The variation of recurrence risks with penetrance for isolated cases of autosomal dominant conditions

O. Frota-Pessoa, P. A. Otto, and J. R. Olivares Plaza

WHEN only one person in a family is affected by a known autosomal dominant disease with incomplete penetrance, a propositus' sib to be born has a risk of being affected which depends on the penetrance in two ways. Indeed, the greater the penetrance the greater the probability of the propositus being due to a new mutation and therefore the smaller the probability that one of the parents is a normal carrier of the gene. On the other hand, the greater the penetrance, the greater the probability that the sib to be born does get affected, should he inherit the gene.

In the present paper the relationship between the penetrance and the recurrence risk for such a case is determined.

The prior probability that the propositus is the product of a new mutation is \( P' = 2\mu K \), where \( K \) is the penetrance of the gene and \( \mu \) is its mutation rate (2\( \mu \) is the probability of occurrence of a new mutation in any of the two gametes originating the propositus). On the other hand, the prior probability \( P'' \) that the propositus has inherited the gene is the sum of a series of partial probabilities, \( p_1, p_2, p_3, \ldots \), such as those listed below:

1. The probability that a) the mutation has occurred in any one of the four gametes originating the propositus' parents, b) was not penetrant, c) was transmitted to the propositus, and d) was then penetrant is the product \( p_1 = 4\mu \cdot (1 - K) \cdot \frac{1}{2} \cdot (1 - K) = 2\mu K(1 - K) \).
2. The probability that a) the mutation had occurred in any one of the eight chromosomes of the propositus' grandparents, b) was not penetrant, c) was transmitted to one of the propositus' parents, d) was again not penetrant, e) was transmitted to the propositus, and f) was then penetrant is the product \( p_2 = 8\mu \cdot (1 - K) \cdot \frac{1}{2} \cdot (1 - K) \).

The sum of this series of probabilities is \( P'' = p_1 + p_2 + p_3 + \ldots = 2\mu K(1 - K) + 2\mu K(1 - K)^2 + 2\mu K(1 - K)^3 + \ldots = 2\mu K(1 - K)^2 \).

Normalizing \( P' \) and \( P'' \), the probability for the propositus being the product of a fresh mutation becomes

\[
P_n = \frac{P'}{P' + P''} = K
\]

and the probability for the propositus having inherited the gene is \( P_h = 1 - P_n = 1 - K \).

In cases of a new mutation, the recurrence risk is negligible (although considerably greater than the mutation rate in the population, since some of the parents may be germinal mosaics). This simplifies the estimation of the risk of recurrence \( R \) for the sib to be born, which becomes the product of three probabilities: a) the probability \( P_h \) of the case being inherited; b) the probability \( \frac{1}{2} \) of the gene being transmitted to the sib; and c) the probability \( K \) of the gene being penetrant in the sib.

Therefore:

\[
R = \frac{P_h K}{2} = K(1 - K)
\]

Figure 1 shows the values of the recurrence risk for different values of the penetrance. The maximum possible risk is \( \frac{1}{2} \) when \( K = 1 - K = \frac{1}{2} \).

Numerical example: Bilateral retinoblastoma is the result of an autosomal dominant gene with 80 percent penetrance. What is the recurrence risk in the case of a propositus with this condition? Applying the above formula it is \( R = 8 \) percent. No direct estimate of penetrance is available or appropriate for the unilateral disease, which is probably heterogeneous. It is believed that 80 percent of the isolated cases of unilateral retinoblastoma are phenocopies, and the remaining 20 percent of the cases are considered due to the same gene producing the bilateral cases. Therefore, the risk of recurrence if the propositus is an isolated unilateral case is

\[
R_i = 0.2R = 1.6 \text{ percent.}
\]

This figure agrees very well with the empirical risk of recurrence of about 1.25 percent (average figure obtained from two studies based on 1,346 families [see Fuhrmann and Vogel]).

An alternative method for solving this problem was presented by Stevenson and Davison; it has the disadvantage of depending not only on an estimate of the penetrance, but also on an estimate of the selection coefficient against the condition. Besides, in their method it has to be assumed that gene frequencies are at equilibrium.

Summary

The relationship between the penetrance and the recurrence risk for sibs of isolated cases of autosomal dominant conditions with incomplete penetrance is presented.

Literature Cited