Calculation of genetic risks in Duchenne muscular dystrophy by geneticists in the United Kingdom

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SUMMARY Pedigrees of Duchenne muscular dystrophy were sent to 32 geneticists in the United Kingdom, asking for their calculations for genetic risks for female relatives. Eighteen participated, of whom only 7 gave correct answers for all pedigrees. The method most used for calculations (the 'Bayesian' method) was most liable to errors in new situations. An alternative, simpler method is presented.

Methods for calculation of genetic risks in lethal X-linked conditions have been given and explained by several workers (Binet *et al.*, 1957; Emery and Morton, 1968; Murphy and Matalik, 1969; Stevenson and Davison, 1970) and are generally thought by clinical geneticists to have been understood. However, in practice, calculations of these risks may be difficult. It was considered to be interesting and instructive to learn to what extent geneticists encountered difficulties in calculations, and to what extent results obtained by them were in agreement. Accordingly, 32 clinical geneticists in the United Kingdom were invited to give the genetic risks for a women in each of 5 pedigrees for Duchenne muscular dystrophy shown in the Fig. They were asked to assume equal mutation rates for the 2 sexes, and also, if they wished, to give the risks assuming that mutation occurred only in males, or only in females. Of the 32 people approached, 24 held appointments as clinical geneticists, and 8 were paediatricians known to be involved in counselling for Duchenne muscular dystrophy.

Results

Of these 32, 18 returned answers. Reasons given by 9 (or their secretaries) who did not participate were that they were out of the country (2), were ill (1), were too busy (2), or were no longer concerned with counselling for Duchenne muscular dystrophy and felt that the

questionnaire was inappropriate (4). Five geneticists did not answer.

The genetic risks provided by the 18 respondents are tabulated in Table 1. Though they had been asked for the 'genetic odds of being a carrier:being normal' only 4 gave their risks in this form. Most gave genetic chances expressed as a fraction and so the results have been presented like this for Table 1. Eleven respondents named the method they used.

Only 5 respondents calculated genetic risks assuming unequal mutation rates, and therefore comparisons will mainly be made between the 18 sets of answers relating to assumed equal mutation rates in the 2 sexes. Most respondents were in agreement with the genetic risks for pedigrees (a) and (b), which had deliberately been made simple. Pedigrees (c), (d), and (e) were more complicated and of the total of 54 (18×3) possible answers, only 27 were 'correct'. Overall, 7 respondents out of the 18 gave entirely 'correct' answers. The reasons for believing these to be the correct answers were the consistencies of risks given by these 7, compared with the variation in answers given by the remaining 11, none of whom agreed with each other; the inclusion in the 7 of those geneticists who had published on the subject of counselling for Duchenne muscular dystrophy; and, most important, the mathematical justifications which will be presented below. In these calculations v = mutation rate in male gametes per X-linked gene per generation, and μ = mutation rate in female gametes.¹

¹ These symbols were introduced by Haldane (1935), but note that Murphy and Matalik (1969) use μ for mutation rate in males and v for that in females.

Fig. Pedigrees of Duchenne muscular dystrophy requesting the genetic risks run by the female relatives marked by arrows.

Methods of calculation

PEDIGREES (a) AND (b)

The risk for a woman being a carrier decreases by a half for her mother or daughter, and therefore in pedigree (a), where her grandmother is an obligatory carrier, the proposita has a $1 \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$ chance of being a carrier. In pedigree (b), as in the other pedigrees, the important question is what is the chance that the mother of an isolated case of an X-linked disorder is a carrier? The answer to this question depends upon whether the disorder is lethal or not in males, and whether the mutation rate is equal in the 2 sexes. It has been shown (Haldane, 1935; Binet *et al.*, 1957; Morton and Chung, 1959; Murphy and Chase, 1975) that in lethal X-linked recessive disorders, assuming equal mutation rates in males and females, the mother of an isolated case has a 2 in 3 chance of being a carrier. This is because if h is the proportion of

Table 1 Genetic risks given for arrowed women being carriers, presented as one chance in x . (Correct answers in bold.)

Geneticist	Values of x for pedigree				
	(a)	(b)	(c)	(d)	(e)
Assuming equal mutation rates in males and females					
1-7	4	6	66	67	36
8	4	6	66	67	66
9	4	6	66	67	18
10	4	6	34	35	36
11	4	6	34	36	34
12	4	3	48	96	32
13	4	6	8	14	36
14	4	3	18	19	18
15	4	4.5	27	29	27
16	5	5.5	41	41	28
17	4	6	100	90	>100
18	4	6	8	9	8
Assuming mutation only in males					
4	4	4	34	35	4
2	4	2.7	12.6	13.6	2.7
11	4	4	128	128	128
15	4	3			18
17	4	4	64	40	4
Assuming mutation only in females					
4	4	8	98	99	68
2	4	5	50	50	34.5
11	4	4	128	128	128
15	4	3	18	19	3
17	4	12	>100	>100	>100

carriers in the population, the next generation will receive $\mu + \nu$ mutant chromosomes plus $\frac{1}{2}h$ (since each woman will, on average, produce 1 daughter). There will also be a loss of $\frac{1}{2}h$ since each woman will, on average, produce 1 son. Therefore, $\mu + \nu + \frac{1}{2}h = h$, and $h = 2\mu + 2\nu$. The proportion of affected boys will be $\frac{1}{2}h + \mu$. When $\mu = \nu$, the proportion of mothers who are carriers will be $\frac{2}{3}$; when $\nu = 0$ it will be $\frac{1}{2}$; and when $\mu = 0$ it will be 1. Presumably this was known to most of those who answered, for the genetic risk for the proposita in pedigree (b) was usually given as 1 in 6 ($\frac{2}{3} \times \frac{1}{2} \times \frac{1}{2}$).

If mutation occurs only in males, then an isolated case, receiving an X chromosome only from his mother, can never be a new mutation. The mother of an affected boy in pedigree (b) is therefore a carrier, and the proposita has a risk of $1 \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$.

If mutation occurs only in females, the probability of the mother being a carrier is $\frac{1}{2}$, which gives the proposita a $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{8}$ chance of being a carrier. This chance was only given by geneticist no. 4 of the 5 who answered this section.

PEDIGREE (c)

In the last 3 pedigrees, the chances that the female relatives of isolated cases are carriers are modified by the presence of healthy brothers or sons. Methods of incorporating such information are listed below, taking pedigree (c) as an example, and assuming firstly equal mutation rates.

(1) 'Bayesian' method, expounded by Murphy and Mutalik (1969), and further explained by Stevenson and Davison (1970), Murphy and Chase (1975), and Emery (1976). This method was used by geneticists 1, 3, 5, 6, 9, 11, 15, 16, and 18. The important factor in pedigree (c) is the patient's grandmother's chance of being a carrier, and the calculations are shown in Table 2.

The proposita in pedigree (c) has half these risks, namely 1 in 66, 1 in 34, and 1 in 98, respectively.

This method is rather complicated and it is easy to make mistakes with it in new situations. For instance, 4 of the 9 geneticists who admitted to using this method got 'wrong' answers.

(2) *Relative probability method* (C. O. Carter, 1977, and J. H. Edwards, 1977, independent personal communications). If one considers first the simple pedigree of an isolated case, his mother, and maternal grandmother, the relative probabilities of the boy being a new mutation: his mother being a new mutation: his grandmother being a carrier are 1:1:1. The probability that the grandmother would have 4 healthy sons, if a carrier, is 1 in 16. Thus the relative probabilities of the 3 situations become 1:1: $\frac{1}{16}$, giving the grandmother a $\frac{1}{16}/2\frac{1}{16}$ chance of being a carrier, namely 1 in 33. Hence the chance of the proposita being a carrier is half this, namely 1 in 66.

If mutation occurs only in males, the initial relative

probabilities become 0:1:1, and if mutation occurs only in females they become 2:1:1.

An alternative way of expressing relative probabilities is shown in Table 3. The proposita in pedigree (c) has half the risks shown, namely 1 in 66, 1 in 34, and 1 in 98, respectively.

This method has the advantage that it avoids the use of μ and ν , and is therefore simpler to calculate and easier to understand.

(3) *Combinatorial method*. Geneticist no. 2 used the method described by Maag and Gold (1975) in which all possible genotype combinations are plotted in a matrix, together with the relative probabilities of each combination occurring. Then the relative probability of a particular individual being a carrier can be calculated. The method is laborious by hand (for example, 8 rows and 12 columns would be necessary for pedigree (c)), though particularly suited to computers.

PEDIGREES (d) AND (e)

Most respondents realised that the change of a brother to a son, in pedigrees (c) and (d), makes little difference. In pedigree (e) the mother's chance of being a carrier is reduced by her 4 healthy sons from $\frac{2}{3}$ to $\frac{1}{3}$ (assuming equal mutation rates), is not altered if mutation occurs only in males, and changes from $\frac{1}{2}$ to $\frac{1}{17}$ if mutation occurs only in females.

Table 2 Bayesian method

	Grandmother of affected boy in pedigree (c)	
	is carrier	is not carrier
<i>Assuming equal mutation rates in two sexes ($\mu = \nu$)</i>		
Prior probability if she has no affected antecedent relatives	$2\mu + 2\nu = 4\mu$	$1 - 4\mu = 1$
Conditional probability, after she has had 4 healthy sons and 1 affected grandson	$\left(\frac{1}{2}\right)^4 \times \frac{1}{4} = \frac{1}{64}$	$\frac{\nu}{2} + \frac{\mu}{2} + \mu = 2\mu$
Joint probability	$\frac{4\mu}{64} = \frac{\mu}{16}$	2μ
Relative probability	1	32
Absolute probability	1/33	32/33
<i>Assuming mutation in males only ($\mu = 0$)</i>		
Prior probability	2ν	$1 - 2\nu = 1$
Conditional probability	$\left(\frac{1}{2}\right)^4 \times \frac{1}{4} = \frac{1}{64}$	$\frac{\nu}{2}$
Joint probability	$\frac{2\nu}{64} = \frac{\nu}{32}$	$\frac{\nu}{2}$
Relative probability	1	16
Absolute probability	1/17	16/17
<i>Assuming mutation in females only ($\nu = 0$)</i>		
Prior probability	2μ	$1 - 2\mu = 1$
Conditional probability	$\left(\frac{1}{2}\right)^4 \times \frac{1}{4} = \frac{1}{64}$	$\frac{\mu}{2} + \mu$
Joint probability	$\frac{2\mu}{64} = \frac{\mu}{32}$	$\frac{3\mu}{2}$
Relative probability	1	48
Absolute probability	1/49	48/49

Table 3 *Relative probability method*

	Relative probability that grandmother of affected boy in pedigree (c)		Absolute probability of being carrier
	is carrier	is not carrier	
<i>Assuming equal mutation rates in two sexes</i>			
After affected grandson	1/3	2/3	
After 4 healthy sons	$(1/2)^4 = 1/16$	1	
Joint probability	$1/3 \times 1/16 = 1/48$	32/48	
Relative probability	1	32	1/33
<i>Assuming mutation in males only</i>			
After affected grandson	1/2	1/2	
After 4 healthy sons	1/16	1	
Joint probability	1/32	16/32	
Relative probability	1	16	1/17
<i>Assuming mutation in females only</i>			
After affected grandson	1/4	3/4	
After 4 healthy sons	1/16	1	
Joint probability	1/64	48/64	
Relative probability	1	48	1/49

Discussion

Several comments were received from participants, ranging from 'you have provided some rather simple cases' to 'the problems took hours' and 'very involved calculations'.

Some pointed out that lack of precision in calculating genetic risks often had little effect in practice, and indeed from the woman's point of view, there is little difference between a risk of 1 in 3 and 1 in 6 say, or between 1 in 66 and 1 in 27. However, some of the genetic risks shown in Table 1 have wider ranges than these; note those provided by geneticists 17 and 18 who are both actively engaged in genetic counselling for Duchenne muscular dystrophy. All but 2 of the errors provided risks which were greater than the correct ones.

More important was the comment that exact calculations of genetic odds were not necessary, in view of the use of estimations of creatine kinase (CK). One centre stated that 'we tend to go much more on the CKs'. Certainly in those few X-linked conditions where carriers can be detected with high precision, the calculation of genetic risks is not necessary. However, the estimation of CK does not provide such a test, for approximately 1 in 3 carriers have levels within 2 SD of the normal range, and approximately 1 in 40 normal women have levels higher than 2 SD from the normal mean, and sometimes much higher. Wilson *et al.* (1965) and Emery and Morton (1968) showed how risks provided by the pedigree and the CK level might be combined by multiplying the odds together. Techniques for measuring CK have not improved much since then and there is no reason why more weight should be given to odds provided by CK level than to genetic odds. Indeed, there are good reasons for declining to do an unreliable test when the

person involved is so far from any affected relative that the *a priori* risks are low.

The above calculations apply to all lethal X-linked recessive diseases and can apply to those that are non-lethal if the prior probabilities are modified appropriately (see Binet *et al.*, 1957; Stevenson and Davison, 1970; Emery, 1976).

I thank those geneticists who participated and promise them anonymity; and I thank Professor J. H. Edwards for suggesting this study and for many helpful discussions. I am grateful to the Muscular Dystrophy Group of Great Britain for support.

Addendum

The same set of problems was presented at the European Society of Human Genetics in Oslo in May 1977, with somewhat better results, 12 of 19 geneticists giving correct answers, as did 2 of 2 computer programmes. All incorrect answers gave risks that were too high, some 20-fold. I am grateful to those members of the Society who took part and to Professor Kåre Berg and Professor Edwards for these results.

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