Risk counselling in autosomal dominant disorders with undetermined penetrance

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SUMMARY A method is presented for estimating the probability of an affected child being born to a clinically unaffected subject who is at risk for having inherited a rare gene for an autosomal dominant disorder of unknown penetrance. The maximal risk is 8.6% for children of persons at 50% risk for having inherited the mutant gene regardless of the true penetrance of the disorder in question. Applications of this maximal risk figure, which should be of benefit in various counselling situations, are summarised.

Genetic counsellors often face situations in which precise risk figures are unavailable. An example of such an occasion is establishing the risk for a clinically affected offspring to be born to an unaffected subject at risk for having inherited a gene for a rare autosomal dominant condition of unknown penetrance. In calculating the worst possible risk for such a subject, we were struck by the relatively low risk values found, regardless of penetrance. Since the derived risks are applicable in various counselling situations, the results appear to be of general interest to genetic counsellors.

The genetic counselling problem

A woman (III.5, fig 1) sought counselling for her risk of having a child with split foot/split hand syndrome (SF/SH), a recognised autosomal dominant disorder with reduced penetrance.¹ Her sister (III.2) and nephew (IV.1) had been previously examined by us and found to have typical SF/SH deformity compatible with the autosomal dominant form. Clinical and radiological examination of the proband and her husband revealed no abnormalities related to SF/SH syndrome. However, a distant relative of the proband (II.12) has a congenital unilateral hand and forearm abnormality including absence of the second, third, and fourth fingers. While this malformation could be coincidental, the infrequency of such a hand defect and its presence in a

FIG 1 Pedigree of the reported family. The proband is indicated with an arrow. + = subjects clearly affected with split foot/split hand syndrome. ? = subjects with hand and arm abnormalities possibly related to split foot/split hand syndrome. A horizontal bar over the pedigree symbol indicates that the subject was personally examined.

kindred with SF/SH syndrome suggest that it may be related to the SF/SH in other family members. In view of the autosomal dominant inheritance and incomplete penetrance of SF/SH syndrome,¹⁻³ it is possible that various clinically unaffected relatives (II.6, I.5, I.7) carried the gene. Calculations based on these assumptions represent the worst possible risk for our consultand having a clinically affected child.

Derivation

Bayesian methods can be used to estimate the risk of an affected child being born to the proband assuming that the upper extremity defect in II.12 was a

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manifestation of SF/SH syndrome. The prior probability that the gene was inherited from II.6, given autosomal dominant inheritance, is 0.5. The conditional probability that having inherited the gene it would remain unexpressed in III.5 is $1-y$ (where y is the penetrance of the gene). The posterior probability (P) that III.5 has inherited the gene, given a normal examination, is:

$$P = \frac{0.5(1-y)}{0.5(1-y) + 0.5} \quad (1)$$

The conditional probability of the child of III.5 being affected is the probability of inheriting the gene multiplied by its penetrance, or $0.5y$. Overall the chance of an affected child being born is the product of these probabilities:

$$P = \frac{0.5(1-y)}{0.5(1-y) + 0.5} \times 0.5y. \quad (2)$$

Algebraic simplification yields:

$$P = \frac{y-y^2}{4-2y}. \quad (3)$$

Evaluating this for various values of y results in the probabilities shown in the table and represented diagrammatically in fig 2. Regardless of the true value of the penetrance (y) for a given condition, the maximal risk of an affected child is approximately 8.6% (at a penetrance of about 0.59). Similar results can be obtained more elegantly by simple calculus, but the algebraic calculations are presented here for ease of presentation and for general comprehensibility.

A more general derivation of the probability P of a child being an affected heterozygote for any value of the prior (Mendelian) probability (R) of heterozygosity in a parent is:

$$P = \frac{R-Ry}{1-Ry} \times 1/2y \quad (4)$$

$$= \frac{R(y-y^2)}{2(1-Ry)}. \quad (5)$$

FIG 2 Curve generated by solving equation (3):

$$P = \frac{y-y^2}{4-2y} \text{ for values of } y \text{ between } 0 \text{ and } 1.0.$$

Penetrance (on the abscissa) is plotted versus the predicted probability of an affected offspring being born to a clinically unaffected subject who is at 50% genetic risk (on the ordinate). The maximum risk is 8.58% when the penetrance (y) is 0.586.

If we denote the complement of R by N (for non-receipt), that is, $N = 1 - R$, then it can be shown that:

$$P_{\max} = (N^{1/2} - N)^2 / 2RN \quad (6)$$

which occurs when the penetrance (y) is $(1 - N^{1/2})/R$.

Then, for example, if the prior probability (R) is 0.25, as would be the risk of heterozygosity of a consultand who was the grandchild of an affected subject and whose parents cannot be examined, the maximal risk for the next generation is 3.59% at a penetrance of 0.536. Various risk values for prior

TABLE Probability of an affected offspring being born to an unaffected subject who is at 50%, 25%, or 12.5% risk of being heterozygous at a locus for a rare autosomal dominant disorder for various values of penetrance (y) in the heterozygote

A priori probability (R) of risk	Penetrance (y)										
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.5	0	0.024*	0.044	0.062	0.075	0.083	0.086	0.081	0.067	0.041	0
0.25	0	0.012	0.021	0.028	0.033	0.036	0.035	0.032	0.025	0.015	0
0.125	0	0.006	0.010	0.014	0.016	0.017	0.016	0.014	0.011	0.006	0

*0.024 = 2.4%, etc.

probabilities of 0.25 and 0.125 are listed in the table. Prior probabilities (R) much higher than 0.5 are rarely, if ever, encountered in autosomal dominant inheritance of rare diseases, but, under such conditions, the maximal risk could be higher than 8.6%.

Discussion

The curve shown in fig 2 is generally applicable in estimating the risk of an affected offspring being born to a subject at an a priori 50% risk for, but not expressing evidence of, any rare autosomal dominant condition. When the penetrance is known, a precise estimate can be given. In the more frequent situation where penetrance is indeterminate, the maximal value of 8.6% may be used. Furthermore, this value may be used in cases such as the one presented here, in which it is not certain whether the proband is at risk for the condition but where 'worst possible scenario' risk counselling seems justified.

This risk estimate is applicable only to conditions in which penetrance is constant regardless of age, such as in autosomal dominant isolated congenital malformations or malformation syndromes or in diseases with age dependent penetrance, where the

proband's age exceeds the age at which constant penetrance is approached. These estimates therefore cannot be used in disorders such as Huntington's disease or polycystic kidney disease in which penetrance becomes maximal late in life.

This estimate of risk has not previously been emphasised as being valuable in counselling for diseases with indeterminate penetrance. Precise figures for penetrance are unavailable for most autosomal dominant conditions. Many dominant disorders manifest at birth appear to have reduced penetrance, for example aplasia cutis congenita with distal limb defects,⁴ vanderWoude syndrome,⁵ ocular colobomata,⁶ and Pfeiffer syndrome.⁷ Others, in which penetrance is incomplete and age dependent, such as progressive diaphyseal dysplasia⁸ and maturity onset diabetes of the young,⁹ may reach maximal penetrance at a relatively early age. In both groups of disorders the estimate of maximal risk given here may be used. Two illustrative examples are given in figs 3 and 4.

A family requested counselling for ocular coloboma/microphthalmia (fig 3). Autosomal dominant coloboma shows a wide range of expression including isolated chorioretinal or irideal coloboma, cystic eye, microphthalmia, and clinical anophthalmia.¹⁰ Subject II.2 (fig 3) had typical iris coloboma, while III.1 had a cystic eye. Given the reduced penetrance in this disease,⁶ the unaffected children (III.2, III.3, III.4), who had completely normal ophthalmological examinations, maximally have an 8.6% risk of each of their offspring being affected.

The second family had progressive diaphyseal dysplasia (Camurati-Engelmann disease) and was seen in our clinic.⁸ The pedigree demonstrates the diminished penetrance of this gene (fig 4): a clearly affected man (IV.1) had an unaffected father (III.2) and paternal grandfather (II.1) in a kindred where these subjects must be carriers of the mutant gene. The risks for affected children being born to six subjects in this kindred (IV.2, IV.3, IV.4, IV.5, IV.6, IV.11) can be predicted using the rule developed in this article. All these persons have a maximum risk

FIG 3 Pedigree of family with dominant ocular coloboma. Patient II.2 has iris colobomata, while subject III.1 has a cystic eye. Bar over the pedigree symbol indicates that the subject was examined, including ophthalmoscopic examination of dilated eyes.

of 8.6% of having children with clinically or radiologically detectable diaphyseal dysplasia.* The risk of clinical disease is indeterminately less than this maximal risk. It would be decreased by the ratio of the two penetrance values (for clinical disease and for radiological manifestation). This ratio is unknown in progressive diaphyseal dysplasia, but is clearly less than one.⁸ The ratio of clinically affected subjects to subjects with radiological evidence of disease is 5/8 in this family.⁸ If this were the true ratio, then the overall risk would be $0.086 \times 5/8$, or about 5½%.

There are some additional dominant disorders in which it is unclear whether penetrance is complete, and some families occasionally seek counselling who have apparent but previously undescribed autosomal dominant disorders with incomplete penetrance. The maximal risk figure of 8.6% for an affected child being born to an unaffected proband at 50% risk for having inherited the gene is applicable for these situations as well.

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*The risk for IV.8 would be lower since he had three clinically and radiologically unaffected children. His actual risk of being a carrier therefore is further reduced.

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Note added in proof

After this manuscript was accepted, an article has come to our attention (Aylesworth AS, Kirkman NH. *Birth Defects* 1979; **XV**, No 5C: 25–38) which details Bayesian calculations for genetic counselling in similar and additional situations involving incomplete penetrance of autosomal dominant disorders.