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Calculation of Recurrence Risks for Heterogeneous Genetic Disorders

Maria Cristina C. Braga, Paulo A. Otto,* and Oswaldo Frota-Pessoa
Departamento de Biologia, Instituto de Biociências, Universidade de São Paulo, Brazil

We present general formulae for several common situations in the genetic counseling of heterogeneous disorders. The occurrence or not of parental consanguinity is taken into account, since it distorts significantly the prior probabilities favoring the different mechanisms. Nonsyndromic deafness is used as a numerical application, since it can be produced by any type of monogenic inheritance and can be mixed with variable proportions of environmental cases. Recurrence risks are calculated including or not including environmental factors in the origin of the defect. In underdeveloped countries the proportion of environmentally determined cases of deafness is significantly higher than in first-world countries. Therefore, when environmental causes cannot be excluded, recurrence risks are always higher in developed than in developing countries. On average, when parental consanguinity is present there is a significant increase in recurrence risks for deafness, whether environmental factors are included or not. Am. J. Med. Genet. 95:36–42, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

In the present article we consider a rare heterogeneous genetic disorder with a coefficient of selection s (i.e., the relative reduction in fitness of affected individuals as compared to that of normals) that is caused by any of the three monogenic mechanisms (autosomal dominant with penetrance coefficient K, fully penetrant autosomal recessive, or X-linked recessive). We assume that a fraction of the cases is due to nongenetic (environmental) factors. The calculation of recurrence risks takes into account the prior probabilities, P_i, favoring each mechanism and the risks, R_i, associated with each of them. The final risk is $R = \Sigma P_i R_i$.

In the case of rare autosomal dominant disorders with incomplete penetrance, the recurrence risk for a sib of an isolated case is $R'_d = K(1 - K)/2$, if there is information about the normality of all direct ancestors of the affected individual [Frota-Pessoa et al., 1976], or by $R''_d = K(1 - K)/[2(1 - K + s)]$, if there is no information about the direct ancestors of the isolated case [Stevenson and Davison, 1970]. The corresponding risks under the hypothesis of X-linked recessive inheritance are respectively $R'_x = 1/6$ and $R''_x = (3 - s)/12$, ignoring the sex of the person for whom the risk is being calculated [Stevenson and Davison, 1970]. Finally, the recurrence risk for the case of autosomal recessive disorders is $R_r = 1/4$, and for the case of environmental factors it is negligible ($R_e \sim 0$). Let P_d, P_r, P_x, and P_e be the respective prior probabilities favoring autosomal dominant, autosomal recessive, X-linked recessive, and nongenetic (environmental) mechanisms. When there exists available information about the normality of the ascendants of the propositus, the recurrence risk is

$$R' = P_d \cdot R'_d + P_r \cdot R_r + P_x \cdot R'_x + P_e \cdot R_e = P_d \cdot K(1 - K)/2 + P_r/4 + P_x/6.$$

When there is no available information about their normality, the recurrence risk is

$$R'' = P_d \cdot R''_d + P_r \cdot R_r + P_x \cdot R''_x + P_e \cdot R_e = P_d \cdot K(1 - K)/[2(1 - K + s)] + P_r/4 + P_x \cdot (3 - s)/12.$$

The present article presents general formulae useful for genetic counseling in the case of heterogeneous genetic disorders. Whether parental consanguinity occurs or not is taken into account since it significantly distorts the prior probabilities. Nonsyndromic deafness will be used for numerical application since it can be produced by any type of monogenic inheritance and can be mixed with variable proportions of environmental cases, such as those secondary to ototoxic drugs, middle ear infections, and maternal rubella.

*Correspondence to: Paulo A. Otto, Departamento de Biologia, Instituto de Biociências, Universidade de São Paulo, Caixa Postal 11461, 05422-970, São Paulo, SP, Brazil. E-mail: otto@usp.br

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RESULTS

Effect of Parental Consanguinity in the Recurrence Risks for Sibs of Isolated Affected Cases

Let c be the population frequency of a type of consanguineous mating (e.g., first-cousin matings). Among the autosomal dominant, X-linked recessive, and environmental cases of the disorder, a proportion c will be born to consanguineous parents, while a fraction $1 - c$ will have parents biologically unrelated, since the probability of being affected is, for each of these mechanisms, independent of parental consanguinity. However, among the recessive cases of the disorder, the frequencies of affected individuals with related and unrelated parents shall no longer be in the ratio $(1 - c)$, because the probability of recessive disorder is directly influenced by consanguinity. Multiplying the prior probabilities c and $1 - c$ by the probabilities of affection q^2 and $(q^2 + Fpq)$, respectively, in the offspring of related and unrelated parents, and normalizing the resulting joint probabilities, we obtain the expressions $c(q + pF)/(q + cpF)$ and $(1 - c)q/(q + cpF)$, respectively, for the proportions of affected children in the offspring of related and unrelated parents.

In the presence of parental consanguinity, therefore, the prior probabilities favoring the hypotheses of autosomal dominant, autosomal recessive, X-linked recessive, and nongenetic (environmental) mechanisms are in the respective ratios:

$$p_1 = P(d,c) = cP_d$$
$$p_3 = P(r,c) = c(q + pF)P_r/(q + cpF)$$
$$p_5 = P(x,c) = cP_x$$
$$p_7 = P(e,c) = cP_e;$$

while in the absence of parental consanguinity these prior probabilities are in the ratios:

$$p_2 = P(d,n) = (1 - c)P_d$$
$$p_4 = P(r,n) = (1 - c)q\,P_r/(q + cpF)$$
$$p_6 = P(x,n) = (1 - c)P_x$$
$$p_8 = P(e,n) = (1 - c)P_e.$$

Therefore, in the presence of parental consanguinity, the prior probabilities favoring the four possible hypotheses become:

$$P(d|c) = p_1/(p_1 + p_3 + p_5 + p_7)$$
$$P(r|c) = p_3/(p_1 + p_3 + p_5 + p_7)$$
$$P(x|c) = p_5/(p_1 + p_3 + p_5 + p_7)$$
$$P(e|c) = p_7/(p_1 + p_3 + p_5 + p_7),$$

while in the absence of parental consanguinity they are:

$$P(d|n) = p_2/(p_2 + p_4 + p_6 + p_8)$$
$$P(r|n) = p_4/(p_2 + p_4 + p_6 + p_8)$$
$$P(x|n) = p_6/(p_2 + p_4 + p_6 + p_8)$$
$$P(e|n) = p_8/(p_2 + p_4 + p_6 + p_8).$$

In the case of first-cousin matings ($F = 1/16$), c is of the order of 0.01 or less for most human populations. In this case, the formula for $p_3 = P(r,c)$ takes the form

$$p_3 = P(r,c) = c(q + pF)P_r/(q + cpF)$$
$$= (15q + 1)P_r/(1599q + 1);$$

as q increases, p tends to 0 and $P(r,c)$ tends to cP_r, so that $P(r\,|\,c) = P_r$; therefore, if q is large, the presence of parental consanguinity does not distort the prior probabilities P_d, P_r, P_x, and P_e. As q decreases, p increases and $P(r,c)$ tends to P_r. For the majority of values P_r can take, when q is small $P(r\,|\,c)$ is a quantity near unity.

The recurrence risk, in the presence of consanguinity, is given therefore by

$$R_1' = P(d|c) \cdot R'_d + P(r|c) \cdot R_r + P(x|c) \cdot R'_x + P(e|c) \cdot R_e$$
$$= P(d|c) \cdot K(1 - K)/2 + P(r|c)/4 + P(x|c)/6$$

or

$$R_1'' = P(d|c) \cdot R''_d + P(r|c) \cdot R_r + P(x|c) \cdot R''_x + P(e|c) \cdot R_e$$
$$= P(d|c) \cdot K(1 - K)/[2(1 - K + s)] + P(r|c)/4$$
$$+ P(x|c) \cdot (3 - s)/12,$$

depending on the presence of available information about the normality of all direct ancestors of the index case. In the formulae that follow, we shall omit the last result, which can be easily obtained by replacing $K(1 - K)/2$ and 1/6 by $K(1 - K)/[2(1 - K + s)]$ and $(3 - s)/12$. For most situations, the risk estimates using R' and R″ do not differ significantly; besides that, there is always information about the normality of the direct ascendants of the index case over some generations, and in this case the numerical analysis of the alternative expressions for the recurrence risk of autosomal dominant and X-linked recessive shows that rapid convergence occurs to $K(1 - K)/2$ and 1/6.

In the absence of consanguinity the recurrence risk becomes

$$R_2 = P(d|n) \cdot R'_d + P(r|n) \cdot R_r + P(x|n) \cdot R'_x + P(e|n) \cdot R_e$$
$$= P(d|n) \cdot K(1 - K)/2 + P(r|n)/4 + P(x|n)/6.$$

In cases where environmental causes can be excluded, the prior probabilities favoring autosomal dominant, autosomal recessive, and X-linked recessive mechanisms become $P'_d = P_d/(P_d + P_r + P_x)$, $P'_r = P_r/(P_d + P_r + P_x)$, and $P'_x = P_x/(P_d + P_r + P_x)$. When consanguinity is present, the probabilities favoring the three possible hypotheses for the isolated case are: $P'(d\,|\,c) = p_1/(p_1 + p_3 + p_5)$, $P'(r\,|\,c) = p_3/(p_1 + p_3 + p_5)$, and $P'(x\,|\,c) = p_5/(p_1 + p_3 + p_5)$; and, when consanguinity is absent, $P'(d\,|\,n) = p_2/(p_2 + p_4 + p_6)$, $P'(r\,|\,n) = p_4/(p_2 + p_4 + p_6)$, and $P'(x\,|\,n) = p_6/(p_2 + p_4 + p_6)$. The corresponding recurrence risks are, respectively,

$$R_3 = P'(d|c) \cdot K(1 - K)/2 + P'(r|c)/4 + P'(x|c)/6$$

and

$$R_4 = P'(d|n) \cdot K(1 - K)/2 + P'(r|n)/4 + P'(x|n)/6.$$

In cases of heterogeneous disorders where the recessive variant can be the result of homozygosis in relation to any of several independent loci, as in the case of nonsyndromic deafness, the probabilities of being affected in the offspring of consanguineous and nonconsanguineous couples are given respectively by $\Sigma q_i^2 + F\Sigma q_i(1 - q_i)$ and Σq_i^2 instead of $q^2 + Fq(1 - q)$ and q^2. If n_r is the number of different recessive loci that independently produce the defect, the expressions for $p_3 = P(r,c)$ and $p_4 = P(r,n)$ become

$$p_3 = P(r,c) = cP_r[F\sqrt{(n_r \cdot \Sigma q^2{}_i)} + (1 - F)\Sigma q^2{}_i]/[cF\sqrt{(n_r \cdot \Sigma q^2{}_i)} + \Sigma q^2{}_i(1 - cF)]$$

and

$$p_4 = P(r,n) = (1 - c) \cdot P_r \cdot \Sigma q^2{}_i/[cF\sqrt{(n_r \cdot \Sigma q^2{}_i)} + \Sigma q^2{}_i(1 - cF)].$$

In the case of nonsyndromic genetic deafness, the number of deafness-causing genes is estimated to range from 50 to 100 [Sundstrom et al., 1999]. At least 26 recessive nonsyndromic loci were detected through linkage [Kimberling, 1999]. Using, for the case of nonsyndromic autosomal recessive deafness, the figure of about 30 different loci [Morton, 1960] and a global frequency of the defect in the offspring of unrelated couples of the order of 0.0005, we obtain for $F = 1/16$, $p_3/p_4 = 16.6$. Therefore, there exists a 16.6-fold risk increase of the defect in the offspring of first cousins as compared to that of nonconsanguineous couples.

When the relative frequency of X-linked recessive cases among hereditary cases is small (as in the case of nonsyndromic deafness), the recurrence risks for all situations listed above are the same, whether the affected individuals be males or females.

Risks for Future Sibs in Sibships With at Least Two Affected Individuals

The presence of more than one affected individual in the same sibship indicates with a high probability that the origin of the disorder is genetic, given that the cases are not due to obvious environmental causes, like the case of whole sibships of children that in times past were hearing impaired because of otitis.

The prior probabilities favoring the hypotheses of autosomal dominant, autosomal recessive, and X-linked recessive mechanisms are obtained by normalizing the following quantities, in the case where the two affected sibs are males and there is no parental consanguinity:

$$a = P'(d|n) \cdot K(1 - K)/2$$
$$b = P'(r|n) \cdot 1/4$$
$$c = P'(x|n) \cdot 1/6.$$

In fact, under each hypothesis, the first part of the expression for a, b, and c is the probability of occurrence of the first affected brother; the second part is the conditional probability of occurrence of the second given the first. The final probabilities favoring the autosomal dominant, autosomal recessive, and X-linked recessive mechanisms are $A = a/(a + b + c)$, $B = b/(a + b + c)$, and $C = c/(a + b + c)$, and the recurrence risk of the affection for the next sib to be born is given by

$$R_5 = A.K/2 + B/4 + C/4.$$

In the case of parental consanguinity, similar expressions are obtained by replacing, in a, b, and c, $P'(d\,|\,n)$, $P'(r\,|\,n)$, and $P'(x\,|\,n)$, respectively, by $P'(d\,|\,c)$, $P'(r\,|\,c)$, and $P'(x\,|\,c)$. Similar reasoning is used to get the expressions for different numbers of affected sibs of either sex.

Risks for the Offspring of Couples in which one of the Spouses is an Isolated Affected Case of the Disorder

When parental consanguinity is absent, depending on the inclusion or not of environmental factors in the cause of the defect, the risks of affected offspring are given respectively by

$$R_6 = P(d|n) \cdot K/2 + P(r|n) \cdot P(\text{het})/2$$

or

$$R_7 = P'(d|n) \cdot K/2 + P'(r|n) \cdot P(\text{het})/2,$$

where $P(\text{het}) = 2pq \sim 2q$ is the chance of the normal spouse being a heterozygote for the same gene that in homozygosis determines the defect in the other.

When the spouses are first-degree cousins, the formula for the risk takes the forms (whether environmental factors are included or not)

$$R_8 = P(d|c) \cdot K/2 + P(r|c) \cdot P(\text{het})/2 + P(x|c) \cdot P'(\text{het})/2$$

or

$$R_9 = P'(d|c) \cdot K/2 + P'(r|c) \cdot P(\text{het})/2 + P'(x|c) \cdot P'(\text{het})/2,$$

where $P(\text{het})$ is defined as before but now takes value $2r = 1/4$, where r is the coefficient of relationship between two relatives and $P'(\text{het})$ is the probability that the female spouse is a heterozygote for the same X-linked gene that produced the defect in her affected husband; the part of the above formulae containing $P'(\text{het})$ is obviously used only when the mothers of the first-cousin couple are sisters and the affected individual is a male.

Risks for the Offspring of Couples in Which One of the Spouses is Affected and There Is a Child Also Affected

The occurrence of the affected child indicates with a large probability, as before, the genetic origin of the disorder and can be explained either by autosomal dominant or recessive mechanisms, with prior probabilities $P_d/(P_d + P_r)$ and $P_r/(P_d + P_r)$, respectively. Since the conditional probabilities of an affected child under dominant and recessive hypotheses are $K/2$ and $2pq/2 \sim q$, the final probabilities favoring them are $A = P_dK/(P_dK + 2P_r\text{q})$ and $B = 2P_rq/(P_dK + 2P_rq)$, which are obtained by normalizing the products (joint probabilities) $P_d/(P_d + P_r).\ K/2$ and $P_r/(P_d + P_r).q$. The recurrence risk for a next affected child is then

$$R_{10} = (AK + B)/2 = (P_dK^2 + 2P_rq)/(2P_dK + 4P_rq).$$

If the affected parent is married to a first-degree cousin, the calculations are similar, with the difference being that under the recessive hypothesis the conditional probability of an affected child is given by 1/8 instead of q. The recurrence risk is then

$$R_{11} = (4P_dK^2 + P_r)/(8P_dK + 2P_r).$$

In the previous calculations, we did not take into account the possibility of the affected parent having a mitochondrial or an X-linked variant of the disorder. If

we had done so, in the X-linked case the recurrence risk would be increased by the possibility of the female partner being a heterozygote as to the same gene that in hemizygosis determined the disorder in her husband, if their mothers are two sisters. However, since the joint probabilities favoring autosomal dominant, recessive, and X-linked mechanisms will be in the ratios $P_dK/2$, $P_r/8$, and $5P_x/48$, the recurrence risk will not differ significantly from the previous one, for any value that P_x can take.

Risks for the Offspring of Nonconsanguineous Couples in Which Both Parents Are Affected

Under the hypothesis that both spouses have an autosomal dominant variant of the defect ($d \times d$) and assuming an average value K for the penetrance coefficient of any dominant form of the disorder, if both spouses have the same variant (parental cross $A_1a \times A_1a$), the probability of affected offspring is given by ¼. 1 + 2 . ¼ . K = (1 + 2K)/4, assuming that the penetrance in affected homozygotes A_1A_1 is 1; in the case of noncoincidence of the locus (parental cross $A_1abb \times aaB_1b$), the probability of affected offspring is given by ¼ · K(2 – K) + 2 . ¼. K = K(4 – K)/4, assuming that in affected individual A_1aB_1b the effects of the genes A_1 and B_1 are independent, so that the penetrance value is $1 - (1 - K)^2 = K(2 - K)$. Since the probabilities favoring locus coincidence or noncoincidence are in ratios (1 – $1/n_d$), where n_d is the number of autosomal dominant variants, the compound risk under the dominant hypothesis becomes

$$P(af|d \times d) = [1 + 2K + (n_d - 1)K(4 - K)]/4n_d.$$

If one of the spouses is affected by an autosomal dominant form and the other spouse by an autosomal recessive form ($d \times r$), the risk for their offspring is

$$P(af|d \times r) = K/2 + 2pq/2 \sim (K + 2q)/2.$$

In case the male partner has an X-linked recessive form and the female partner has an autosomal dominant form ($d \times x$) or if one of the spouses is affected by a dominant form and the other by a variant secondary to nongenetic factors ($d \times e$), the risk for their offspring decreases to

$$P(af|d \times x) = P(af|d \times e) = K/2.$$

Under the hypothesis that both spouses have an autosomal recessive form of the defect ($r \times r$), the risk for their offspring will be 1 if the involved loci are the same (probability $1/n_r$, where n_r is the number of autosomal recessive variants) or $2pq \sim 2q$ otherwise (probability 1 – $1/n_r$). Hence, the compound risk under recessive hypothesis is

$$P(af|r \times r) = [1 + 2q(n_r - 1)]/n_r.$$

In cases where the male spouse has an X-linked recessive form and the female an autosomal recessive form ($x \times r$), or if one of the spouses has the recessive form and the other a nongenetic one ($r \times e$), the risks are given by

$$P(af|x \times r) = P(af|r \times e) = 2pq/2 \sim q.$$

In unions where the male is affected for an X-linked recessive form and the female for a nongenetic one ($x \times e$), or if both spouses are affected by nongenetic forms, the risk for their offspring is zero:

$$P(af|x \times e) = P(af|e \times e) = 0.$$

Assuming that P_d, P_r, P_x, and P_e (with $P_d + P_r + P_x + P_e = 1$) are the prior probabilities favoring each one of the mechanisms (relative frequencies of autosomal dominant, autosomal recessive, X-linked recessive, and nongenetic mechanisms among all cases of the defect), compound expressions for the offspring risk can be determined without any difficulties, considering four different situations in which environmental factors are: (1) included in both spouses; (2) excluded in the male partner; (3) excluded in the female partner; or (4) excluded in both spouses.

Environmental Factors Included for Both Spouses. In this case, the probabilities favoring autosomal dominant, autosomal recessive, X-linked recessive, and environmental hypotheses, respectively, are P_d, P_r, P_x, and P_e for the male partner; and $P_d/(P_d + P_r + P_e)$, $P_r/(P_d + P_r + P_e)$, 0, and $P_e/(P_d + P_r + P_e)$ for the female spouse. The probabilities of formation of the several possible types of matings involving two affected individuals are:

$$P(d \times d) = P_d^{\,2}/(P_d + P_r + P_e)$$
$$P(d \times r) = 2P_dP_r/(P_d + P_r + P_e)$$
$$P(d \times x) = P_dP_x/(P_d + P_r + P_e)$$
$$P(d \times e) = 2P_dP_e/(P_d + P_r + P_e)$$
$$P(r \times r) = P_r^{\,2}/(P_d + P_r + P_e)$$
$$P(r \times x) = P_rP_x/(P_d + P_r + P_e)$$
$$P(r \times e) = 2P_rP_e/(P_d + P_r + P_e)$$
$$P(x \times e) = P_xP_e/(P_d + P_r + P_e)$$
$$P(e \times e) = P_e^{\,2}/(P_d + P_r + P_e).$$

The global risk for the offspring of affected couples is obtained multiplying these probabilities by the corresponding conditional risks and adding all these products:

$$\begin{aligned} R_{12} &= P(d \times d) \cdot P(af|d \times d) + \ldots + P(e \times e) \cdot P(af|e \times e) \\ &= \{P_d^{\,2}[1 + 2K + (n_d - 1)K(4 - K)]/4n_d \\ &\quad + P_dP_r(K + 2q) + P_dP_xK/2 \\ &\quad + P_dP_eK + P_r^{\,2}[1 + 2q(n_r - 1)]/n_r + P_rP_xq \\ &\quad + 2P_rP_eq\}/(P_d + P_r + P_e). \end{aligned}$$

Using a similar reasoning, we obtained the global risks for the offspring of affected couples in the situations that follow.

Environmental Factors Excluded in the Male Spouse.

$$\begin{aligned} R_{13} &= \{P_d^{\,2}[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) \\ &\quad + P_dP_r(K + 2q) + P_dP_xK/2 + P_dP_eK/2 \\ &\quad + P_r^{\,2}[1 + 2q(n_r - 1)]/n_r + P_rP_xq \\ &\quad + P_rP_eq\}/[(P_d + P_r + P_e)(P_d + P_r + P_x)]. \end{aligned}$$

Environmental Factors Excluded in the Female Spouse

$$\begin{aligned} R_{14} &= \{P_d^{\,2}[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) \\ &\quad + P_dP_r(K + 2q) + P_dP_xK/2 + P_dP_eK/2 \\ &\quad + P_r^{\,2}[1 + 2q(n_r - 1)]/n_r + P_rP_xq + P_rP_eq\}/(P_d + P_r). \end{aligned}$$

It is evident that

$$R_{14}/R_{13} = 1 + P_x P_e/(P_d + P_r).$$

Environmental Factors Excluded in Both Spouses

$$R_{15} = \{P_d^2[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) + P_d P_r(K + 2q) + P_d P_x K/2 + P_r^2[1 + 2q(n_r - 1)]/n_r + P_r P_x q\}/[(P_d + P_r + P_x)(P_d + P_r)].$$

Assuming that the relative rates of the various genetic mechanisms, $A = P_d/(P_d + P_r + P_x)$, $B = P_r/(P_d + P_r + P_x)$, and $C = P_x/(P_d + P_r + P_x)$, should not differ significantly from place to place, new values A', B' and C' can be obtained for a region with a different environmental rate P_e' according to the formulae

$$P_d' = P_d(1 - P_e')/(P_d + P_r + P_x) = A.\ (1 - P_e')$$
$$P_r' = P_r(1 - P_e')/(P_d + P_r + P_x) = B.\ (1 - P_e')$$

and

$$P_x' = P_x(1 - P_e')/(P_d + P_r + P_x) = C.\ (1 - P_e'),$$

with

$$P_d' + P_r' + P_x' + P_e' = 1.$$

Risks for the Offspring of Consanguineous Couples (First-Degree Cousins) With Both Spouses Affected

The risk $P(af|d \times d)$ is the same as in the previous item, if we ignore the negligible identical-by-descent contribution $(1 - K)^3\ K/8$.

If one of the spouses shows the autosomal dominant form and the other a recessive one, the risk for their offspring is

$$P(af|d \times r) = K/2 + 1/8 = (1 + 4K)/8.$$

The risks $P(af|d \times x)$, $P(af|d \times e)$, $P(af|x \times e)$, and $P(af|e \times e)$ are independent from parental consanguinity and take exactly the values derived in the previous item.

Under the hypothesis that both spouses have an autosomal recessive form of the defect, the probability of locus identical-by-descent coincidence $(q/4)$ is negligible when compared to the total probability of coincidence $1/n_r$; since the offspring risks associated with locus coincidence (probability $1/n_r$) or not (probability $1 - 1/n_r$) are, respectively, 1 and ¼, the compound risk does not differ significantly from

$$P(af|r \times r) = [1 + (n_r - 1)/4]/n_r.$$

In a case where the male has an X-linked recessive form and his female partner has an autosomal recessive one $(x \times r)$, or if the mating is of type $(r \times e)$, the risks for their offspring will be

$$P(af|x \times r) = P(af|r \times e) = 1/8.$$

Since there is parental consanguinity, finally, a nonspecific increment in the risk for recessive defects in the offspring, of the order of $n_r\ (q^2 + Fpq) - n_r\ .q^2 = n_r\ Fpq = n_r\ pq/16$, can be added to the global risks listed below.

If environmental causes can not be excluded in both spouses, the risk for their offspring is:

$$R_{16} = P(d \times d) \cdot P(af|d \times d) + \ldots = \{P_d^2[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) + P_d P_r(1 + 4K)/4 + P_d P_x K/2 + P_d P_e K + P_r^2[1 + (n_r - 1)/4]/n_r + P_r P_x/8 + P_r P_e/4\}/(P_d + P_r + P_e).$$

If environmental causes can be excluded in the male, the risk for the offspring becomes:

$$R_{17} = P(d \times d) \cdot P(af|d \times d) + \ldots = \{P_d^2[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) + P_d P_r(1 + 4K)/4 + P_d P_x K/2 + P_d P_e K/2 + P_r^2[1 + (n_r - 1)/4]/n_r + P_r P_x/8 + P_r P_e/8\}/[(P_d + P_r + P_e)(P_d + P_r + P_x)].$$

When environmental causes can be excluded in female, the risk for offspring becomes:

$$R_{18} = P(d \times d) \cdot P(af|d \times d) + \ldots = \{P_d^2[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) + P_d P_r(1 + 4K)/4 + P_d P_x K/2 + P_d P_e K/2 + P_r^2[1 + (n_r - 1)/4]/n_r + P_r P_x/8 + P_r P_e/8\}/(P_d + P_r).$$

If environmental causes can be discarded in both spouses, the recurrence risk is given by:

$$R_{19} = P(d \times d) \cdot P(af|d \times d) + \ldots = \{P_d^2[1 + 2K + (n_d - 1)K(4 - K)]/(4n_d) + P_d P_r(1 + 4K)/4 + P_d P_x K/2 + P_r^2[1 + (n_r - 1)/4]/n_r + P_r P_x/8\}/[(P_d + P_r + P_x)(P_d + P_r)].$$

Risks for the Offspring of Nonconsanguineous Affected Couples With One Affected Child

As before, the situation indicates with a high probability the genetic origin of the defect, so that the occurrence of the cases can be explained by autosomal dominant or recessive mechanisms. The possible matings that explain the affected child occur with probabilities:

$$P(d \times d) = P_d^2/(P_d + P_r)^2$$
$$P(d \times r) = 2P_d P_r/(P_d + P_r)^2$$
$$P(r \times r) = P_r^2/(P_d + P_r)^2.$$

In dominant × dominant matings, the probabilities of occurrence of the affection in the child by effect of the same or different loci are respectively $(1 + 2K)/[1 + 2K + (n_d - 1)K(4 - K)]$ and $K(4 - K)(n_d - 1)/[1 + 2K + (n_d - 1)K(4 - K)]$; therefore, the recurrence risk for a next child is:

$$P(af|d \times d) = [(1 + 2K)^2 + (n_d - 1)K^2(4 - K)^2]/\{4[1 + 2K + (n_d - 1)K(4 - K)]\}.$$

Under the hypothesis that one of the spouses has the dominant form and the other the recessive one, the chances favoring one or other mechanism are, respectively, $K/(K + 2q)$ and $2q/(K + 2q)$. The recurrence risk for a next child is then

$$P(af|d \times r) = (K^2 + 2q)/[2(K + 2q)].$$

Under the hypothesis that both spouses have an autosomal recessive form of the defect, the probabilities of the child being affected by a disorder produced by genes located or not in the same locus are, respectively, $1/[1 + 2q(n_r - 1)]$ and $2q(n_r - 1)/[1 + 2q(n_r - 1)]$. The recurrence risk in this case is then

$$P(af|r \times r) = [1 + q(n_r - 1)]/[1 + 2q(n_r - 1)].$$

The global risk for the future offspring is then

$$\begin{aligned} R_{20} &= P(d \times d) \cdot P(af|d \times d) + \ldots \\ &= \{P_d{}^2[(1 + 2K)^2 + (n_d - 1)K^2(4 - K)^2]/ \\ &\quad \{4[1 + 2K + (n_d - 1)K(4 - K)]\} \\ &\quad + P_dP_r(K^2 + 2q)/(K + 2q) + P_r{}^2[1 + q(n_r - 1)]/ \\ &\quad [1 + 2q(n_r - 1)]\}/(P_d{}^2 + 2P_dP_r + P_r{}^2). \end{aligned}$$

Risks for the Offspring of Affected First-Degree Cousins With One Affected Child

In matings $d \times d$, the recurrence risk in the offspring $P(af|d \times d)$ has the same value derived for the corresponding case without consanguinity.

If the mating is of type $d \times r$, the chances favoring the dominant and recessive patterns in the affected child are, respectively, $4K/(1 + 4K)$ and $1/(1 + 4K)$, expressions obtained by normalizing $K/2$ and ⅛. The recurrence risk for a next child thus becomes

$$P(af|d \times r) = (1 + 4K^2)/[2(1 + 4K)].$$

Under the hypothesis that both spouses have an autosomal recessive form of the defect, the probabilities of occurrence of the affected child by locus coincidence or not are obtained by normalizing the products $(1/n_r).1$ and $(1 - 1/n_r).1/4$, being respectively $4/(3 + n_r)$ and $(n_r - 1)/(3 + n_r)$. The recurrence risk for a next affected child is then

$$P(af|r \times r) = (7 + n_r)/[2(3 + n_r)].$$

As in the corresponding situation without an affected child, an increment (for any autosomal recessive disorder) in the risk for recessive defects in the offspring, $n_r Fpq = n_r pq/16$, can be added to the global risk.

The global risk for a next child born to the couple is

$$\begin{aligned} R_{21} &= P(d \times d) \cdot P(af|d \times d) + \ldots \\ &= \{P_d{}^2[(1 + 2K)^2 + (n_d - 1)K^2(4 - K)^2]/ \\ &\quad \{4[1 + 2K + (n_d - 1)K(4 - K)]\} \\ &\quad + P_dP_r(1 + 4K^2)/(1 + 4K) \\ &\quad + P_r{}^2(7 + n_r)/[2\,(3 + n_r)]\}/(P_d{}^2 + 2P_dP_r + P_r{}^2). \end{aligned}$$

EXAMPLE OF NUMERICAL APPLICATION: THE CASE OF NONSYNDROMIC DEAFNESS

Nonsyndromic deafness has an astonishing degree of heterogeneity. It includes all monogenic mechanisms plus multifactorial polygenic cases. Mitochondrial cases also occur. The proportion of environmentally determined cases is significant, being estimated in about 50% of cases in developed countries [Marazita et al., 1993] and in about 80% in developing countries like Brazil [Braga et al., 1999]. Therefore, this category has a much higher frequency in developing countries than it does in first-world countries, being clearly and negatively correlated with the prevailing sanitary, medical, nutritional, and educational levels.

Using data from studies performed in the United States and in England [Stevenson and Davison, 1970; Ruben et al., 1982; Feinmesser et al., 1986; Marazita et al., 1993] and data from five studies performed in Brazil [Salerno et al., 1979; Castro et al., 1980; Castagno and Carvalhal, 1985; Lavinsky, 1990; Braga et al., 1999], we obtained approximate average figures of 0.38 and 0.84, respectively, for the proportion of nongenetic cases among all cases of deafness in developed and developing countries (which are represented by Brazil). For estimating the proportions of autosomal dominant, autosomal recessive, and X-linked recessive cases among all hereditary forms of nonsyndromic deafness, we used data from a Brazilian study [Braga et al., 1999] and from five different international surveys [Stevenson and Cheeseman, 1956; Kloepfer et al., 1970; Fraser, 1976; Feinmesser et al., 1986; Marazita et al., 1993]. We also used the figures cited in Stevenson and Davison [1970]. The approximate average figures for the relative proportions of autosomal dominant, autosomal recessive, and X-linked recessive forms of hereditary deafness were 0.19, 0.78, and 0.03, respectively. These figures do not differ significantly from those recently cited by Van Laer et al. [1999]. Assuming that these relative proportions do not vary significantly from place to place and combining them with the frequencies of genetic and nongenetic cases, we obtain the following proportions P_d, P_r, P_x, and P_e of autosomal dominant, autosomal recessive, X-linked recessive, and environmental (nongenetic) cases, respectively, among all cases of nonsyndromic deafness:

1. For developed, industrialized countries: 0.12, 0.48, 0.02, and 0.38;
2. For developing countries (Brazil): 0.03, 0.12, 0.005, and 0.84.

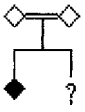
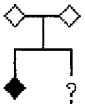
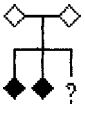
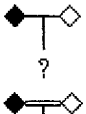
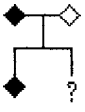
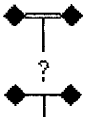
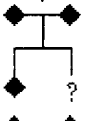
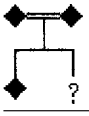
These figures are easily translated to geographic regions with different proportions of environmental cases. For the composition of the recurrence risks shown in Table I, we assumed the following numerical values:

1. Average number of autosomal recessive loci: $n_r = 30$, corresponding to an average gene frequency of $q = 0.004$;
2. Average number of autosomal dominant loci: $n_d = 20$, with a penetrance value of $K = 0.80$;
3. Coefficient of selection of deaf patients $s = 0.25$.

These values were averaged from several sources [references in Fraser, 1976; details are given in Braga et al., 1999]. The value of $c = 0.01$ was rounded from an estimate of 0.0137 obtained by Freire-Maia [1957] for the frequency of first-cousin marriages in Brazilian populations.

For situations 1 to 5 (Table I) the risks were calculated on the hypotheses of available information or not about the normality of all direct ancestors of the propositi. For some of these situations the differences were less than 0.01, and only one figure is shown. For the

TABLE I. Risks of Nonsyndromic Deafness in Different Situations

	Environmental factors included		Environmental factors excluded
	Brazil	Developed countries	
	$R_1 = 0.17$	$R_1 = 0.23–0.24$	$R_3 = 0.25$
	$R_2 = 0.03$	$R_2 = 0.13–0.14$	$R_4 = 0.21–0.23$
	—	—	$R_5 = 0.26–0.27$
	$R_6 = 0.01$	$R_6 = 0.05$	$R_7 = 0.09$
	$R_8 = 0.09$	$R_8 = 0.12$	$R_9 = 0.13$
	—	—	$R_{10} = 0.40$
	—	—	$R_{11} = 0.46$
	$R_{12} = 0.03$[a] $R_{13} = 0.09$[b] $R_{14} = 0.10$[c]	$R_{12} = 0.10$[a] $R_{13} = 0.14$[b] $R_{14} = 0.14$[c]	$R_{15} = 0.18$
	$R_{16} = 0.06$[a] $R_{17} = 0.20$[b] $R_{18} = 0.21$[c]	$R_{16} = 0.22$[a] $R_{17} = 0.29$[b] $R_{18} = 0.29$[c]	$R_{19} = 0.36$
	—	—	$R_{20} = 0.74$
	—	—	$R_{21} = 0.52$

[a]Environmental causes included in both spouses.
[b]Environmental causes excluded in male partner.
[c]Environmental causes excluded in female partner.

situations in which the differences were larger than this, two figures are shown, the higher one corresponding to the case where no information was available. These differences are generally negligible.

The remarks that follow are suggested by the values obtained in Table I.

1. The recurrence risks are of same order of magnitude whether the index cases are male or female due to the low proportion of X-linked cases.
2. When environmental causes cannot be excluded, the recurrence risks are always higher in developed countries than in developing countries.
3. Parental consanguinity produces on average a two-fold increase in recurrence risks, when environmental factors cannot be excluded; when these factors are excluded, the risk is generally slightly higher.

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