Duchenne's Muscular Dystrophy and the Xg Blood Groups: a Search for Linkage

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Clark, Puite, Marczyński, and Mann (1962) determined the Xg groups of a series of families with Duchenne's muscular dystrophy, living in the State of Michigan and in the northern part of Indiana. The results showed that the loci for the two genes involved were not close to each other on the X chromosome. Details of the families and the linkage calculations were given in a later paper by the same authors (1963). The present paper contributes more information and supports these earlier results.

For linkage studies it is important to ensure as far as is possible that each group of families considered is genetically homogeneous. Clinical differences may be assumed to represent genetic differences provided that all affected members of a given family belong to one and the same clinical group. Becker (1955) and Becker and Kiener (1955) noted that the typical X-linked recessive pattern of inheritance might be associated with a relatively benign form of Duchenne type muscular dystrophy, as well as with the more usual severe form with its early onset, rapid progression, and death at the beginning of the third decade at the latest. Becker's conclusion that two different mutations might be concerned is now generally shared. He suggested further that the two mutant genes might be alleles, but there is no evidence yet either for or against this view.

To facilitate clinical grouping, families with the severe form of the disease may be distinguished by the criterion suggested by Stevenson (1953) and Blyth and Pugh (1959) that all patients are, or are expected to be, unable to walk unsupported by the age of 11 years. Families with the milder type of disability may similarly be distinguished as those in which all patients are, or are expected

to be, able to walk unsupported at the age of 11 years. In the opinion of some of the present authors this age could be advanced by a year or two. The division of cases into severe and mild to be used in the linkage analysis is that made by the individual authors.

Informative Data

The red cells of 335 members of 50 kindred with X-linked Duchenne's muscular dystrophy were tested with anti-Xg^a. In 12 kindred, 14 mothers showed themselves to be heterozygous both for the Duchenne and the Xg genes. Some details of these informative families are given in Table I. Two families present the mild form of the dystrophy and 10 the severe.

Linkage Analysis

The data were analysed by the application of the lod scores of Morton (1955) as instructed by Maynard-Smith, Penrose, and Smith (1961). The lod scores are given in Table II together with the anti-logs of their sums. These antilogs represent the relative probabilities of θ , the recombination fraction, and they are plotted in the Figure.

The curve for the severe form of the dystrophy shows that Xg and the gene responsible for this form are probably not within measurable distance of each other. The lower limit of θ at the 1 in 20 level of probability is about 0.35, a figure obtained by the method recommended by Professor C. A. B. Smith, of counting the graph paper squares below the curve and cutting off from the tail one-twentieth of their number.

The question of *a priori* corrections in X-linkage calculations was raised by Dr. J. H. Renwick (Davies, Gavin, Goldsmith, Graham, Hamper, Hardisty, Harris, Holman, Ingram, Jones, McAfee, McKusick, O'Brien, Race, Sanger, and Tippett,

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TABLE I

DUCHENNE'S MUSCULAR DYSTROPHY AND Xg GROUPS: FAMILIES GIVING LINKAGE INFORMATION

Family	Duchenne's m.d.	Anti-Xg*	Family History of m.d.	Type	Investigator	Identification and Notes
1 Father Mother 1. Son 2. Daughter her son 3. Daughter 4. Daughter 5. Son* 6. Daughter 7. Son	— — + + + + + + —	+ d. + + + + + + +	Probably	Mild Mild Mild	Blyth	Part of family M.21 (Blyth and Pugh, 1959). (British)
2 Mother 1. Son 2. Son Mother's sister her son her son her son	— + + — — — +	+ + + — + + —	Yes	Mild Mild Mild	Carter	Wan. (British)
3 Father Mother 1. Daughter 2. Son 3. Daughter 4. Daughter her son* her son 5. Daughter 6. Daughter 7. Son	— — — — — — + — — — +	— + + + + + + + + + d.	Yes	Severe Severe	Dubowitz	Bar. (Dubowitz, 1963) (British)
4 Father Mother 1. Son* 2. Son	— — + —	+ — — —	Yes	Severe	Dubowitz	Gro. (British) Part of family D 1 (Walton, 1956) and family 21 (Dubowitz, 1960)
5 Mother 1. Daughter 2. Daughter 3. Son* 4. Son	— — — + —	+ + + — —	Yes	Severe	Dubowitz	Tur. (British)
6 Father Mother 1. Son 2. Son* 3. Son 4. Daughter	— — — + — —	— + + + + +	Yes	Severe	Dubowitz	Bin. (British)
7 Father Mother 1. Daughter her son* her son her son	— — + + + +	— + + + + —	Yes	Severe Severe	McKusick and Emery	Ham. (Maryland)
8 Father Mother 1. Daughter her son* her son her son	— d. + + + +	— d. + — — —	No	Severe Severe Severe	McKusick and Emery	Kah. (Maryland) Scored as 3 rec.: if mother were mutant score would be z_1 3:0, e_1 3:0
9 Mother 1. Son* 2. Son	— + +	+ — +	Yes	Severe Severe	McKusick and Emery	She. (Maryland)
10 Mother 1. Son 2. Son* 3. Son	— — + +	+ — — —	No	Severe Severe	McKusick and Emery	Goa. (Maryland) Score same whether mother mutant or not
11 Mother 1. Son* 2. Son	— + +	+ + —	No	Severe Severe	McKusick and Emery	Hor. (Maryland)
12 Father Mother 1. Daughter her husband her son her son* her son her son her daughter her son her daughter her daughter	— — — — — + + — — — — —	+ + + — — + + + + + + +	No	Severe Severe	Johnston	Hat. (British) Scored as 3 non-rec.: 2 rec.; if mother were mutant then score would be z_1 3:2, e_1 3:2

Note: The full pedigrees of most of the families showed the pattern expected of an X-linked character: X-linkage is presumed in families 8, 10, 11, and 12. In the column headed 'Family history of m.d.' 'Yes' opposite a member's name means that other cases are known in earlier generations or in sibs and that the person so indicated cannot therefore represent a fresh mutation: 'No' means that the person could represent a fresh mutation.

*The proband is marked with an asterisk when present in the part of a family shown in this Table.

TABLE II
 DUCHENNE'S MUSCULAR DYSTROPHY AND Xg: LOD SCORES OF FAMILIES IN TABLE I

				Recombination Fraction, θ								
				0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45
Mild type	Family	1 (M.21)	z ₁ 2 : 2, e ₁ 3 : 1 1 n-rec.	-1.461	-0.899	-0.592	-0.392	-0.252	-0.152	-0.082	-0.035	-0.009
				0.279	0.255	0.230	0.204	0.176	0.146	0.114	0.079	0.041
		2 (Wan.)	z ₁ 1 : 1, e ₁ 2 : 0 z ₁ 3 : 0, e ₁ 2 : 1	-0.584	-0.340	-0.215	-0.138	-0.087	-0.052	-0.028	-0.012	-0.003
				0.485	0.427	0.364	0.296	0.228	0.160	0.098	0.047	0.012
Sum of lod scores				-1.281	-0.557	-0.213	-0.030	0.065	0.102	0.102	0.079	0.041
Antilog = relative probabilities of θ				0.052	0.277	0.612	0.933	1.161	1.265	1.265	1.199	1.099
Severe type	Family	3 (Bar.)	z ₁ 1 : 1 1 n-rec. : 1 rec.	-0.721	-0.444	-0.292	-0.194	-0.125	-0.076	-0.041	-0.018	-0.004
				-0.721	-0.444	-0.293	-0.194	-0.125	-0.076	-0.041	-0.018	-0.005
		4 (Gro.)	z ₁ 1 : 1, e ₁ 1 : 1	-0.825	-0.528	-0.358	-0.243	-0.160	-0.099	-0.054	-0.024	-0.005
		5 (Tur.)	z ₁ 1 : 1, e ₁ 1 : 1	-0.825	-0.528	-0.358	-0.243	-0.160	-0.099	-0.054	-0.024	-0.005
		6 (Bin.)	z ₁ 2 : 1, e ₁ 2 : 1	-0.769	-0.482	-0.321	-0.216	-0.140	-0.086	-0.047	-0.020	-0.005
		7 (Ham.)	1 n-rec. : 2 rec.	-1.721	-1.143	-0.816	-0.592	-0.426	-0.298	-0.196	-0.115	-0.051
		8 (Kah.)	: 3 rec.	-3.000	-2.097	-1.569	-1.194	-0.903	-0.666	-0.465	-0.291	-0.138
		9 (She.)	z ₁ 1 : 1, e ₁ 2 : 0	-0.584	-0.340	-0.215	-0.138	-0.087	-0.052	-0.028	-0.012	-0.003
		10 (Goa.)	z ₁ 2 : 1, e ₁ 2 : 1	-0.769	-0.482	-0.321	-0.216	-0.140	-0.086	-0.047	-0.020	-0.005
		11 (Hor.)	z ₁ 1 : 1, e ₁ 2 : 0	-0.584	-0.340	-0.215	-0.138	-0.087	-0.052	-0.028	-0.012	-0.003
		12 (Hat.)	3 n-rec. : 2 rec.	-1.163	-0.633	-0.356	-0.184	-0.074	-0.006	0.032	0.043	0.031
Sum of lod scores				-11.682	-7.461	-5.114	-3.552	-2.427	-1.596	-0.969	-0.511	-0.193
Antilog = relative probabilities of θ				0.000	0.000	0.000	0.000	0.004	0.025	0.107	0.308	0.641

FIG. The linkage relations of the genes for Duchenne's muscular dystrophy and for the Xg blood groups: the left curve relates the mild form of the dystrophy, the right curve the severe.

1963; Clark *et al.*, 1963). No correction has been applied to the data in Table II or in the Figure. A correction can be applied later when more is known about the length of the X.

From the description it seems likely that the families studied by Clark *et al.* (1963) were all of the severe type. If the lod scores (uncorrected) of these families are added to those of Table II then the resulting antilog curve moves a little to the right of that in the Figure and the lower limit of θ at the 1 in 20 level of probability is increased from 0.35 to 0.38.

The curve for the mild form of the dystrophy (Fig.) is much too low to be significant of measurable linkage with Xg: it is, however, an indication that more families with the mild form should be grouped. If the gene for the mild form were found to be within measurable distance of Xg, this would be of interest in showing that the mild and severe forms are not controlled by allelic genes.

Summary

Members of 50 kindred in which X-linked Duchenne's muscular dystrophy occurs were tested for the Xg blood groups. Twelve of the kindred provided useful linkage information: two of them showed the mild form of the dystrophy and ten the severe. Analysis by the lod score method gives no hint of measurable linkage between the genes for Xg and the severe form of dystrophy, and this supports the previous results of Clark, Puite, Marczyński, and Mann. Nothing can yet be said about the linkage relation of Xg and the mild form of dystrophy: more families will have to be tested.

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