The Calculation of Reproductive Fitness and the Mutation Rate of the Gene for Chondrodystrophy[1]

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IN HIS comprehensive study of chondrodystrophy and its inheritance, Mørch (1941) provided estimates of the mutation rate of the gene for this anomaly. These estimates, 4.2×10^{-5} by the direct method and 4.8×10^{-5} by the indirect, have generally been accepted as among the more reliable of those which have been calculated for human genes. Stern (1949) employed Mørch's data in his Principles of Human Genetics (pp. 407–410) to exemplify the two approaches to the estimation of a mutation rate. Neel (1952), in a recent general discussion of the study of human mutation, included Mørch's rates for chondrodystrophy in his list of available estimates. However, it is the writer's contention that the indirect estimate of the mutation rate, 4.8×10^{-5}, reported by Mørch, corresponds to an error in the calculation of the relative reproductive fitness of chondrodystrophics.

The determination of relative reproductive fitness depends upon the consideration that a defect such as chondrodystrophy (which is transmitted as an autosomal dominant) generally interferes to some extent with the likelihood of an individual's reproduction. That is to say, the number of children produced by heterozygous carriers of a dominant abnormal allele tends to be less than that of the normal population (Stern 1949). Therefore, relative reproductive fitness may be expressed as the ratio of the average number of offspring produced by affected persons to the average (or an estimated average) for the normal population. Mørch's sample comprised 108 chondrodystrophics, living and dead. Altogether these had 27 children of which one half, theoretically, were chondrodystrophic. Mørch found the fecundity of this group with regard to the abnormal allele to be $\frac{1}{2} \times 27/108 = 0.1250$. The 108 dwarfs had 457 normal sibs who had a total of 582 children. The fecundity of these sibs was held to be, $582/457 = 1.2735$ and, therefore, the relative reproductive fitness (f) of the chondrodystrophics followed as, $0.1250/1.2735 = 0.098$. The error which exists in this method of calculation may be clarified by an example. Suppose that chondrodystrophy did *not* affect reproductive fitness. This would

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mean, by definition, that the chondrodystrophics produced as many offspring as their normal sibs ($f = 1$). In this instance the sibs averaged 1.2735. The 108 dwarfs would therefore have to have 108×1.2735 or approximately 138 children. If this had occurred, the gene frequencies of (D), the allele for chondrodystrophy, in the parental and first generation of offspring would be as follows:

$$\text{Frequency of } D\text{, parental generation: } \frac{108/(108 + 108 + 216 + 914 + 914) = .048}{108(Dd) \times 108(dd) \qquad 457(dd) \times 457(dd)}$$

$$\downarrow \qquad\qquad \downarrow$$

$$\text{Frequency of } D\text{, first gen. offspring: } \frac{138(69Dd,\ 69dd) \qquad 582(dd)}{69/(69 + 69 + 138 + 1164) \qquad = .048}$$

It will be observed that the frequency of the dwarf allele has remained unchanged from the parental generation to the offspring as would be expected if the gene did not affect reproductive fitness. But if the relative fitness is now calculated for these hypothetical data by Mørch's procedure it will be found that,

$$f = \frac{(\frac{1}{2})(138)}{108} \Big/ \frac{582}{457} = \text{approx. } \frac{1}{2}.$$

It would therefore be necessary to conclude that the chondrodystrophics had a relative reproductive fitness of only $\frac{1}{2}$ and consequently, that the frequency of the gene D had decreased by 50% in the first generation of offspring. As shown above this would not be the case.

Mørch's error lies in the fact that numbers of alleles and numbers of offspring were confused in the calculation of relative reproductive fitness. The abnormal alleles of the offspring of the chondrodystrophics (numbering $\frac{1}{2} \times 27$) were derived from 108 abnormal alleles present in the parental generation. This gives an effective fecundity for the chondrodystrophics of $\frac{1}{2} \times 27/108 = 0.1250$, as obtained by Mørch. On the other hand, the offspring of the 457 non-chondrodystrophic sibs derived 582 of their normal alleles from $2 \times 457 = 914$ parental alleles. The frequency of normal alleles had therefore *decreased* by $582/914 = 0.6368$ instead of increasing by a factor of 1.2735 as maintained by Mørch. Thus, the correct value of f, the relative reproductive fitness of the chondrodystrophics, is $0.1250/0.6368 = 0.1963$. Parenthetically, it may be noted that the same result is obtained if the calculation is performed in terms of numbers of offspring, that is

$$\frac{27}{108} \Big/ \frac{582}{457} = 0.2500/1.2735 = 0.1963.$$

The direct estimate of the mutation rate of the gene for chondrodystrophy, obtained by Mørch, was based upon the occurrence of 10 chondrodystrophics

among 94,075 births in the Rigshospital, Copenhagen over a period of thirty years. Of the 10, two had one chondrodystrophic parent. Thus among 94,073 offspring of normal parents, 8 were chondrodystrophic. This corresponds to one mutant allele in 23,518 or a mutation rate of 4.25×10^{-5}. Substitution of the new value of f, derived above, in the formula

$$u = \tfrac{1}{2}(1 - f)x$$

gives an indirect estimate of the mutation rate of

$$\tfrac{1}{2}(1 - 0.1963)10/94{,}075 = 4.27 \times 10^{-5}.$$

This estimate is in much closer agreement with that obtained by the direct method than is the old value of 4.8×10^{-5} which corresponds to the error in the calculation of reproductive fitness discussed above.

REFERENCES

MØRCH, E. T. 1941. Chondrodystrophic Dwarfs in Denmark. *Opera Ex Domo Biol. Hered. Human. Univ. Hafn.* 3: 1–200.

NEEL, J. V. 1952. The Study of Human Mutation Rates. *Am. Natur.* 86: 129–144.

STERN, C. 1949. *Principles of Human Genetics.* 617 pp. San Francisco: W. H. Freeman & Co.