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Linkage studies in Duchenne and Becker muscular dystrophies

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SUMMARY We have studied the inheritance of four cloned DNA sequences which recognise restriction fragment length polymorphisms on the short arm of the X chromosome in families with Becker and Duchenne muscular dystrophy. We have confirmed linkage of two probe loci to the disease loci and have combined our results with those previously published to give a maximum lod score of 11·642 at a recombination fraction of 0·15 for *DXS41* (probe 99·6), and a maximum lod of 15·84 at a recombination fraction of 0·15 for *DXS84* (probe 754). Linkage of these diseases to the loci defined by the pERT87 probes and probe pXJ1·1 has also been studied, giving maximum lod scores of 8·634 and 5·118 at recombination fractions of 0·02 and 0·00 respectively. The information obtained using these polymorphic DNA markers, combined with pedigree and CK data, can be used to give more accurate genetic counselling to women at risk in Becker and Duchenne families.

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X linked recessive muscle disorders. DMD is more common and more severe than BMD, with an incidence of approximately 1 in 3000 to 3500[1] newborn males, compared to approximately 1 in 30 000 for BMD. They are clinically similar in the pattern of muscle involvement, but BMD follows a more benign course.

The localisation of DMD on the X chromosome initially came from the study of several girls who manifested the clinical signs of muscular dystrophy and who were all found to have X;autosome translocations, with a common breakpoint at Xp21.[2 3] Further evidence came from the linkage of DMD to polymorphic loci defined by cloned DNA sequences, RC8[4] and L1·28.[5] Since then, other DNA probes have been isolated from this region and have been studied in kindreds showing a family history of DMD and BMD.[6–10] BMD was originally thought to be linked to colour blindness on the terminal portion of Xq,[11 12] but markers linked to DMD have also been shown to be linked to BMD.[6 13] This has been further substantiated by the finding of deletions of the same DNA sequences in both DMD and BMD,[14 15] and by the fact that two of the girls with X;autosome translocations involving Xp21 have had relatively mild diseases, more compatible with a diagnosis of Becker than Duchenne muscular dystrophy.[16 17]

In order to increase their usefulness in clinical situations, the linkage of polymorphic loci to the disease loci must be studied in pedigrees. We have investigated the linkage of four polymorphic loci defined by probes 99·6 (*DXS41*[18]), pERT87 (*DXS164*[19]), 754 (*DXS84*[7]), and pXJ1·1[20] to DMD and BMD. Locus *DXS84* is centromeric to the disease locus and *DXS41* is telomeric, while the precise locations of the others have not yet been defined relative to the disease locus.[15]

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Materials and methods

SUBJECTS

We have studied five BMD families and 20 DMD families taken from the total clinic population described by Hodgson *et al.*[21] Each kindred contained at least two affected males. Subjects used in linkage analysis were unaffected and affected males and females who were obligate carriers. Information is available on a total of 35 meiotic events in three

TABLE 1 *Information on the DNA probes used in this study.*

Probe	*Locus*	*Restriction enzyme*	*Band sizes (kb)*	*Heterozygosity frequency (%)*	*Origin of probe*
99·6	*DXS41*	*Pst*I	22+13	41	Kunkel[18 24]
pERT87·15	*DXS164*	*Xmn*I	2·8+(1·6 + 1·2)	41·5	Kunkel[15]
pERT87·15	*DXS164*	*Taq*I	3·3+3·1	37	Kunkel[15]
pERT87·8	*DXS164*	*Bst*XI	4·4+2·2	41	Kunkel[15]
pERT87·1	*DXS164*	*Xmn*I	8·7+7·5	36	Kunkel[15]
pXJ1·1		*Taq*I	3·8+3·1	30	Worton[20]
754	*DXS84*	*Pst*I	12+9	50	Pearson[7]

generation families and 30 meiotic events in two generation families (appendix). Serum CK results on carrier females were usually available, but were not used in the calculation of linkage results.

DNA PREPARATION

DNA was extracted from whole blood using the method described by Kunkel *et al*.[22] DNA (10 μg) was digested with the appropriate restriction enzymes for the various probes (table 1) and the resulting fragments were separated on 0·8% agarose gels by electrophoresis overnight at constant voltage (45 to 55V). The separated DNA was transferred to Zetaprobe membranes (Biorad) by Southern blotting.[23]

ORIGIN OF PROBES

Probe 754 was selected from a flow sorted X chromosome library as a single copy sequence. It has been localised proximal to the DMD locus using rodent-human cell hybrids.[7] Probe 99·6 was also isolated from a flow sorted X chromosome specific library,[18 24] and maps distal to the DMD locus. The pERT probes were selected from a library highly enriched for human DNA from Xp21, which had been constructed using DNA isolated from a male patient who had a cytogenetically visible deletion and three X linked disorders.[19] pXJ1·1 is the cloned junction fragment of the (X;21) translocation causing muscular dystrophy in a girl with the karyotype 46,X,t(X;21)(p21·1;p12) or (p21·2;p12).[17 20]

HYBRIDISATION

Prehybridisation was carried out using salmon sperm DNA (100 μg/ml) at 65°C. Hybridisation was also carried out at 65°C in 3 × SSC, 0·1% SDS, 100 μg/ml salmon sperm DNA, and 2 × Denhardt's. Probes 754 and 99·6 were labelled by nick translation using Amersham nick-kit; pERT probes and pXJ1·1 were labelled using a hexanucleotide primed reaction.[25] Hybridisation was for 48 hours and filters were washed to 1 × SSC, 0·1% SDS or 0·2 × SSC, 0·1% SDS, depending on the properties of the probe.

LINKAGE ANALYSIS

Linkage analysis was carried out using two point analysis on the computer programme LIPED (IBM

TABLE 2 *Lod scores for Duchenne muscular dystrophy and marker loci defined by the probes used.*

θ	*99·6 (n=10)*	*pERT87·15 (n=11)*	*pERT87·8 (n=7)*	*pERT87·1 (n=8)*	*Combined pERT (n=16)*	*pXJ1·1 (n=8)*	*754 (n=14)*
0·00	−∞	4·708	−∞	−∞	−∞	3·613	−∞
0·01	1·892	4·590	1·024	2·122	4·783	3·530	−0·670
0·02	2·117	4·473	1·266	2·336	4·928	3·446	0·405
0·03	2·217	4·356	1·383	2·428	4·952	3·364	0·983
0·04	2·265	4·329	1·449	2·467	5·011	3·280	1·352
0·05	2·283	4·247	1·486	2·476	4·988	3·195	1·609
0·06	2·284	4·601	1·505	2·468	4·784	3·110	1·794
0·07	2·271	3·882	1·512	2·447	4·695	3·025	1·930
0·08	2·251	3·765	1·510	2·419	4·597	2·941	2·030
0·09	2·223	3·645	1·501	2·384	4·440	2·856	2·102
0·10	2·187	3·528	1·487	2·342	4·383	2·771	2·152
0·11	2·147	3·410	1·467	2·295	4·268	2·686	2·183
0·12	2·105	3·290	1·444	2·244	4·148	2·600	2·199
0·13	2·058	3·171	1·419	2·190	4·024	2·514	2·203
0·14	2·008	3·054	1·390	2·137	3·901	2·430	2·197
0·15	1·956	2·935	1·359	2·077	3·775	2·343	2·180
0·16	1·901	2·817	1·326	2·017	3·644	2·257	2·155
0·17	1·844	2·701	1·292	1·955	3·517	2·172	2·125

n=number of informative Duchenne families.
Maximum lod scores are underlined.

PC/XT 1985 version).[26] Lod scores were calculated at appropriate recombination fraction intervals. Pedigrees were checked manually for the number of recombinant events between the disease loci and the loci *DXS41, DXS164, DXS84,* and the locus defined by DNA probe pXJ1·1.

Results

Five BMD and 20 DMD kindreds were analysed for linkage to each of the probe loci. The genotypes of informative subjects used in the linkage analysis are shown on the pedigrees in the appendix. The lod scores obtained at 0·01 intervals of the recombination fraction θ for linkage between the four polymorphic loci and the disease loci are shown in table 2 for DMD, table 3 for BMD, and table 4 for the combined DMD and BMD families (the maximum lod scores are also shown in these tables). We have presented the data for the loci defined for the three pERT87 probes separately and have also presented combined data for the *DXS164* locus.

Discussion

The data presented confirm genetic linkage between

TABLE 3 *Lod scores for Becker muscular dystrophy and marker loci defined by the probes used.*

θ	*99·6 (n=3)*	*pERT87·15 (n=4)*	*pERT87·1 (n=2)*	*Combined pERT (n=5)*	*pXJ1·1 (n=2)*	*754 (n=2)*
0·00	−∞	2·364	0·903	2·966	1·505	1·505
0·01	−0·053	2·317	0·881	2·901	1·475	1·475
0·02	0·212	2·268	0·860	2·836	1·444	1·444
0·03	0·352	2·219	0·837	2·768	1·412	1·412
0·04	0·441	2·169	0·815	2·701	1·381	1·381
0·05	0·502	2·120	0·793	2·634	1·349	1·349
0·06	0·545	2·070	0·771	2·567	1·318	1·318
0·07	0·575	2·019	0·749	2·498	1·285	1·285
0·08	0·595	1·967	0·726	2·428	1·252	1·252
0·09	0·608	1·915	0·703	2·358	1·219	1·219
0·10	0·616	1·862	0·680	2·287	1·185	1·185
0·11	0·620	1·809	0·658	2·217	1·152	1·152
0·12	0·618	1·757	0·635	2·146	1·118	1·118
0·13	0·613	1·703	0·612	2·074	1·083	1·083
0·14	0·607	1·648	0·588	2·000	1·048	1·048
0·15	0·597	1·594	0·566	1·929	1·014	1·014
0·16	0·585	1·539	0·543	1·857	0·979	0·979
0·17	0·571	1·483	0·520	1·756	0·943	0·943

n=numbers of informative Duchenne families.
Maximum lod scores are underlined.

TABLE 4 *Lod scores for Duchenne and Becker muscular dystrophy (combined) defined by the probes used.*

θ	*99·6 (n=13)*	*pERT87·15 (n=15)*	*pERT87·8 (n=7)*	*pERT87·1 (n=10)*	*Combined pERT (n=22)*	*pXJ1·1 (n=10)*	*754 (n=16)*
0·00	−∞	7·072	−∞	−∞	−∞	5·118	−∞
0·01	1·839	6·907	1·024	3·003	8·585	5·005	0·805
0·02	2·329	6·741	1·266	3·196	8·634	4·890	1·849
0·03	2·569	6·575	1·383	3·265	8·560	4·776	2·395
0·04	2·706	6·498	1·449	3·282	8·521	4·661	2·733
0·05	2·785	6·637	1·486	3·260	8·400	4·544	2·958
0·06	2·829	6·071	1·505	3·239	8·095	4·428	3·112
0·07	2·846	5·901	1·512	3·196	7·910	4·310	3·215
0·08	2·846	5·732	1·510	3·145	7·711	4·193	3·282
0·09	2·831	5·560	1·510	3·087	7·453	4·075	3·321
0·10	2·803	5·390	1·487	3·022	7·294	3·956	3·337
0·11	2·767	5·219	1·467	2·953	7·079	3·838	3·335
0·12	2·723	5·047	1·444	2·879	6·857	3·718	3·317
0·13	2·671	4·874	1·419	2·802	6·631	3·597	3·286
0·14	2·615	4·702	1·390	2·725	6·403	3·478	3·245
0·15	2·553	4·529	1·359	2·643	6·176	3·357	3·194
0·16	2·486	4·356	1·326	2·560	5·943	3·236	3·134
0·17	2·415	4·184	1·292	2·475	5·686	3·115	3·068

n=number of informative families.
Maximum lod scores are underlined.

DMD and the four polymorphic loci and also between BMD and the polymorphic loci described. This is consistent with previous studies showing similar linkage relationships of BMD and DMD.[6 13] We believe that the combined information from translocations, deletions, and linkage studies now strongly supports the hypothesis that DMD and BMD are allelic and justifies pooling the linkage data for clinical predictive testing. By using hybrid cell lines, translocations, and linkage data, the loci *DXS41* and *DXS84* have been located relative to the disease locus in the following order[8]: telomere→ *DXS41*→*BMD/DMD*→*DXS84*→centromere.

We have combined our results for these two loci with those that have previously been published (tables 5 and 6). This shows linkage between *BMD/DMD* and locus *DXS41,* with a maximum lod score of 11·642 at a recombination fraction of 0·15. The maximum lod score of linkage between locus *DXS84* and *BMD/DMD* is 15·84 at a recombination fraction of 0·15. The lod scores from each study are comparable.

The other two polymorphic loci that we have studied, *DXS164* and the locus defined by probe pXJ1·1, have been shown to be deleted from some boys suffering from DMD and BMD. Approximately 7% of DMD patients have a deletion of the DNA sequences of the pERT87 locus.[15] The screening of affected boys with these two DNA probes has led to the following tentative relationship[15]: telomere→*DXS41*→*DXS164*→pXJ1·1→*DXS84*→ centromere.

The precise location of the closer DNA sequences relative to the disease locus is not known. Hybridisation of these cloned DNA sequences to somatic cell hybrids containing the translocated chromosomes from female patients suffering from BMD and DMD show that the breakpoints of the X chromosome, although cytologically visible at Xp21, do vary, and that some are distal to pXJ1·1 and pERT 87, while others are proximal.[27] The breakpoints all lead to manifestations of the disease, suggesting that both loci are within the region functionally related to muscular dystrophy.

Although locus *DXS164* shows deletions in affected boys, it has been reported to show recombination at about 5%.[15] We have found one crossover between *DXS164* and the disease locus (family

TABLE 5 *Lod scores for DXS84(754) versus (a) BMD, (b) DMD, and (c) BMD + DMD.*

θ	*Walker et al**	*Brown et al*[10]	*Wilcox et al*[8]	*Dorkins et al*[6]	*Davies et al*[9]	*Total*
(a) BMD/754						
0·01	1·475	−5·740				−4·265
0·05	1·349	−0·236	−1·08			0·033
0·10	1·185	1·459	−0·33			2·314
0·15	1·014	2·005	0·04			3·059
0·20	0·835	2·063	0·22			3·118
0·25	0·652	1·861	0·32			2·833
0·30	0·468	1·505	0·35			2·323
0·35	0·294	1·072	0·33			1·696
0·40	0·143	0·630	0·26			1·033
0·45	0·148	0·255	0·15			0·553
(b) DMD/754						
0·01	−0·670	−5·810				−6·480
0·05	1·609	−0·822	4·46	2·78	2·35	10·377
0·10	2·152	0·804	4·24	2·89	2·68	12·766
0·15	2·180	1·411	3·84	2·72	2·63	12·781
0·20	1·996	1·587	3·40	2·43	2·41	11·823
0·25	1·701	1·528	2·91	2·06	2·20	10·399
0·30	1·347	1·318	2·38	1·64	1·72	8·404
0·35	0·973	1·020	0·88	1·19	1·29	5·353
0·40	0·608	0·677	0·60	0·74	0·84	3·465
0·45	0·168	0·326	0·30	0·33	0·39	1·514
(c) BMD + DMD/754						
0·01	0·805	−11·550				−10·745
0·05	2·958	−1·058	3·38	2·78	2·35	10·410
0·10	3·337	2·263	3·91	2·89	2·68	15·080
0·15	3·194	2·416	3·88	2·72	2·63	15·840
0·20	2·831	3·650	3·62	2·43	2·41	14·941
0·25	2·353	3·389	3·23	2·06	2·20	13·232
0·30	1·815	2·823	2·73	1·64	1·72	10·727
0·35	1·267	2·092	1·21	1·19	1·29	7·049
0·40	0·751	1·307	0·86	0·74	0·84	4·498
0·45	0·316	0·581	0·45	0·33	0·39	2·067

Maximum lod scores are underlined.
*This study.

TABLE 6 *Lod scores for DXS41 (99·6) versus (a) BMD, (b) DMD, and (c) BMD+DMD.*

θ	*Walker et al**	*Brown et al*[10]	*Wilcox et al*[8]	*Total*
(a) BMD/99·6				
0·01	−0·053	−1·394		−1·447
0·05	0·502	2·198	0·94	3·640
0·10	0·616	3·194	0·85	4·660
0·15	0·597	3·392	0·76	4·749
0·20	0·520	3·234	0·66	4·414
0·25	0·411	2·871	0·56	3·842
0·30	0·287	2·369	0·46	3·116
0·35	0·165	1·718	0·35	2·223
0·40	0·061	1·154	0·24	1·455
0·45	0·001	0·546	0·12	0·667
(b) DMD/99·6				
0·01	1·892	−2·945		−1·053
0·05	2·283	0·679	3·21	6·172
0·10	2·187	1·752	3·04	6·979
0·15	1·956	2·057	2·88	6·893
0·20	1·666	2·049	2·46	6·175
0·25	1·349	1·860	2·08	5·289
0·30	1·024	1·568	1·68	4·272
0·35	0·710	1·211	1·27	3·191
0·40	0·424	0·823	0·85	2·097
0·45	0·182	0·414	0·42	1·016
(c) BMD+DMD/99·6				
0·01	1·839	−4·339		−2·500
0·05	2·785	2·877	4·15	9·812
0·10	2·803	4·946	3·89	11·639
0·15	2·553	5·449	3·64	11·642
0·20	2·186	5·283	3·12	10·589
0·25	1·760	4·731	2·64	9·131
0·30	1·311	3·937	2·14	7·388
0·35	0·875	2·992	1·62	5·487
0·40	0·485	1·997	1·09	3·572
0·45	0·183	0·960	0·54	1·683

Maximum lod scores are underlined.
*This study.

D6 in the appendix). Our data show a maximum lod score of 8·634 at θ=0·02, supporting the use of a recombination fraction of about 5% for genetic counselling purposes. These two loci are, therefore, closer than any of the previously published linked loci, and so will give a more accurate figure for carrier risks and in prenatal diagnosis. The heterozygote frequencies of the pERT probes indicate that 95% of women will be heterozygous for at least one polymorphic site.

In families where the affected boy shows a deletion of a pERT or pXJ1·1 DNA sequence, the appropriate probe can often be used to give even more accurate counselling, particularly where prenatal diagnosis is required, since the disease causing mutation is effectively being probed directly.

Prenatal diagnosis is best undertaken when the expectant mother is heterozygous for DNA probes which define loci flanking the disease locus.[28] The risk of error then becomes the risk of a double recombinational event, which is very low. Unfortunately, the pERT probes and pXJ1·1 cannot currently be used as flanking markers, in conjunction with other probes, as their precise location relative to the disease locus is not known and may, indeed, vary from family to family. It is, therefore, important to test women with more loosely linked DNA probes as well, to try and establish heterozygous flanking markers. For calculating carrier risks, the pedigree and CK data must also be taken into account.[29]

It is important that the linkage between the disease locus and loci newly defined by DNA probes is constantly reviewed, so that up to date figures can be used in calculating carrier risks and enabling prenatal diagnosis to be carried out more accurately in families at risk for Duchenne and Becker muscular dystrophy.

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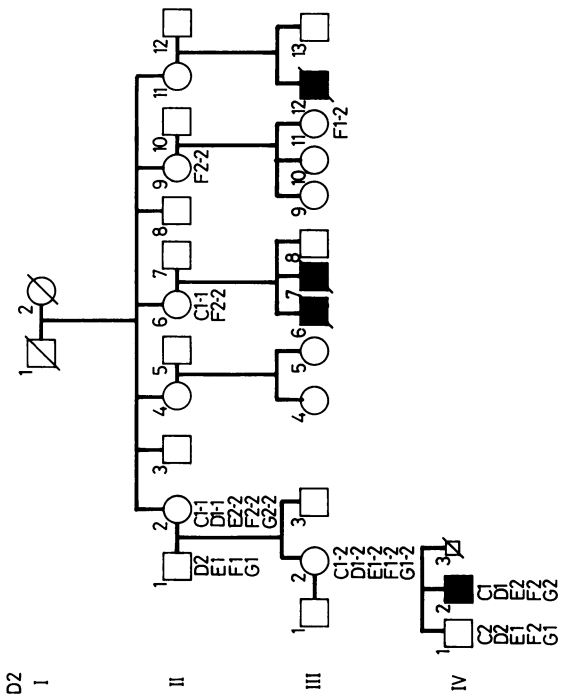
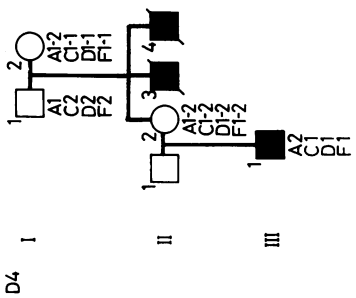
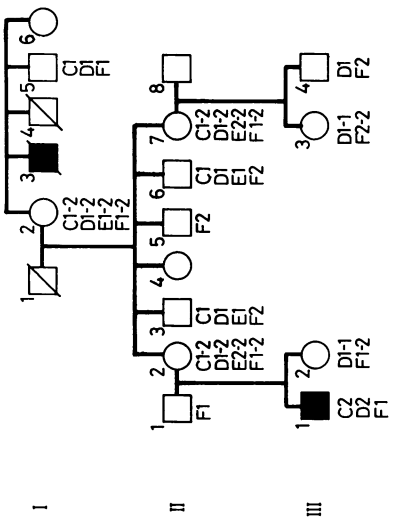
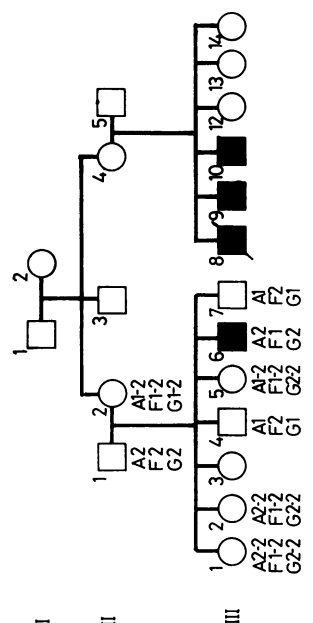
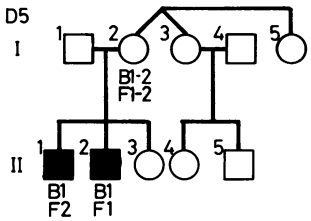
APPENDIX *Pedigrees with genotypes of families used in this study. Prefix B denotes a Becker family and prefix D a Duchenne family. Key to pedigrees: A=99·6. B=pERT87·15/XmnI. C=pERT87·8/BstXI. D=pERT87·1/XmnI. E=pXJ1·1. F=754. G=pERT87·15/TaqI. 1=larger allele size. 2=smaller allele size.*

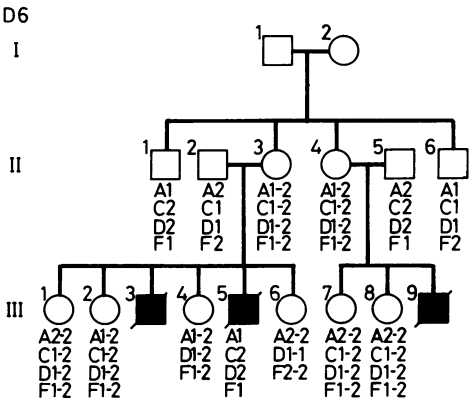


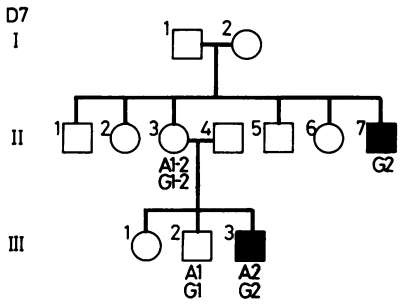


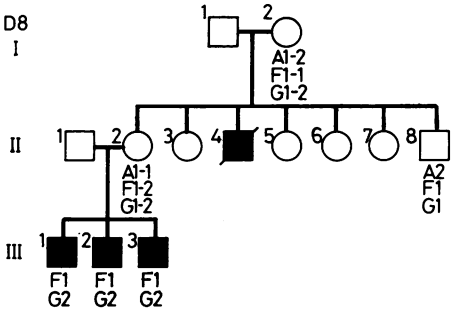


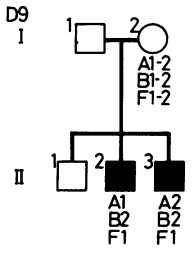


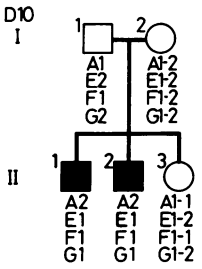


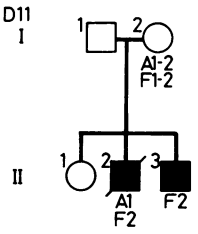


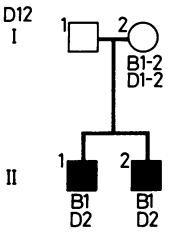


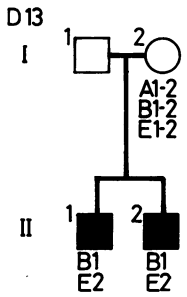


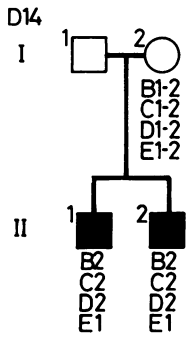


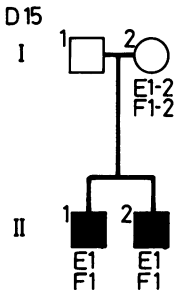


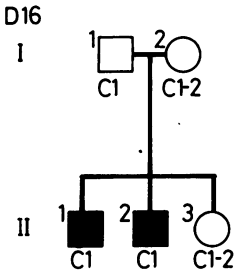


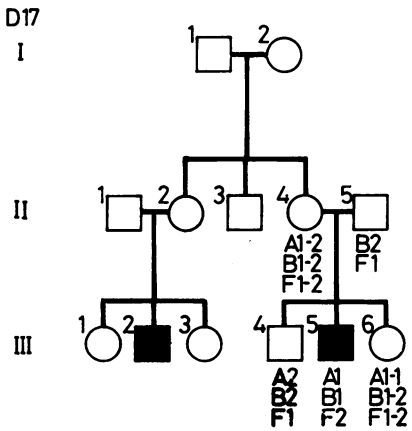


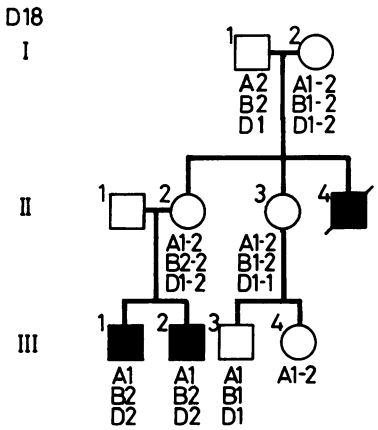


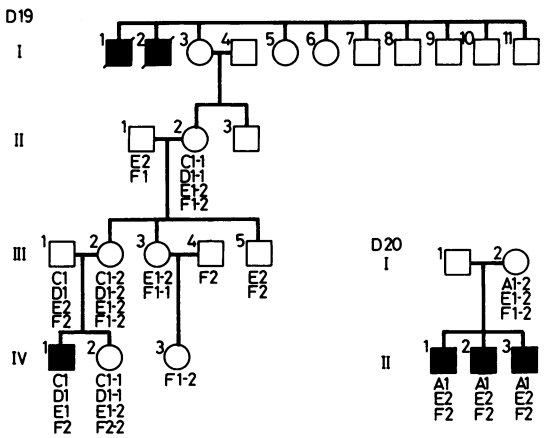


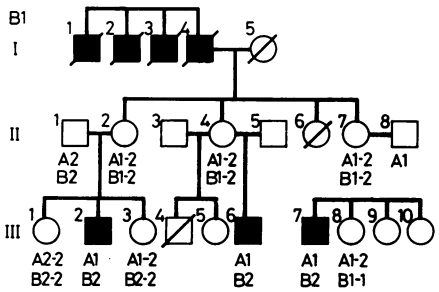


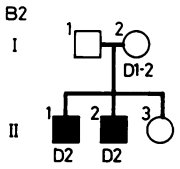


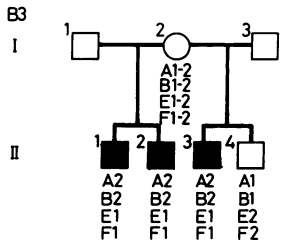


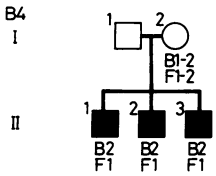


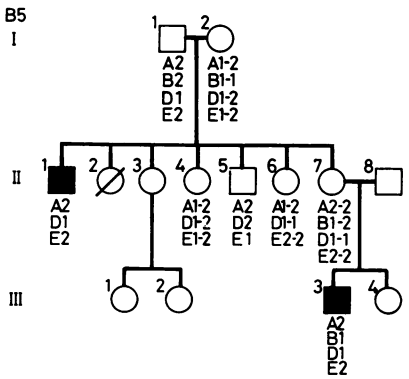












Linkage studies in Duchenne and Becker muscular dystrophies.

A Walker, K Hart, C Cole, S Hodgson, L Johnson, V Dubowitz and M Bobrow

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Notes