Emery-Dreifuss muscular dystrophy: localisation to Xq27.3→qter confirmed by linkage to the factor VIII gene

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SUMMARY Two families with Emery-Dreifuss muscular dystrophy (EMD) have been studied with DNA markers mapping to Xq27.3→qter. No recombination was observed in 11 phase known meioses informative for the factor VIII gene (*F8C*) and eight phase known meioses informative for *DXS15* (DX13), giving maximum lod scores of 3.50 and 2.50 respectively at a recombination fraction of zero. *DXS52* (St14) showed one recombinant in 12 phase known meioses giving a maximum lod score of 2.62 at a recombination fraction of 0.07. These results map *EMD* to the distal end of the long arm of the X chromosome and are an important step in the development of tests for carrier detection and prenatal diagnosis.

Emery-Dreifuss muscular dystrophy (McKusick Catalogue No 31030¹) is a rare X linked condition clinically distinct from Duchenne and Becker muscular dystrophies.^{2,3} Onset is in childhood, but progression of the disease is slow so that ambulation is often maintained until later adult life. In the upper limbs there is usually marked wasting and weakness of the humeral muscles with the shoulders less severely affected. In the lower limbs the original family had proximal muscle involvement,² but the majority of cases reported since then have had predominantly peroneal wasting and weakness.³ This raises the possibility of heterogeneity and has prompted debate about nomenclature.⁴ Contractures involving the neck, elbows, and ankles are an early and prominent feature. Muscle hypertrophy does not occur. Cardiac involvement with conduction disturbances is a frequent and serious complication with a risk of sudden death.⁵

The present study was undertaken with the aim of confirming reports suggesting linkage with the DNA marker *DXS15*.⁵

Patients and methods

Two families with Emery-Dreifuss muscular dystrophy were studied. Family 1 (figure) was ascertained through subjects IV.7 and IV.8 by the Department of Neurology, Medical Academy, Warsaw, Poland. The family showed an X linked recessive pattern of inheritance with eight males affected. Clinical and laboratory findings in the six surviving males with the disorder are summarised in table 1. The disease ran a much milder course than Duchenne muscular dystrophy and the particular features pointing to a diagnosis of Emery-Dreifuss rather than Becker muscular dystrophy were the early development of elbow contractures, absence of calf hypertrophy, only moderately raised serum creatine kinase levels, muscle histology showing type 1 fibre atrophy, and electrocardiographic evidence of early cardiac involvement. Both II.1 and II.3 were ambulant up to 40 years of age when they suffered sudden and unexpected deaths. Colour vision in the family was normal.

The second family studied (family 2) has been described elsewhere.⁴

Blood samples were obtained from available family members and DNA extracted and used in

Southern blotting procedures as described previously.⁶ The families were studied with the DNA probes *F8C* (clotting factor VIII gene), *DXS15*

(DX13), and *DXS52* (St14), which all map to distal Xq and recognise restriction fragment length polymorphisms.⁷

TABLE 1 Clinical and laboratory findings in affected males in family 1.

	IV.2	IV.3	IV.5	IV.7	IV.8	IV.9
Age at onset of symptoms (y)	4		2	3	5	
Age at first examination (y)	10	7	5	15	13	10
Ambulant	+	+	+	+	+	+
Lumbar lordosis	+	+	+	+		
Muscle involvement						
Upper limbs: proximal	+	+	+++	++	+/-	-
distal*	++	+/-	+++	++	+	+/+
Lower limbs: proximal	+	+	+++	++	+/-	-
distal	++	+/-	+++	++	+	+/-
Flexion contractures of elbows	+	-	-	++	++	+/-
Shortening of Achilles tendons	+++	+	+	+++	++	+/-
Calf hypertrophy	-	-	-	-	-	+/-
Intelligence quotient	101	120	96	120	117	104
Creatine kinase (IU)‡	212	147	123	78	185	68
Electromyography: myopathic	+	+	+++	+	+	+
Muscle biopsy						
Type 1 fibre atrophy	+	+	†	+	+	+
Type 2 fibre predominance	+	+				
Electrocardiography: abnormal			+	+		

- = absent, +/- = slight, + = mild, ++ = moderate, +++ = severe.

*Predominantly wrist extensors.

†Muscle biopsy reported to show "fibre necrosis and accumulation of lipid in some fibres".

‡Normal range 0-34 IU.

TABLE 2 *Lod scores $Z(\theta)$ at recombination fraction θ for Emery-Dreifuss muscular dystrophy versus the three marker loci. The maximum lod score and corresponding recombination fraction are denoted by $\hat{Z}$ and $\hat{\theta}$ respectively. Confidence limits for θ are also given.*

Marker locus	$Z(0)$	$Z(0.001)$	$Z(0.05)$	$Z(0.1)$	$Z(0.2)$	$Z(0.3)$	$Z(0.4)$	$\hat{Z}$	$\hat{\theta}$	Confidence limits for θ
<i>F8C</i>	3.50	3.50	3.23	2.94	2.32	1.64	0.88	3.50	0	0-0.17
<i>DXS15</i>	2.50	2.50	2.31	2.10	1.67	1.19	0.64	2.50	0	0-0.24
<i>DXS52</i>	$-\infty$	1.21	2.60	1.58	2.19	1.60	0.87	2.62	0.07	0.003-0.30

The computer programme LIPED⁸ was used to compute the lod scores. Confidence limits were determined by the method recommended at the Eighth International Workshop on Human Gene Mapping,⁹ taking values of the recombination fraction corresponding to a lod score one unit less than the maximum.

Results

The family pedigrees and marker results are shown in the figure. No recombination was observed in 11 phase known meioses informative for *F8C* and eight phase known meioses informative for *DXS15*. Family 1 showed a recombinant with *DXS52* since I.2 had two affected sons (II.1 and II.3) with different restriction fragment patterns. This was the only recombinant with *DXS52* in 12 phase known meioses.

Lod scores combining the data from both families are summarised in table 2.

Discussion

A lod score of 3.50 establishes linkage between the factor VIII gene (*F8C*) and Emery-Dreifuss muscular dystrophy (*EMD*) and localises this disease locus to the distal end of the long arm of the X chromosome, since *F8C* has been physically mapped to Xq27.3→qter.^{10 11} Lod scores of 2.62 with *DXS52* and 2.50 with *DXS15* are to be expected since these markers are tightly linked to *F8C*.¹²⁻¹⁴

These results are supported by a previous study suggesting linkage with *DXS15*.⁵ In addition, there is a report suggesting linkage between deutan colour blindness (*CBD*) and a condition referred to as X linked scapuloperoneal syndrome¹⁵ which may be the same as Emery-Dreifuss muscular dystrophy. *CBD* is closely linked to haemophilia A.¹⁶

Independent confirmation of these findings comes from the work of Thomas *et al*,¹⁷ also published in this issue, showing linkage between *EMD*, *F8C*, and *DXS15*.

Taken together there is now a substantial body of evidence mapping *EMD* to the distal long arm of the

X chromosome and confirming that this locus is distinct from the Duchenne and Becker muscular dystrophy loci which are located on the short arm of the X chromosome.¹⁸

In the present study the observation of a recombinant between *EMD* and *DXS52*, but apparently no recombination with *F8C* or *DXS15*, provides little evidence for order since recombination with *F8C* and *DXS15* cannot be excluded. In family 1 (figure) the status of I.2 with respect to these markers is uncertain, and this subject could have been homozygous for either or both of them, in which case recombination would go unnoticed.

The demonstration that Emery-Dreifuss muscular dystrophy is linked to several DNA markers on distal Xq is an important step in the development of tests for carrier detection and prenatal diagnosis of this disorder.

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