Mutation Rate in Duchenne Type of Muscular Dystrophy

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The mutation rate in the Duchenne type of muscular dystrophy has generally been estimated by the indirect method of Haldane (1935) using his formula for X-linked recessive traits

\[ U = \frac{1}{3} (1 - f) x \]

where \( U \) is the mutation rate, \( f \) the effective fertility of affected males, and \( x \) the incidence of affected individuals in the male population. Since the effective fertility of males with this disorder is zero, the mutation rate amounts to \( 1/3 \) of the incidence among males. Estimates on this basis have varied from \( 4.3 \times 10^{-5} \) (Walton, 1955) to \( 9.5 \times 10^{-5} \) per gene per generation (Stephens and Tyler, 1951).

Perhaps the most satisfactory population study was that of Stevenson (1958) whose figures give a mutation rate of \( 6.0 \times 10^{-5} \). Morton and Chung (1959) used the technique of segregation analysis of sporadic cases to obtain a figure of \( 8.9 \times 10^{-5} \), but they appear to have included some cases of the benign X-linked (Becker) type of muscular dystrophy in their calculations, which invalidate the result obtained.

Carrier detection techniques provide a basis for more direct estimation. The serum creatine kinase level is now well established as the most useful index of the carrier state. Results of surveys from many centres show that over-all about 75% of known carriers can be detected (Walton and Gardner-Medwin, 1969). Investigation of large series of mothers of isolated cases of muscular dystrophy shows that relatively few of them are detected as carriers (Thompson, Murphy, and McAlpine, 1967; Gardner-Medwin, 1969). Most of the remainder are presumably the non-carrier mothers of those cases which have arisen by new mutation.

A considerable problem, however, is posed by the possibility that some cases of 'Duchenne' muscular dystrophy are inherited as an autosomal recessive trait (Lamy and de Grouchy, 1954; Blyth and Pugh, 1959). As a result of a recent review the author believes such cases to be very rare. The reasons can be summarized briefly as follows: (a) proof of the existence of an autosomal recessive childhood dystrophy depends on the discovery of females with the disease. The published reports of such females very rarely give satisfactory histological evidence of the diagnosis, and in view of the fact that secondary myopathic change may occur in chronically denervated muscle and cause serious diagnostic difficulty, whether clinical, enzymological, electromyographic, or histological criteria are used for diagnosis. (b) In a study of cases of muscular dystrophy which began in childhood and predominated in the lower limbs, the absolute prevalence of the disease in a population of 3.3 million in the north of England was males (Duchenne type) 91, females 2; the minimum prevalence of cases of benign spinal muscular atrophy with onset before 12 years was males 12 and females 14. (c) The 2 females with muscular dystrophy and 3 others referred from elsewhere were compared with the Duchenne cases and were found to have a similar age of onset but slower progression and longer survival; similar clinical features, though asymmetry was commoner in females; lower or similar serum creatine kinase levels in the late stage of the disease (no information was available for females in the early stages); less severe histological abnormalities; and electrocardiograms which lacked the typical features of Duchenne dystrophy (Perloff, de Leon, and O'Doherty, 1966). Two male cases, not diagnosed as of the Duchenne type on clinical grounds, more closely resembled the female cases. Thus it...
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appears not only that autosomal cases are rare but that they are usually distinguishable from X-linked cases by appropriate investigation. The possibility of autosomal recessive inheritance in typical cases of Duchenne muscular dystrophy is therefore discounted in the present study.

Methods

Creatine kinase (CK) assays were performed by the method of Pearce, Pennington, and Walton (1964). Up to March 1969 the results in 34 normal control subjects and 190 female relatives of patients with Duchenne muscular dystrophy were available. The upper limit of normal, calculated as the mean + 2 standard deviations of the logarithms of the results in normal subjects, was 75 international units/litre (Gardner-Medwin, 1969). For the purpose of the present study, however, a serum CK level of 67 I.U./litre was chosen as giving the best discrimination between control subjects (among whom the highest observed serum CK level was 67 I.U./litre) and known carriers. The 'known carriers' included 24 women with affected sons and affected brothers or maternal uncles and 11 mothers of 2 or more affected sons without other affected relatives. The detection rate for known carriers was 22/35 (63%) and for mothers of isolated cases 15/56. On the assumption that the detection rate for true carriers is the same in the two groups, one would expect \( 56 - (35/22)15 = 32 \) non-carriers among the mothers of isolated cases. This gives a prevalence of new mutants of 57.5% of the isolated cases. The equivalent figure derived from the data of Thompson et al. (1967) is 49%.

The mutation rate can now be calculated using the number of cases of Duchenne muscular dystrophy ascertained at the Newcastle Regional Neurological Centre for each year of birth from 1949 to 1964. In earlier years the records are unreliable; in later ones the numbers diminish, presumably because some cases born in these years have not yet been referred. The years 1952 to 1960 inclusive have been chosen as giving the most reliable data (Table I).

The cases included have all been diagnosed as having Duchenne muscular dystrophy by Professor J. N. Walton during a period when his interest in the disease was widely known and virtually every case in the Newcastle Regional Hospital Board area may be assumed to have been referred for his opinion. All cases now diagnosed as having the Becker type and all females are excluded. The place of birth was not recorded in 7 cases, but in an attempt at complete ascertainment cases cannot be excluded for this reason, and the assumption is made that the possible inclusion of some cases born outside the area is balanced by the emigration before referral of other cases. All cases known or strongly suspected to have been born elsewhere are excluded from the study. In one case born in 1956 and now lost to follow-up the notes imply, but do not state explicitly, that no other member of the family was affected.

The incidence of a disease which is not apparent at birth should be expressed not in relation to live births but to live-born children surviving to the age of ascertainment. Table II shows the live births for the years 1952 to 1960. The columns headed 'Deaths before 5 years'...
give the sum of the infant mortality for the subsequent
year, together with an estimate of the expected addi-
tional mortality between the age of 1 and 5 years (which
remains relatively constant from year to year). All the
figures are based on the medical statistical tables of the
General Register Office (G.R.O.) for the relevant years.
Mortality between 5 years and the mean age at ascen-
tainment can be ignored.

A further complication arises because the G.R.O.
tables give figures for the ‘Northern Area’ which differs
from the Regional Hospital Board area by the inclusion
of the whole instead of only part of Westmorland and
of the North Riding of Yorkshire. The live births in the
Regional Hospital Board Area were however also rec-
corded in the years 1963 to 1967, and throughout this
later period the ratio of numbers of live births in the
Regional Hospital Board area to those in the whole
Northern Area remained constant at 0·935. The as-
sumption has been made that this ratio applied also be-
tween 1952 and 1960 and that the mortality rate in the
two areas was the same. The figure for total numbers of
live-born children surviving to age 5 in the Northern
Area has therefore been multiplied by 0·935. This
gives a total population of children surviving to the age of
5 years who were born in the Newcastle Regional Hospital
Board area in the years 1952–1960 inclusive of 459,500,
of whom 236,200 were males.

Results

The total number of ascertained cases of Duchenne
muscular dystrophy born in the region in the nine-
year period was 77, of which 43 (56%) or possibly 42
were isolated cases. This gives an incidence of 16·8
cases per 100,000 children of both sexes attaining the
age of 5 (32·6 per 100,000 males).

Using Haldane’s formula the mutation rate is
10·9 x 10⁻⁵ per gene per generation.

Using the relatively direct method based on
carrier detection, where U = mutation rate, J = num-
er of isolated cases born in the period, R = the
proportion of isolated cases whose mothers are non-
carriers, and T = number of males born in the period
who attained the age of 5, then

\[ U = \frac{JR}{T} = \frac{43 \times 0.575}{236,200} = 10.5 \times 10^{-5} \]

This figure is expressed as mutations per male
live birth or as mutations per gene per generation.
If the mutation rate is equal in ovum and sperm
then there should be twice as many new mutant
carrier females in the population (each with two X
chromosomes) as new mutant affected males (with
one X chromosome).

Discussion

The method is attractively direct, but it depends
for its accuracy upon the reliability of ascertainment
of isolated cases and the uniformity of results of
serum creatine kinase estimations. Some diffi-
culties over ascertainment have been discussed; the
error at the most can hardly exceed 10%. The iso-
lated cases upon which mothers the serum CK
studies were performed and those which appear in
Table I were not always the same. But only 8 of the
1952–1960 series are not in the serum CK
series, and there is no reason to expect the two
groups to differ significantly. Nor is there any
obvious source of error or bias which might invali-
date the results of the CK studies.

The figure of 32·6 x 10⁻⁵ for the incidence of the
disease among males is higher than in previous
studies where the following figures were obtained:
28·6 x 10⁻⁵ (Stephens and Tyler, 1951), 13·0 x 10⁻⁵
(Walton, 1955), 18·2 x 10⁻⁵ (Stevenson, 1958),
14·1 x 10⁻⁵ (Blyth and Pugh, 1959), and 27·9 x 10⁻⁵
(Morton and Chung, 1959). Falsely high ascen-
tainment is unlikely, but even after exclusion of the
7 cases whose birth place was uncertain the inci-
dence is 29·6 x 10⁻⁵. Incomplete ascertainment is
more probable and 32·6 x 10⁻⁵ should perhaps be
considered as a minimum figure.

The mutation rate based on carrier detection
agrees closely with that obtained by the Haldane
method. The latter method assumes normal
fertility in carrier females; yet most women who
know or fear that they may bear a dystrophic child
purposely restrict their fertility. Some evidence
for this is shown in Table I where the proportion of
cases where the mothers are definite or probable
carriers is relatively low. The expected propor-
tion of sporadic cases is \( \frac{mu}{2u+v} \) for a sex-linked
gene where \( m \) = the selection coefficient against
affected males (1 in this disease) and \( u \) and \( v \) are
the mutation rates in ovum and sperm, respectively
(Morton and Chung, 1959). If \( u \) and \( v \) are equal
the frequency should be 0·33. In the present
series it is 43/77 = 0·56, a figure that strongly sug-
ests that genetic advice is beginning to have some
effect upon the incidence of the disease. One might
therefore expect the Haldane method to give a
falsely low result. The actual close agreement in
the mutation rates calculated by this method and the
carrier-detection method (which is independent of
the fertility of carriers) is difficult to explain.

The 21 cases with affected brothers in Table I in-
cluded 7 first-affected, 12 second-affected, and 2
third-affected boys. Their mothers were clearly
carriers. The incidence of first-affected boys born
in the population in the 9 years was therefore 43 +
7 = 50, of whom about 0·575 x 43 (= 25) were new
mutants and about 7 + 43 (1 - 0·575) = 25 were
born to unwitting (and probably mostly mutant)
carriers. In the same period the remaining 27 affected boys were born to mothers who could have been suspected to be carriers, and their births alone could theoretically have been prevented by prompt diagnosis and genetic counselling.

Summary

The incidence of Duchenne muscular dystrophy in North Eastern England between 1952 and 1960 was about 32.6 per 100,000 males surviving to the age of 5 years. The mutation rate calculated by a method founded upon carrier detection was about \(10.5 \times 10^{-5}\) per gene per generation. Some evidence suggesting that autosomal recessive inheritance in 'Duchenne' cases is rare is briefly summarized. Only about one-third of cases of this disease are theoretically preventable by ideal genetic counselling.

I am very grateful to Professor J. N. Walton and Dr. D. F. Roberts for valuable advice and Mrs. Y. Chisholm for typing the manuscript.

References


