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Heterozygosity Probabilities for Normal Relatives of Isolated Cases Affected by Incompletely Penetrant Conditions and the Calculation of Recurrence Risks for Their Offspring. I. Autosomal Dominant Genes.

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Heterozygosity probabilities P(het) for relatives of isolated cases produced by incompletely penetrant autosomal dominant genes and recurrence risks for their offspring, R = P(het).K/2, where K is the penetrance value, have been calculated in the literature for some simple particular situations. Bayes theorem and elements from the theory of finite difference equations enabled us to derive the heterozygosity probability for any individual belonging to a pedigree containing an isolated case affected with an incompletely penetrant autosomal dominant disorder. The generalized formula here derived is valid for most particular cases thus far studied in the literature. Am. J. Med. Genet. 95:43–48, 2000.

KEY WORDS: genetic risks; Bayes theorem; difference equations

INTRODUCTION

Estimating recurrence risks for the offspring of relatives of an isolated case affected with an incompletely penetrant autosomal dominant condition is a rather complicated problem unless the relatives under consideration are his or her direct descendants; algorithms such as the ENCU system [Chase et al., 1971; Murphy and Chase, 1975] were developed to cope efficiently with this situation. Elston and Stewart [1971] provided the theoretical basis for likelihood calculation in simple pedigree situations; their algorithm and its extensions [Lange and Elston, 1975] provided, within pedigrees, the complex calculations that are needed for risk assessment, forming the basis of several computer programs with this aim. Some computer programs, such as the LINKAGE program [Lathrop et al., 2000, V.5.2: ftp://linkage.rockefeller.edu/software/linkage; Terwilliger and Ott, 1994] and the SAGE (Statistical Analysis for Genetic Epidemiology) program [Elston et al., 2000, V.3.0: http://darwin.mhme.cwru.edu/pub/sage.html], which enable the calculation of pedigree likelihoods that generally cannot be expressed in closed form, can perform risk estimations directly or indirectly for complex pedigree structures. Heterozygosity probabilities [P(het)] for relatives of isolated cases were calculated previously for some particular situations [Aylsworth and Kirkman, 1979; Emery, 1986; Frota-Pessoa et al., 1976; Murphy and Chase, 1975; Otto and Frota-Pessoa, 1979; Pauli and Motulsky, 1981; Stevenson and Davison, 1970] but did not include deriving recurrence risks for the offspring of any relative of an isolated case within a pedigree. In this article we derive the heterozygosity probability for individual C at the generalized case shown in the pedigree depicted in Fig. 1, where the shaded symbol indicates an affected isolated individual.

The formula used for calculating this probability was derived by combining the following quantities: (a) probability of heterozygosis for normal individuals; (b) probability of heterozygosis for the direct ancestors of a known carrier of the gene; (c) probability of heterozygosis for a normal descendant of an individual whose heterozygosity probability is known; (d) probability of heterozygosis for an individual who has normal descendants.

Probability of Heterozygosis for Normal Individuals

The probability of heterozygosis for a normal individual in the case with information about all his or her

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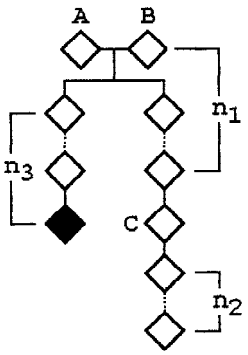

Fig. 1. Individual C belonging to this generalized pedigree seeks genetic counseling to ascertain his or her probability of being a heterozygote for the autosomal dominant gene with incomplete penetrance that caused the disease in the relative represented by the shaded symbol.

direct ancestors, none of them being known to have had an autosomal dominant disorder with incomplete penetrance, is given by

$$\begin{aligned} P_1(\text{het}) &= 2\mu(1-K) + 2\mu(1-K)^2 + 2\,\mu(1-K)^3 + \ldots \\ &= \sum_{i=1}^{\inf} 2\mu(1-K)^i = 2\mu(1-K)\sum_{i=0}^{\inf}(1-K)^i \\ &= 2\mu(1-K)/K, \end{aligned}$$

where K is the penetrance value and μ is the mutation rate, both quantities being assumed to have a constant value from generation to generation. The formula for the situation above described, first considered by Frota-Pessoa et al. [1976], takes into account the possibility of the mutation having occurred in any of the ancestors of the propositus and being transmitted to him, without becoming penetrant in any of the individuals in the genealogy. In fact, $2\mu(1-K)$ is the probability of the propositus being a nonmanifesting heterozygote because the mutation occurred in any of the two gametes that originated him and then did not become evident; the second term of the series, $2\mu(1-K)^2$, is the product of the following probabilities: of the mutation having occurred in any of the four gametes that originated the parents of the propositus (4μ), being nonpenetrant ($1-K$), being transmitted to the propositus (1/2) and then again being nonpenetrant ($1-K$); and so on. Since in the absence of inbreeding the number of direct ancestors doubles and the segregation ratio is 1/2 per generation, the term for the mutation occurring in any of the gametes produced by the direct ancestors that existed n generations before the propositus is exactly $2\mu(1-K)^n$.

For the situation in which there is no information about any of the ancestors of this individual, the probability of heterozygosis for a normal individual takes the form

$$\begin{aligned} P_2(\text{het}) &= 2\mu(1-K) + 2\mu(1-K)(1-s'K) \\ &\quad + 2\mu(1-s'K)^2 + \ldots \\ &= \sum_{i=1}^{\inf} 2\mu(1-K)w^{i-1} = 2\mu(1-K)\sum_{i=0}^{\inf} w^i \\ &= 2\mu(1-K)/(1-w) = 2\mu(1-K)/s, \end{aligned}$$

where μ and K have the same meaning as before and $w' = 1-s'$ and $w = K.w'+(1-K).1 = 1-K(1-w') = 1-Ks' = 1-s$ are, respectively, the fitness value of affected heterozygotes and the average fitness value of all heterozygotes (and s' and s are the corresponding coefficients of selection or relative rates of decrease in fitness). This formula, first derived by Stevenson and Davison [1970], takes into account the possibilities of the mutation having occurred: (a) in any of the two gametes that gave rise to the propositus and then of becoming nonpenetrant $[2\mu(1-K)]$; (b) in any of the four gametes that gave rise to the parents of the propositus, becoming penetrant (with probability K) and enabled him or her to survive with probability $w' = 1-s'$ and to transmit the gene to the propositus with probability l/2 or was not penetrant and was transmitted to the propositus, being then nonpenetrant $[4\mu Kw'.1/2.(1-K) + 4\mu(1-K).1/2.(1-K) = 2\mu(1-K)(1-Ks')]$ and so on. As in the previous model, the term for the mutation occurring in any of the gametes produced by the direct ancestors existing n generations before the propositus is derived, taking the value $2\mu(1-K)(1-Ks')^{n-1}$ or $2\mu(1-K)(1-s)^{n-1} = 2\mu(1-K)w^{n-1}$. The sum of all these terms gives us the probability P_2 shown above that the propositus is a nonpenetrant heterozygote.

The two expressions P_1 and P_2 just derived are perfectly equivalent when **s = K**, that is, when the dominant gene is lethal (i.e., produces a phenotype that dies before reproduction or causes sterility). In fact, when this takes place, the average relative decrease in fitness of all heterozygotes (s) is exactly the penetrance value K. When this takes place, one knows also that equivalently none of the direct ancestors of the individual was affected.

When there is no information about the ancestors of the individual, the formula for an expression for P(het) that encompasses both situations 1 and 2 is

$$P(\text{het}) = 2\mu(1-K)/s.$$

When there is information about the normality of both parents of the individual the formula takes the form

$$\begin{aligned} P(\text{het}) &= 2\mu(1-K) + 2\mu(1-K)^2\,(w^0 + w^1 + w^2 + \ldots) \\ &= 2\mu(1-K) + 2\mu(1-K)^2/s. \end{aligned}$$

When there is information about the normality of both parents and all four grandparents the formula becomes

$$\begin{aligned} P(\text{het}) &= 2\mu(1-K) + 2\mu(1-K)^2 \\ &\quad + 2\mu(1-K)^3(w^0 + w^1 + w^2 + \ldots) \\ &= 2\mu(1-K) + 2\mu(1-K)^2 + 2\mu(1-K)^3/s, \end{aligned}$$

and so on, so that when there is information about the normality of all direct ancestors over the first n generations the formula becomes

$$\begin{aligned} P(\text{het}) &= 2\mu(1-K) + 2\mu(1-K)^2 + \ldots + 2\mu(1-K)^n \\ &\quad + 2\mu(1-K)^{n+1}\,(w^0 + w^1 + w^2 + \ldots) \\ &= 2\mu(1-K)\,\{[1-(1-K)^n]/K + (1-K)^n/s\}. \end{aligned}$$

When n = 0,

$$P(\text{het}) = 2\mu(1-K)\,[(1-1)/K + 1/s] = 2\mu(1-K)/s;$$

when n tends to infinity,

$$P(het) = 2\mu(1 - K)\,[(1 - 0)/K + 0/s] = 2\mu(1 - K)/K,$$

as expected.

The formula shown above can be rewritten as

$$P(het) = 2\mu(1 - K)/K.[1 + (K - s)\,(1 - K)^n/s],$$

showing that, if we consider the situations in which the penetrance values are high (as it usually happens, being of the order of 0.9 or more and certainly always larger than 0.5), as n increases $(1–K)^n$ tends to zero and the above expression tends rapidly to the form $P(het) = 2\mu(1–K)/K$. If the relative decrease in fitness s is high and of the order of K, the latter expression becomes even more likely.

The result just obtained is an important formulation because it encompasses two extreme situations studied with some detail in the literature.

A really generalized formula is not possible in simple analytic form, because it will depend on different numbers and positions of direct ascendants falling into three categories: normal ascendants with full information about the normality of their direct ancestors, normal ascendants without any information about the normality of their direct ancestors, and direct ancestors about whose normality nothing is known. To illustrate the point, let us consider the probability of heterozygosis of individual E in Fig. 2, where individuals A, B, C and E are normal but nothing is known about individual D nor all the ancestors of B. Individual E, whose probability of heterozygosis we want to determine, can be a heterozygote because (1) he or she is the result of a nonpenetrant fresh mutation, with probability

$$2\mu(1 - K) = P_0;$$

or (2) the gene was transmitted to him or her by A, with probability

$$2\mu(1 - K)/K.[(1 - K)/2]^2 = P_1.\Theta^2, \text{ where } \Theta = (1 - K)/2;$$

or (3) the gene was transmitted to him or her by B, with probability

$$2\mu(1 - K)/s.[(1 - K)/2]^2 = P_2.\Theta^2;$$

or (4) the gene was transmitted to him or her by D, about whom nothing is known, with probability

$$\begin{aligned} &2\mu K/s \,.\, w' \,.\, [(1 - K)/2] + 2\mu(1 - K)/s \,.\, 1 \,.\, [(1 - K)/2] \\ &\quad = 2\mu(1 - K + Kw')/s \,.\, [(1 - K)/2] \\ &\quad = 2\mu(1 - Ks')/s \,.\, [(1 - K)/2] \\ &\quad = 2\mu(1 - s)/s \,.\, [(1 - K)/2] \\ &\quad = P_3.\Theta; \end{aligned}$$

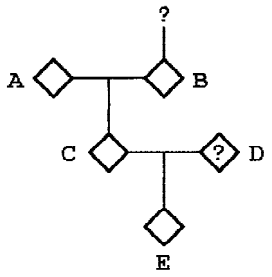

Fig. 2. Nothing is known about individual D and all the ancestors of B; B and D are direct ancestors of E, which heterozygosis probability is going to be determined.

or, finally, (5) the gene was transmitted to him or her by C, in whom the gene originated through a fresh mutation (we have already considered the case in which the gene gets to E from A or B through C), with probability

$$2\mu(1 - K) \,.\, [(1 - K)/2] = P_0.\Theta;$$

therefore, the final probability of heterozygosis for E is

$$\begin{aligned} P(E = het) &= 2\mu(1 - K) \,.\, \{1 + [(1 - K)/2]^2 \,.\, (1/K + 1/s) \\ &\quad + [(1 - K)/2 + (1 - s)/2s]\} \\ &= P_0 + (P_1 + P_2)\Theta^2 + (P_3 + P_0)\Theta. \end{aligned}$$

The calculation of the probability of heterozygosis conditional to the information structure of a genealogy is easily and readily obtained for any other possible situation, five of which are depicted on Fig. 3; for the genealogies shown, the probabilities of heterozygosis for individual E are respectively:

a) $P(het) = P_0 + (P_2 + P_3)\Theta$

b) $P(het) = P_0 + 2[P_0 + (P_2 + P_3)\Theta]\Theta$

c) $P(het) = P_0 + (P_1 + P_3)\Theta$

d) $P(het) = P_0 + (P_1 + P_2)\Theta$

e) $P(het) = P_0 + [2P_0 + (P_1 + P_2 + 2P_3)\Theta]\Theta,$

where, as defined above, $P_0 = 2\mu(1 - K)$, $P_1 = 2\mu(1 - K)/K$, $P_2 = 2\mu(1 - K)/s$, $P_3 = 2\mu(1 - s)/s$, and $\Theta = (1 - K)/2$.

Probability of Heterozygosis for a Couple with an Isolated Affected Descendant

The occurrence of a heterozygote can be explained by one of two mutually exclusive events: (a) the gene is the result of a new mutation occurring in one of the gametes that gave rise to him or her (probability 2μ); (b) one of his or her parents is heterozygous [probability $4\mu(1–K)/K$, using the situation in which there is information about all the direct ancestors and all were known to be normal] and transmitted the gene to him

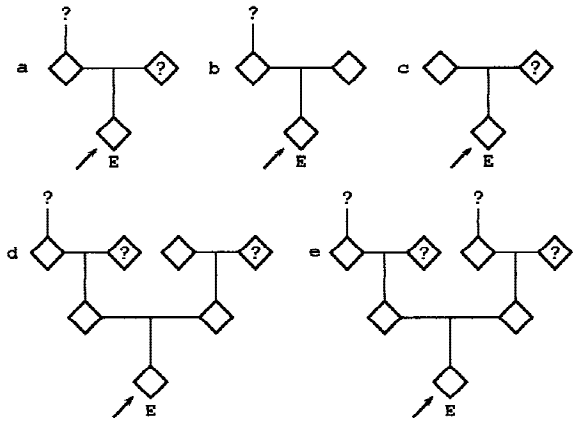

Fig. 3. Pedigrees used in examples of calculation of heterozygosity probability for individual E. The question marks indicate that there is no available information about one or more persons or their direct ancestors.

or her (probability 1/2), the final probability figure being $2\mu(1-K)/K$.

Normalizing these two probabilities gives the probability of heterozygosis for the parents as:

$$P(A \text{ or } B = het) = [2\mu(1-K)/K]/[2\mu(1-K)/K + 2\mu] = 1 - K,$$

the probability of heterozygosity for each parent being

$$P(A = het) = P(B = het) = P(A \text{ or } B = het)/2 = (1-K)/2.$$

The quantity just derived $[(1-K)/2 = \Theta]$ is the conditional probability $P(D = het \mid E = het)$ of heterozygosis for an individual D, given that his or her child (E) is a heterozygote. Using this quantity, the probability of heterozygosis for any of the individuals in the genealogy of Fig. 4 is determined as:

$$\begin{aligned} P(E = het) &= P(F = het) \,.\, P(E = het \mid F = het) \\ &= 1 \,.\, (1-K)/2 = (1-K)/2 = \Theta \\ P(D = het) &= P(E = het) \,.\, P(D = het \mid E = het) \\ &= [(1-K)/2]^2 = \Theta^2 \\ P(C = het) &= P(D = het) \,.\, P(C = het \mid D = het) \\ &= [(1-K/2]^3 = \Theta^3 \\ P(A \text{ or } B = het) &= P(C = het) \,.\, P(A = het \mid C = het) \\ &\quad + P(C = het) \,.\, P(B = het \mid C = het) \\ &= [(1-K)/2]^3\,(1-K) = 2[(1-K)/2]^4 \\ &= 2\Theta^4. \end{aligned}$$

If there are n_3 individuals (one per generation), descendants of the couple [A,B] down to the affected case inclusive, the probability of heterozygosis for [A,B] is given by

$$P(A \text{ or } B = het \mid n_3) = 2[(1-K)/2]^{n3} = 2\Theta^{n3}.$$

When there is no information about the ascendants of either A or B, the probability of heterozygosis for the parents of a known heterozygote is obtained now by normalizing the probabilities $2\mu(1-K)/s$ and 2μ, so that $P'(A \text{ or } B = het) = (1-K)/(1-K+s)$ and $P'(A = het) = P'(B = het) = (1-K)/[2(1-K+s)]$. For all other individuals in Fig. 4, the conditional probability $[(1-K)/2]$ of being a heterozygote given that a son or a daughter is a heterozygote is valid. Therefore, if there are n_3 individuals (one per generation) descendants of the couple [A,B] down to the affected case inclusive, the probability of heterozygosis for [A,B] is given by

$$P'(A \text{ or } B = het \mid n_3) = 2\,[(1-K)/2]^{n3}/(1-K+s).$$

Other expressions for the probability of heterozygosis for a couple given that they have an isolated affected descendant are easily obtained when the level of information about the ascendants of both A and B varies between the two extreme cases just considered.

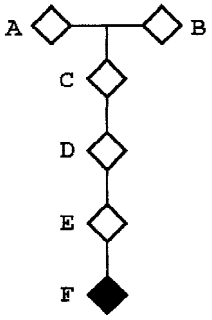

Fig. 4. Pedigree illustrating the situation in which a couple (A, B) has an isolated affected descendant (F).

Probability of Heterozygosity for an Individual, Descendant of an Individual Whose Heterozygosity Probability is Known

If a normal individual belonging to the nth generation (Fig. 5) has a probability P_n of being heterozygote, the probability that a normal child born to this person is also a heterozygote (P_{n+1}) is obtained easily by applying Bayes theorem (see Table I), so that $P_{n+1} = P_n(1-K)/(2-P_nK)$, which is the first order fractional difference equation $P_{n+1} = [a+bP_n]/[c+dP_n]$, with $a = 0$, $b = 1-K$, $c = 2$, and $d = -K$. Its general solution is given by

$$P_n = [(b-r_1)(dP_0 + r_2 - b)r_2^n + (r_2 - b)(dP_0 + r_1 - b)r_1^n]/[d(dP_0 + r_2 - b)r_2^n - d(dP_0 + r_1 - b)r_1^n],$$

where $r_1 = (b + c + D^{1/2})/2 = 1 - K$, $r_2 = (b + c - D^{1/2})/2 = 2$,

$D = (b-c)^2 + 4ad = (-1-K)^2$, and $P_0 = P(A \text{ or } B = het)$.

Taking into account the elements shown in Fig. 5, this formula can be rewritten as

$$\begin{aligned} P(C = het \mid n_1) &= P_0(1+K)\,(1-K/2)^{n1}/\{1 + K - KP_0 \\ &\quad [1-(1-K/2)^{n1}]\} \\ &= P_0\,(1+K)\Theta^{n1}/[1 + K - KP_0\,(1-\Theta^{n1})], \end{aligned}$$

where, as before, $\Theta = (1-K)/2$.

Probability of Heterozygosis for an Individual With Normal Descendants

The probabilities of occurrence of one child, one child and one grandchild, etc. (one descendant per generation, all normal) are always 1 if C (Fig. 1) is a homozygote and has the following values $P_1, P_2, \ldots, P_{n_2}$ if C is a heterozygote:

$$\begin{aligned} P_1 &= 1/2 + (1-K)/2 = 1/2 + \Theta \\ P_2 &= 1/2 + \Theta(1/2 + \Theta) \\ &= 1/2 \cdot (1 + \Theta) + \Theta^2 \\ P_3 &= 1/2 + \Theta\,[1/2 + \Theta(1/2 + \Theta)] \\ &= 1/2 \cdot (1 + \Theta + \Theta^2) + \Theta^3 \\ P_4 &= 1/2 + \Theta\{1/2 + \Theta[1/2 + \Theta(1/2 + \Theta)]\} \\ &= 1/2 \cdot (1 + \Theta + \Theta^2 + \Theta^3) + \Theta^4 \\ &\;\;\vdots \\ P_{n_2} &= 1/2 \cdot (1 + \Theta + \Theta + \ldots + \Theta^{n2-1}) + \Theta^{n2} \\ &= 1/2 \cdot [(1-\Theta^{n2})/(1-\Theta)] + \Theta^{n2} = (1 + K\Theta^{n2})/(1+K), \end{aligned}$$

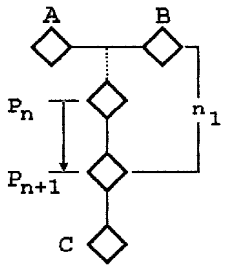

Fig. 5. Pedigree illustrating the situation in which individual C descends from a direct ancestor (A or B), which heterozygosis probability is known.

TABLE I. Probabilities for C of Heterozygosis and Homozygosis

	Heterozygosis		Homozygosis
Prior	$P_n/2$		$1 - P_n/2$
Conditional (to be normal)	$1 - K$		1
Joint probability	$P_n(1 - K)$	:	$2 - P_n$

where $\Theta = (1 - K)/2$ and n_2 is the number of direct descendants (1 by generation). So, given that C has had n_2 direct descendants, the conditional probabilities of being a non-penetrant heterozygote or a normal homozygote are in the ratios

$$(1 + K\Theta^{n2})/(1 + K):1.$$

If the prior probability of heterozygosis of C is P_h, then the probability of heterozygosis for C, given that he or she has n_2 direct normal descendants, is

$$P(C = het \mid n_2) = P_h \,.\, P_{n_2}/(P_h \,.\, P_{n_2} + 1 - P_h).$$

Generalization

We consider the general situation presented in Fig. 1.

Setting $P_0 = P(A \text{ or } B\text{-het} \mid n_3)$ we obtain the probabilities of C for heterozygosis and homozygosis shown in Table II, where the quantities in line (1) are the combined probabilities of occurrence of n_3 individuals (one per generation) between the couple [A,B] and the affected individual inclusive ($P_0 = 2\Theta^{n_3}$) and of n_1 direct ascendants of the propositus up to the couple [A,B] inclusive; and the quantities in line (2) are the conditional probabilities of occurrence of n_2 normal descendants of C. The expression at left of line (1) was imported directly from the end of the section before the last; the expression shown at right is its mutual complement. The ratios shown on line (2) were taken directly from last section above. Replacing P_0 with $2\Theta^{n_3}$ we obtain:

$$(1)\ \ P_0\,(1 + K)\Theta^{n1} = 2\,(1 + K)\Theta^{n3+n1}:1 + K - P_0\,(K + \Theta^{n1})$$
$$= 1 + K - 2\Theta^{n3}\,(K + \Theta^{n1})$$
$$(2)\qquad (1 + K\Theta^{n2})/(1 + K):1$$

Therefore, the joint probabilities are

$$2\Theta^{n3+n1}\,(1 + K\Theta^{n2}):1 + K - 2\Theta^{n3}\,(K + \Theta^{n1}),$$

so that

$$P(C = het \mid n_1,n_2,n_3) = 2\Theta^{n3+n1}(1 + K\Theta^{n2})/$$
$$[1 + K - 2K\Theta^{n3}(1 - \Theta^{n1+n2})].$$

By introducing the logical operator δn_3 ($\delta n_3 = 1$ if $n_3 = 0$, $\delta n_3 = 0$ if $n_3 \neq 0$), the formula includes the case $n_3 = 0$ (A or B affected):

$$P(C = het \mid n_1,n_2,n_3) = 2\Theta^{n3+n1}\,(1 + K\Theta^{n2})/$$
$$[(1 + K)\,(1 + \delta_{n_3})$$
$$- 2K\Theta^{n3}\,(1 - \Theta^{n1+n2})].$$

The latter expression reduces to

$$P(het \mid n_1,n_2,n_3) = 2\Theta^{n3+n1}\,(1 + K\Theta^{n2})/[1 + K - 2K\Theta^{n3}$$
$$(1 - \Theta^{n1+n2})]$$

when $n_3 \neq 0$ (so that $\delta n_3 = 0$); and to

$$P(het \mid n_1,n_2) = \Theta^{n1}\,(1 + K\Theta^{n2})/(1 + K\Theta^{n1+n2})$$

when $n_3 = 0$ (so that $\delta n_3 = 1$).

The generalization just derived allows the calculation of the probability of heterozygosity for any relative of an affected case, six situations of which are shown in Fig. 6. The formula above reduces to the following values for examples (a)–(f):

(a) $P(A \text{ or } B = het \mid n_1 = 0,n_2,n_3 = 0)$
$= (1 + K\Theta^{n2})/[1 + K - K(1 - \Theta^{n2})]$
$= (1 + K\Theta^{n2})/(1 + K\Theta^{n2}) = 1.$

(b) $P(C = het \mid n_1 = 1,n_2 = 0,n_3 = 0) = \Theta(1 + K)/$
$[1 + K - K(1 - \Theta)] = (1 - K)/(2 - K).$

(c) $P(A \text{ or } B = het \mid n_1 = 0,n_2 = 0,n_3 = 1) = 2\Theta\,(1 + K)/$
$[1 + K - 2K\Theta(1 - 1)] = 1 - K.$

(d) $P(C = het \mid n_1 = 1,n_2 = 1,n_3 = 1)$
$= 2\Theta^2 \,.\, (1 + K\Theta)/[1 + K - 2K\Theta(1 - \Theta^2)]$
$= [(1 - K)^3 + (1 - K)^2]/\,[(1 - K)^3$
$+ (1 - K)^2 + 2(1 - K) + 4K].$

(e) $P(A \text{ or } B = het \mid n_1 = 0,n_2 = 0,n_3 = 2)$
$= 2\Theta^2.\,(1 + K)/[1 + K - 2\Theta^2.$
$(1 - 1)] = (1 - K)^2/2.$

(f) $P(C = het \mid n_1 = 2,\ n_2 = 0,n_3 = 2)$
$= 2\Theta^4 \,.\, (1 + K)/[1 + K - 2K\Theta^2 \,.\, (1 - \Theta^2)]$
$= (1 - K)^4/[8 - K(1 - K)^2 \,.\, (3 - K)].$

In all formulae just derived, it was assumed that there is information about the normality of all ascendants of A and B and we started by putting $P_0 = P(A \text{ or } B = het \mid n_3) = 2\Theta^{n_3}$.

Other formulae are easily obtained by replacing this latter value for the appropriate expressions that correspond to the levels of information we have about the ascendants of both A and B. When this is taken into account, our formulae are valid for all particular cases thus far studied in the literature.

RECURRENCE RISKS FOR RELATIVES OF ISOLATED CASES

Multiplying the probability of heterozygosis $P(C = het \mid n_3, n_1, n_2)$ by K/2 we obtain the recurrence risk of the disease in the offspring of any individual. For instance, in the common case of a couple with a single affected child, the risk of a new affected child is given by

$$R1 = K(1 - K)/2$$

TABLE II. Probabilities for C of Heterozygosis and Homozygosis

Heterozygosis		Homozygosis
(1) $P_0(1 + K)\Theta^{n1}/[(1 + K) - KP_0\,(1 - \Theta^{n1})]$	:	$1 - P_0(1 + K)\,\Theta^{n1}/[(1 + K) - KP_0\,(1 - \Theta^{n1})]$
(2) $(1 + K\Theta^{n2})/(1 + K)$	:	1

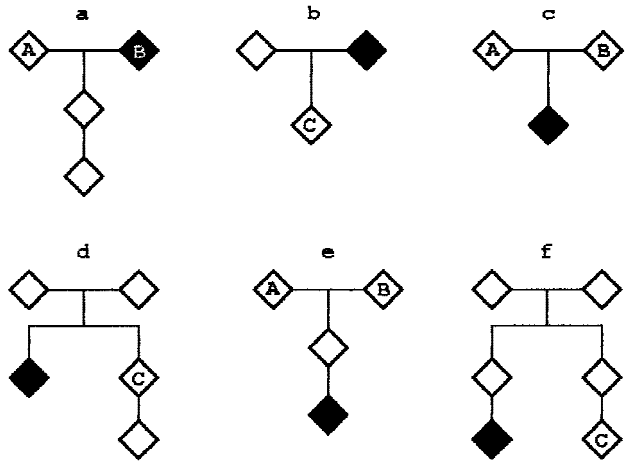

Fig. 6. Pedigrees used in six examples of heterozygosis probability calculations by means of the generalized formula.

which corresponds to the case in which all the direct ancestors of the affected individual were known to be normal; and

$$R2 = K(1 - K)/2(1 - K + s)$$

which corresponds to the case in which there is no information at all about any of the direct ancestors of the affected individual.

The two expressions for R_1 and R_2 shown previously were first derived by Frota-Pessoa et al. [1976] and Stevenson and Davison [1970], respectively. The results of Stevenson and Davison [1970] also were obtained by Aylsworth and Kirkman [1979], Pauli and Motulsky [1981] and Emery [1986].

The formulae just presented can be adapted to include phenocopies or somatic mutations, situations very frequent in dominant conditions. We shall illustrate this point with the following example [Frota-Pessoa et al., 1976]: bilateral retinoblastoma is the result of an autosomal dominant gene with 80% penetrance. The recurrence risk for a sib of an isolated case is $R_1 = K(1–K)/2 = 0.08$ or 8%. No direct estimate of penetrance is available or appropriate for the unilateral disorder, which is heterogeneous. About 80% of the isolated cases of unilateral retinoblastoma are due to somatic mutations that behave as phenocopies, since they are not transmitted. The remaining 20% of the cases are considered to be due to the same gene producing the bilateral cases. Therefore, the risk of recurrence is $R = 0.2 \times R_1 = 0.016$ or 1.6%. The empiric recurrence risk is obtained from two studies based on 1,846 families [Fuhrmann and Vogel, 1969; Vogel, 1967] and is 1.25%. The calculated risk of 1.6% agrees very well with this figure (chi-square = 1.47; 1 d.f.; $P > 0.10$).

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