K)\times\left[\frac{2-K}{2}\right]^n + K\right\};$$

$$P(\text{rec}) \approx q^2\times(\tfrac{3}{4})^n = \mu_r\times(\tfrac{3}{4})^n;$$

$$P(\text{Xlin}) = 4\mu_x\times\tfrac{1}{2}\times(\tfrac{1}{2})^{n_m} + \mu_x\times 1^{n_m};$$

$$P(\text{env}) = \phi_e\times(1-\phi_e)^n \approx \phi_e;$$

As before, the expressions above can be partitioned as:

P(mechanism)	=	P(mec, inher)	+	P(mec, noninher)
P(dom)	=	$2\mu_d(1 - K)[(2 - K)/2]^n$	+	$2\mu_d K$
P(rec)	=	$\mu_r(3/4)^n$	+	0
P(Xlin)	=	$2\mu_x(1/2)^{nm}$	+	μ_x
P(env)	=	0	+	ϕ_e

As previously, P(inher|mec) = P (mec,inher)/P(mec) is the probability of the affected child being an inherited case, taking into account that he/she already has n_m normal brothers and n_f normal sisters.

So, the recurrence risks of the defect for another child are obtained in each case by multiplying P(inher|mec) by the risk associated to the corresponding mechanism (respectively K/2, 1/4, 1/4 and 0):

$$r(\text{dom}) = \frac{K(1-K)(2-K)^n}{2[(1-K)(2-K)^n + K2^n]};$$

$$r(\text{rec}) = \tfrac{1}{4};$$

$$r(\text{Xlin}) = \frac{1}{2(2+2^{n_m})} = \frac{1}{4+2^{n_m+1}};$$

$$r(\text{env}) = 0.$$

Since the probabilities of normal sibs are different for each mechanism of inheritance, their number distorts the prior probabilities D, R, L and E favoring each one of them. Taking this observation into account, when an isolated case arises in the offspring of a couple that already has n_m normal male and n_f normal female children, the probabilities favoring each one of the mechanisms are:

$$D' = \frac{P(\text{dom})}{P(\text{dom})+P(\text{rec})+P(\text{Xlin})+P(\text{env})}$$

$$D' = \frac{D\left\{(1-K)\left[\frac{(2-K)}{2}\right]^n + K\right\}}{D\left\{(1-K)\left[\frac{(2-K)}{2}\right]^n + K\right\} + R(\tfrac{3}{4})^n + L\frac{\left[2(\tfrac{1}{2})^{n_m}+1\right]}{3} + E}$$

$$R' = \frac{P(\text{rec})}{P(\text{dom})+P(\text{rec})+P(\text{Xlin})+P(\text{env})}$$

$$R' = \frac{R(\tfrac{3}{4})^n}{D\left\{(1-K)\left[\frac{(2-K)}{2}\right]^n + K\right\} + R(\tfrac{3}{4})^n + L\frac{\left[2(\tfrac{1}{2})^{n_m}+1\right]}{3} + E}$$

$$L' = \frac{P(Xlin)}{P(dom)+P(rec)+P(Xlin)+P(env)} = \frac{L\frac{\left[2(1/2)^{n_m}+1\right]}{3}}{D\left\{(1-K)\left[\frac{(2-K)}{2}\right]^n + K\right\} + R(3/4)^n + L\frac{\left[2(1/2)^{n_m}+1\right]}{3} + E}$$

$$E' = \frac{P(env)}{P(dom)+P(rec)+P(Xlin)+P(env)} = \frac{E}{D\left\{(1-K)\left[\frac{(2-K)}{2}\right]^n + K\right\} + R(3/4)^n + L\frac{\left[2(1/2)^{n_m}+1\right]}{3} + E}.$$

The recurrence risk is calculated after:

$$r = r(dom)\times D' + r(rec)\times R' + r(Xlin)\times L' + r(env)\times E' =$$

$$\frac{r(dom)\times D\left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + r(rec)\times R(3/4)^n + r(Xlin)\times L\frac{\left[2(1/2)^{n_m}+1\right]}{3} + r(env)\times E}{D\left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R(3/4)^n + L\frac{\left[2(1/2)^{n_m}+1\right]}{3} + E},$$

an expression that can be simplified into:

$$r = \frac{D\times\frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2} + R\times\frac{(3/4)^n}{4} + L\times\frac{(1/2)^{n_m}}{6}}{D\times\left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R\times(3/4)^n + L\times\frac{\left[2(1/2)^{n_m}+1\right]}{3} + E}.$$

This expression is correct, since:

a) for $n_m = n_f = 0$,

$$r = \frac{D\times\frac{K(1-K)}{2} + \frac{R}{4} + \frac{L}{6}}{D+R+L+E} = D\times\frac{K(1-K)}{2} + \frac{R}{4} + \frac{L}{6};$$

b) for D = 1,

$$r = \frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2\left[(1-K)\left[\frac{2-K}{2}\right]^n + K\right]} = \frac{K(1-K)(2-K)^n}{2[(1-K)(2-K)^n + K2^n]};$$

c) for R = 1,

$$r = \frac{\frac{(3/4)^n}{4}}{(3/4)^n} = \frac{1}{4};$$

d) for L = 1,

$$r = \frac{\frac{(1/2)^{n_m}}{6}}{\frac{2(1/2)^{n_m}+1}{3}} = \frac{1}{2[2+2^{n_m}]} = \frac{1}{4+2^{n_m+1}};$$

e) for E = 1,

$$r = \frac{0}{E} = 0$$

The expression thus derived for the recurrence risk of the defect in future sibs of the isolated case with n_m brothers and n_f normal sisters,

$$r = \frac{D\times\frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2} + R\times\frac{(3/4)^n}{4} + L\times\frac{(1/2)^{n_m}}{6}}{D\times\left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R\times(3/4)^n + L\times\frac{\left[2(1/2)^{n_m}+1\right]}{3} + E},$$

that is applicable if the propositus is a male and environmental causes can not be excluded, is reduced to the following in these special cases:

a) male propositus, environmental causes excluded:

$$r = \frac{D\times\frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2} + R\times\frac{(3/4)^n}{4} + L\times\frac{(1/2)^{n_m}}{6}}{D\times\left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R\times(3/4)^n + L\times\frac{\left[2(1/2)^{n_m}+1\right]}{3}};$$

b) female propositus, environmental causes not excluded:

$$r = \frac{D\times\frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2} + R\times\frac{(3/4)^n}{4} +}{D\times\left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R\times(3/4)^n + E};$$

c) female propositus, environmental causes excluded:

$$r = \frac{D \times \frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2} + R \times \frac{(3/4)^n}{4}}{D \times \left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R \times (3/4)^n}.$$

The relative frequencies of the different mechanisms of inheritance responsible for deafness were estimated at D/(D + R + L) = 0.19; R/(D + R + L) = 0.78; and L/(D + R + L) = 0.03 (Braga *et al*., 1999; 2000). Since these relative frequencies are not likely to vary significantly from one region to another, new values of D', R' and L' can be obtained from a generic E' rate of environmental cases, by using the formulae D' = D(1 - E')/(D + R + L) = 0.19.(1 - E'); R' = R(1 - E')/(D + R + L) = 0.78.(1 - E'); and L' = L(1 - E')/(D + R + L) = 0.03.(1 - E').

Table 1 shows the recurrence risks for a future sib of an isolated case, as a function of the rate of environmental cases with the defect and of the number of normal brothers (n_m) and sisters (n_f) that the affected individual already has. In this and in the following tables, a penetrance value of K = 0.8 was assumed for dominant cases.

In all tables, regular type fonts = negligible risks (lower than 5%); bold and italic = medium risks (ranging from 5 to 10%); underlined bold = high risks (larger than 10%).

Next, we estimated the recurrence risks for a consanguineous couple with a single affected child (an isolated case) and n_m normal sons and n_f normal daughters.

As already detailed in another paper (Braga *et al*., 2000), if **c** is the population frequency of consanguineous marriages, among dominant, X-linked, and environmental cases of deafness, a proportion **c** will be born to consanguineous parents, while **1 - c** will have nonconsanguineous parents, since the probability of affection by these three mechanisms is independent from parental consanguinity. For the recessive cases, however, the frequency of affected individuals, with or without consanguineous parents, will no longer be within the ratios **c**: **1 - c**, because the probability of a recessive disease is directly influenced by consanguinity. By multiplying the prior probabilities **c** and **1 - c** by the probabilities of affection $\mathbf{q}^2 + \mathbf{Fpq}$ and $\mathbf{q}^2$, respectively (in case of a single recessive locus), in the offspring of consanguineous and nonconsanguineous parents, and normalizing the resulting joint probabilities, we obtained the final figures of **c(q + pF)/(q + cpF)** and **(1 - c)q/(q + cpF)**, respectively, for the proportions of affected children in the offspring of consanguineous and nonconsanguineous parents.

Table 1 - Recurrence risks for a future sib of an isolated case of deafness, as a function of the rate of environmental cases (E) and of the number of normal brothers (n_m) and sisters (n_f) that the affected child already has.

n_m	n_f	E										
		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0	0	**0.215**	**0.194**	**0.172**	**0.151**	**0.129**	**0.108**	***0.086***	***0.065***	0.043	0.022	0.000
0	1	**0.203**	**0.178**	**0.154**	**0.132**	**0.110**	***0.090***	***0.070***	***0.051***	0.033	0.016	0.000
1	0	**0.202**	**0.177**	**0.153**	**0.131**	**0.109**	***0.089***	***0.069***	***0.051***	0.033	0.016	0.000
0	2	**0.189**	**0.161**	**0.136**	**0.113**	***0.092***	***0.074***	***0.056***	0.040	0.026	0.012	0.000
1	1	**0.188**	**0.160**	**0.135**	**0.112**	***0.091***	***0.072***	***0.055***	0.040	0.025	0.012	0.000
2	0	**0.188**	**0.159**	**0.134**	**0.111**	***0.091***	***0.072***	***0.055***	0.039	0.025	0.012	0.000
0	3	**0.174**	**0.144**	**0.118**	***0.096***	***0.076***	***0.060***	0.045	0.032	0.020	0.010	0.000
1	2	**0.173**	**0.142**	**0.116**	***0.094***	***0.075***	***0.058***	0.044	0.031	0.020	0.009	0.000
2	1	**0.172**	**0.141**	**0.115**	***0.093***	***0.074***	***0.058***	0.043	0.031	0.019	0.009	0.000
3	0	**0.172**	**0.141**	**0.115**	***0.093***	***0.074***	***0.057***	0.043	0.030	0.019	0.009	0.000
0	4	**0.158**	**0.126**	**0.100**	***0.080***	***0.062***	0.048	0.036	0.025	0.015	0.007	0.000
1	3	**0.156**	**0.124**	***0.098***	***0.078***	***0.061***	0.046	0.034	0.024	0.015	0.007	0.000
2	2	**0.155**	**0.123**	***0.097***	***0.077***	***0.060***	0.046	0.034	0.024	0.015	0.007	0.000
3	1	**0.154**	**0.122**	***0.097***	***0.076***	***0.059***	0.045	0.034	0.023	0.015	0.007	0.000
4	0	**0.154**	**0.122**	***0.096***	***0.076***	***0.059***	0.045	0.033	0.023	0.014	0.007	0.000
0	5	**0.142**	**0.109**	***0.085***	***0.066***	***0.051***	0.038	0.028	0.019	0.012	0.006	0.000
1	4	**0.139**	**0.106**	***0.082***	***0.063***	0.049	0.037	0.027	0.019	0.011	0.005	0.000
2	3	**0.137**	**0.104**	***0.080***	***0.062***	0.048	0.036	0.026	0.018	0.011	0.005	0.000
3	2	**0.136**	**0.104**	***0.080***	***0.062***	0.047	0.036	0.026	0.018	0.011	0.005	0.000
4	1	**0.136**	**0.103**	***0.079***	***0.061***	0.047	0.035	0.026	0.018	0.011	0.005	0.000
5	0	**0.136**	**0.103**	***0.079***	***0.061***	0.047	0.035	0.026	0.018	0.011	0.005	0.000

Therefore, in the presence of parental consanguinity, the probabilities of a given case being autosomal dominant (D), autosomal recessive (R), X-linked recessive (L), or environmental (E) will be, respectively:

$$P_1 = c \times D$$

$$P_2 = c \times \frac{(q + (1-q) \times F) \times R}{q + c \times (1-q) \times F}$$

$$P_3 = c \times L$$

$$P_4 = c \times E.$$

The probabilities favoring the four possible hypotheses for the isolated case, given that parental consanguinity is present, are given by:

$$D = \frac{P_1}{P_1 + P_2 + P_3 + P_4}$$

$$R = \frac{P_2}{P_1 + P_2 + P_3 + P_4}$$

$$L = \frac{P_3}{P_1 + P_2 + P_3 + P_4}$$

and

$$E = \frac{P_4}{P_1 + P_2 + P_3 + P_4}$$

For the numerical evaluation of risks shown in the tables below we used the following values: K = 0.8; c = 0.01; and q = 0.004 (average gene frequency for about 30 reces-

Table 2 - Recurrence risks for a sib of an isolated case, with consanguineous parents and F = 1/4 (full sibs, parent-child), in function of the rate of environmental cases (E) and of the number of normal sibs ($n = n_m + n_f$) that the affected child already has.

n	E										
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0	**0.249**	**0.248**	**0.246**	**0.245**	**0.243**	**0.240**	**0.236**	**0.229**	**0.216**	**0.186**	0.000
1	**0.248**	**0.247**	**0.245**	**0.243**	**0.240**	**0.236**	**0.231**	**0.222**	**0.207**	**0.172**	0.000
2	**0.247**	**0.246**	**0.243**	**0.241**	**0.237**	**0.232**	**0.225**	**0.214**	**0.196**	**0.155**	0.000
3	**0.247**	**0.244**	**0.241**	**0.238**	**0.233**	**0.227**	**0.218**	**0.205**	**0.183**	**0.138**	0.000
4	**0.245**	**0.242**	**0.238**	**0.234**	**0.228**	**0.220**	**0.209**	**0.193**	**0.168**	**0.120**	0.000
5	**0.244**	**0.240**	**0.235**	**0.229**	**0.221**	**0.211**	**0.198**	**0.179**	**0.151**	**0.102**	0.000

Table 3 - Recurrence risks for a sib of an isolated case, with consanguineous parents and F = 1/8 (half brothers, uncle-niece, double first cousins), in function of the rate of environmental cases (E) and of the number of normal sibs ($n = n_m + n_f$) that the affected child already has.

n	E										
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0	**0.248**	**0.247**	**0.245**	**0.242**	**0.239**	**0.235**	**0.229**	**0.219**	**0.203**	**0.165**	0.000
1	**0.247**	**0.245**	**0.243**	**0.240**	**0.235**	**0.230**	**0.222**	**0.211**	**0.190**	**0.148**	0.000
2	**0.246**	**0.243**	**0.240**	**0.236**	**0.231**	**0.224**	**0.214**	**0.200**	**0.176**	**0.130**	0.000
3	**0.245**	**0.241**	**0.237**	**0.232**	**0.225**	**0.216**	**0.204**	**0.187**	**0.160**	**0.112**	0.000
4	**0.243**	**0.238**	**0.233**	**0.226**	**0.218**	**0.207**	**0.193**	**0.173**	**0.143**	***0.095***	0.000
5	**0.241**	**0.235**	**0.228**	**0.219**	**0.209**	**0.196**	**0.179**	**0.157**	**0.125**	***0.079***	0.000

Table 4 - Recurrence risks for a sib of an isolated case, with consanguineous parents and F = 1/16 (first cousins, uncle-half-niece couples), in function of the rate of environmental cases (E) and of the number of normal sibs ($n = n_m + n_f$) that the affected child already has.

n	E										
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0	**0.247**	**0.244**	**0.241**	**0.237**	**0.233**	**0.226**	**0.217**	**0.203**	**0.180**	**0.135**	0.000
1	**0.245**	**0.242**	**0.238**	**0.233**	**0.227**	**0.219**	**0.207**	**0.191**	**0.165**	**0.117**	0.000
2	**0.244**	**0.239**	**0.234**	**0.228**	**0.220**	**0.210**	**0.196**	**0.177**	**0.148**	***0.099***	0.000
3	**0.242**	**0.236**	**0.229**	**0.221**	**0.212**	**0.199**	**0.183**	**0.161**	**0.130**	***0.083***	0.000
4	**0.239**	**0.232**	**0.223**	**0.213**	**0.201**	**0.186**	**0.168**	**0.144**	**0.112**	***0.068***	0.000
5	**0.235**	**0.226**	**0.215**	**0.203**	**0.189**	**0.172**	**0.151**	**0.126**	***0.095***	***0.054***	0.000

Table 5 - Recurrence risks for a sib of an isolated case, with consanguineous parents and F = 1/32 (first-degree once removed cousins), in function of the rate of environmental cases (E) and of the number of normal sibs ($n = n_m + n_f$) that the affected child already has.

n	E										
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0	**0.245**	**0.240**	**0.235**	**0.229**	**0.222**	**0.212**	**0.198**	**0.179**	**0.151**	**0.102**	0.000
1	**0.242**	**0.237**	**0.230**	**0.223**	**0.213**	**0.201**	**0.185**	**0.164**	**0.133**	***0.085***	0.000
2	**0.240**	**0.233**	**0.224**	**0.215**	**0.203**	**0.188**	**0.170**	**0.147**	**0.115**	***0.069***	0.000
3	**0.236**	**0.227**	**0.217**	**0.205**	**0.191**	**0.174**	**0.154**	**0.129**	***0.097***	***0.056***	0.000
4	**0.231**	**0.220**	**0.207**	**0.193**	**0.177**	**0.158**	**0.136**	**0.111**	***0.081***	0.045	0.000
5	**0.226**	**0.212**	**0.196**	**0.179**	**0.161**	**0.141**	**0.118**	***0.094***	***0.066***	0.035	0.000

Table 6 - Recurrence risks for a sib of an isolated case, with consanguineous parents and F = 1/64 (second cousins), in function of the rate of environmental cases (E) and of the number of normal sibs ($n = n_m + n_f$) that the affected child already has.

n	E										
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0	**0.241**	**0.234**	**0.226**	**0.217**	**0.205**	**0.191**	**0.173**	**0.150**	**0.118**	***0.072***	0.000
1	**0.237**	**0.229**	**0.219**	**0.207**	**0.193**	**0.177**	**0.157**	**0.132**	**0.100**	***0.058***	0.000
2	**0.233**	**0.222**	**0.209**	**0.195**	**0.179**	**0.161**	**0.139**	**0.114**	***0.083***	0.046	0.000
3	**0.227**	**0.213**	**0.198**	**0.182**	**0.164**	**0.144**	**0.121**	***0.096***	***0.068***	0.036	0.000
4	**0.220**	**0.203**	**0.185**	**0.167**	**0.147**	**0.126**	**0.104**	***0.080***	***0.055***	0.028	0.000
5	**0.211**	**0.190**	**0.170**	**0.149**	**0.128**	**0.107**	***0.086***	***0.064***	0.043	0.022	0.000

sive loci). In all instances we used the formula derived before,

$$r = \frac{D \times \frac{K(1-K)\left[\frac{2-K}{2}\right]^n}{2} + R \times \frac{(\frac{1}{4})^n}{4} + L \times \frac{(\frac{1}{2})^{n_m}}{6}}{D \times \left\{(1-K)\left[\frac{2-K}{2}\right]^n + K\right\} + R \times (\frac{1}{4})^n + L \times \frac{\left[2(\frac{1}{2})^{n_m} + 1\right]}{3} + E},$$

where D, R, L and E took the values defined right above.

Tables 2, 3, 4, 5, and 6 present recurrence risks for the offspring of consanguineous couples with F values of 1/4, 1/8, 1/16, 1/32, and 1/64, respectively.

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