

# Genetic counselling of consanguineous families<sup>1</sup>

## Use of Smith's method to calculate recurrence risks in multifactorial inheritance in consanguineous matings

CATHERINE BONAÏTI

From Groupe de Recherches de Génétique Epidémiologique, INSERM, Château de Longchamp, Bois de Boulogne, 75016 Paris, France

**SUMMARY** A modification of Smith's method is described for deriving recurrence risks for multifactorial conditions when parents are related. Using cleft palate as an example, the possible increased risks caused by consanguinity are discussed.

Smith (1971) described a method for deriving the recurrence risk of conditions with multifactorial inheritance in non-consanguineous families. In our paper the method is extended to those cases in which the parents are related.

Some results are presented of specific examples in order to give some idea of the increased risk caused by consanguinity in some of the simple cases likely to be met in genetic counselling.

### Methods

The multifactorial model assumes an underlying continuous liability to a disease, the liability being the sum of many genetic and environmental effects, and thus being normally distributed. The disease becomes manifest if an individual's liability exceeds a critical threshold level (Falconer, 1965).

This model has only two parameters, namely the population frequency ( $f$ ) and the heritability of liability ( $h^2$ ) which is the ratio of the genetic variance (supposed to be entirely additive) to the total phenotypic variance.

Wright (1951) showed that if the contributions of genes and environmental factors are additive, the effect of an inbreeding coefficient  $F$  is to increase the genetic variance by a factor  $1 + F$  and the phenotypic variance by a factor  $1 + h^2F$ .

### SMITH'S METHOD TO DERIVE RECURRENCE RISKS

The original method proposed by Smith is explained in his paper (1971). The method depends on partitioning the genetic distribution of liability into a number of classes, estimating the risk to individuals in each class (and the risks to their relatives) and numerically integrating over all classes.

Assume a standardised normal phenotypic distribution of liability. The corresponding genetic distribution (variance:  $h^2$ ) can be divided into an ordered series of genetic classes, each with a known frequency.

For a sibship family, if the father belongs to a genetic class  $g_i$  (frequency  $f_i$ ) and the mother to a genetic class  $g_j$  (frequency  $f_j$ ), the mean genetic value of the offspring is then  $(g_i + g_j)/2$ . The residual variances are  $1 - h^2$  for the parents and  $1 - h^2/2$  for the offspring. For each of them the deviation from the threshold and thus the proportion of a class exceeding the threshold can be derived giving  $P_i$  and  $P_j$  for the father and mother and  $P_{ij}$  for the offspring.

For example, in a sibship with a normal father, an affected mother and with  $s$  children,  $r$  of whom are affected, the probability of the family for the  $i$  and  $j$  parental classes is:

$$Q_{ij} = f_i f_j (1 - P_i) P_j (1 - P_{ij})^{s-r} P_{ij}^r$$

The recurrence risk can then be found by summing over all the possible combinations of the  $i$  and  $j$  parental classes, that is:

$$R = \frac{\sum_{ij} Q_{ij} P_{ij}}{\sum_{ij} Q_{ij}}$$

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The number of genetic classes chosen by Smith was 21, which gives an accuracy of 0.1% in calculating the risks.

The method is extended to second and third degree relatives by treating them through their genetic relationship with the father or the mother, which provides good approximate risks. Thus, if there are  $n$  relatives other than parents, and if  $D_k$  is the probability of the disease status of the relative  $k$  ( $D_k = P_k$  if  $k$  is affected and  $1 - P_k$  if unaffected) for the above  $i$  and  $j$  parental classes, the probability of the family for this combination of classes is:

$$Q_{ij} = f_i f_j (1 - P_i) P_j \prod_{k=1}^n D_k.$$

The method has been used to derive a set of tables of recurrence risks for common congenital malformations (Bonaïti-Pellié and Smith, 1974; Bonaïti-Pellié et al., 1976).

**EXTENSION TO CASE OF RELATED PARENTS**

In Smith's method it is assumed that the genetic values of the parents  $g_i$  and  $g_j$  are independent. How can the method be modified if the parents are related with a coefficient of relationship  $r$ ?<sup>1</sup>

The first consequence of such a relationship is that the genetic distribution of liability of the mother depends on the genetic value of the father (or inversely). If the father belongs to the genetic class  $g_i$ , the mean genetic value of the mother is  $rg_i$  and the residual genetic variance =  $h^2(1 - r^2)$ .

<sup>1</sup>The coefficient of relationship between two individuals is the correlation of additive genetic values between them. The relation between the coefficient of relationship  $r$  between two individuals and the coefficient of inbreeding  $F$  of their progeny is  $r = 2F$  (Falconer, 1960). For example, in the case of first cousins,  $F = 1/16$  and  $r = 1/8$ .

The second consequence is that relatives (other than offspring) are related to both parents instead of one and thus must be treated through their genetic relationship with the father and the mother. This problem can be solved by the mean of multiple regression.

Let  $r'$  and  $r''$  be the coefficients of relationship between a relative and the father and the mother respectively, then the mean genetic value of the relative  $g_k$  is:

$$g_k = b'_k g_i + b''_k g_j$$

where  $b'_k$  and  $b''_k$  are the coefficients of multiple regression<sup>2</sup>, and the variance  $V_k$ :

$$V_k = h^2(b'_k r' + b''_k r'')$$

and the residual variance  $1 - V_k$ .

As regards the offspring, the mean genetic value is not changed and remains  $(g_i + g_j)/2$ , whatever the relationship between the parents; nor does the residual variance which remains  $1 - h^2/2$ .<sup>2</sup> Thus, the calculation of  $P_{ij}$  is the same as in Smith's method and the increase of risk results only from the relation between the genetic values of the parents, which is the cause of the increase of the phenotypic variance mentioned above.

**Examples and discussion**

Since it is not possible to present the possibilities for all parameters and family histories, the particular example of cleft palate is considered and the risks are given in the Table for some coefficients of inbreeding in some simple family histories.

<sup>2</sup> See Appendix 1.

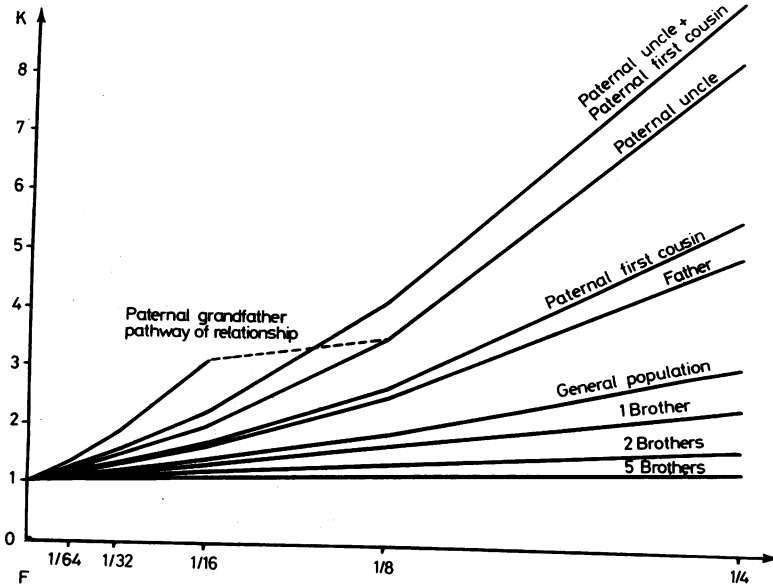


Fig. 1 Relative increase in recurrence risk (K) for cleft palate for various coefficients of inbreeding (F) and various affected relatives.

Table Recurrence risks (%) for progeny when various relatives are affected with cleft palate and parents are related

Affected relatives	$F = 0$	$F = 1/64$	$F = 1/32$	$F = 1/16$	$F = 1/8$	$F = 1/4$
1 brother	3.2	3.4	3.7	3.7	5.2	7.4
2 brothers	11.1	11.2	11.7	11.7	14.7	17.9
5 brothers	31.7	31.9	32.3	32.3	35.0	37.9
Father	3.7	4.1	4.7	4.7	9.1	18.1
Paternal uncle	0.5	0.6	0.7	0.7	1.8	4.2
Paternal first cousin	0.2	0.2	0.2	0.2	0.5	1.0
Paternal uncle + 1st cousin	0.9	1.2	1.5	1.5	3.9	8.8
Paternal grandfather (pathway of relationship)	0.5	0.7	0.9	0.9	1.8	4.2

Parameters used (%): (Briard *et al.*, 1974, and more recent data). Frequency, males: 0.03, females: 0.06, both sexes: 0.05. Heritability of liability: 94

The relative increase in risk,  $K$  (ratio of the risk when  $F > 0$  to the risk when  $F = 0$ ), is represented for all these cases in Fig. 1. Note that the risk and relative increase for sib matings are given for maximal possible values.

Figure 1 shows that the relative increase may be somewhat different depending on the type of relative affected. In the case of sibs, the relative increase diminishes as the number of affected sibs rises, but, of course, the risk itself increases. This is because children are always related to both parents and the increase of risk is the result only of the increased variance. The more sibs affected the greater the genotypic values of the parents and the smaller the effect of inbreeding. (At a 50% risk there would be no further increase; when the risk exceeds 50% the effect of inbreeding would be to decrease the risk.)

When affected relatives are on one side of the pedigree, paternal uncle for example, the fact that he is also related to the mother leads to a higher relative increase as in the case of sibs and this increase rises with the number of such affected relatives.

The highest relative increase is obtained when a relative who is on the pathway of relationship between the parents is affected. This case is illustrated by the paternal grandfather when the coefficient of inbreeding does not exceed 1/16 (afterwards he becomes a common ancestor) (Fig. 1).

An example of maximal risk is given by the pedigrees in Fig. 2 where several paternal relatives are affected with cleft palate. When the parents are not related, the risk for the unborn child is only 5%, which is not very high, but rises to 20% when the parents are

first cousins. Of course, this represents an extreme case, since this type of family is uncommon for a multifactorial disease and is unlikely to be met in genetic counselling. Usually, the increase of risk is not very high (between 1 and 3 when the parents are first cousins). So, when counselling patients who have a relative with a multifactorial condition, consanguinity is not a strong argument against marriage or procreation. However, in some instances it seems reasonable to calculate the exact risk to be certain that it does not become too high, as shown in this particular example.

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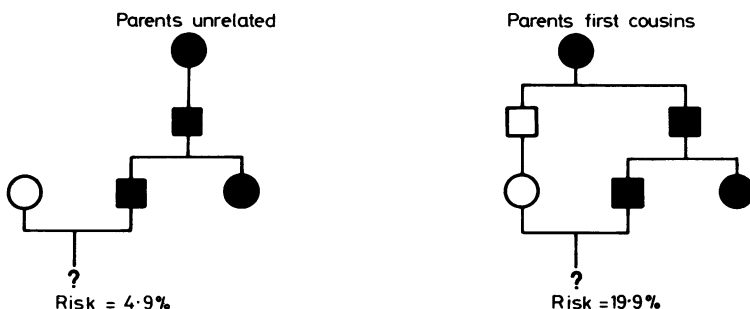


Fig. 2 Recurrence risk in a family having several relatives with cleft palate.

### Appendix 1

This appendix gives a regression equation giving the mean genetic value  $g_k$  and the variance  $V_k$  of a relative of the child at risk.

Let  $X$ ,  $Y$ , and  $Z$  be the random variables of the genetic values of the father, the mother, and the relative, respectively; the mean genetic value of the relative  $k$  is given by the equation of multiple regression.

$$g_k = E(Z/(X = g_i \text{ and } Y = g_j)) =$$

$$\begin{bmatrix} \text{cov } XZ & \text{cov } YZ \end{bmatrix} \begin{bmatrix} \text{var } X & \text{cov } XY \\ \text{cov } XY & \text{var } Y \end{bmatrix}^{-1} \begin{bmatrix} g_i \\ g_j \end{bmatrix}$$

and

$$V_k =$$

$$\begin{bmatrix} \text{cov } XZ & \text{cov } YZ \end{bmatrix} \begin{bmatrix} \text{var } X & \text{cov } XY \\ \text{cov } XY & \text{var } Y \end{bmatrix}^{-1} \begin{bmatrix} \text{cov } XZ \\ \text{cov } YZ \end{bmatrix}$$

Let  $r'$  and  $r''$  be the coefficients of relationship between the relative and the father and the mother, respectively, and  $r$  the coefficient of relationship between the parents, thus:

$$\text{cov } XZ = r'h^2$$

$$\text{cov } YZ = r''h^2$$

$$\text{cov } XY = rh^2$$

by definition of the coefficient of relationship, and:

$$\text{var } X = h^2$$

$$\text{var } Y = h^2$$

The coefficients of regression  $b'_k$  and  $b''_k$  are given by the product of the first two matrices and the regression equation can be written:

$$g_k = b'_k g_i + b''_k g_j$$

and

$$V_k = b'^2_k r'^2 h^2 + b''^2_k r''^2 h^2 = h^2(b'^2_k r'^2 + b''^2_k r''^2)$$

When the relative is an offspring,  $Z = (X + Y)/2$  and  $g_k = (g_i + g_j)/2$

$$V_k = \text{var} \left( \frac{X + Y}{2} \right) = \frac{1}{4} \text{var } X + \frac{1}{4} \text{var } Y + \frac{1}{2} \text{cov}(X, Y)$$

thus

$$V_k = \frac{h^2}{2} + \frac{rh^2}{2}$$

The total variance of a consanguineous individual being increased by a factor  $1 + h^2F$  (or  $1 + h^2r/2$ ), the residual variance is:

$$1 + \frac{h^2r}{2} - \frac{h^2}{2} - \frac{rh^2}{2} = 1 - \frac{h^2}{2}$$

### Appendix 2

Computer programme for deriving recurrence risks for multifactorial inheritance when parents are related.

Smith's original programme (1972) has been simplified; in particular it does not take account of any severity—age class, and assumes that heritability of liability is the same for both sexes. It has been written in 'BASIC' for a Hewlett-Packard 9830 A calculator.

The input information includes the following data:

- Heritability of liability, H
- Frequency of the condition in males : F (1)
- Frequency of the condition in females : F (2)
- Frequency of the condition both sexes : F (3)
- Number of relatives (other than parents) : N
- Disease status of the father : X (1 : affected, 0 : unaffected)
- Disease status of the mother : Y (1 : affected, 0 : unaffected)
- Coefficient of relationship between the parents : B1
- Matrix of relatives : M (N,5), the five columns for each relative being:

1. sex (1 : ♂, 2 : ♀)
2. Disease status (1 : affected, 0 : unaffected)
3. Coefficient of relationship with the father
4. Coefficient of relationship with the mother
5. Type of relative (1 : sib, 0 : not sib).

For example, for one affected brother, one unaffected sister, and one paternal aunt affected the matrix of relatives is (parents first cousins)

$$\begin{matrix} 1, & 1, & 0.5, & 0.5, & 1 \\ 2, & 0, & 0.5, & 0.5, & 1 \\ 2, & 1, & 0.5, & 0.125, & 0 \end{matrix}$$

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Requests for reprints to Dr Catherine Bonaïti, Groupe de Recherches de Génétique Epidémiologique, I.N.S.E.R.M., Château de Longchamp, Bois de Boulogne, 75016 Paris, France.