An exclusion map for facioscapulohumeral (Landouzy-Déjérine) disease

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SUMMARY By using the genetic linkage data between the facioscapulohumeral muscular dystrophy (FSHD) gene and 57 markers on various autosomes, we have constructed an exclusion map for this disorder. The maximum likelihood location of the FSHD gene and the percentage of the excluded areas on each chromosome are presented here. This exclusion map shows that more than 80% of the genome has been excluded as a likely location of any locus responsible for FSHD in the majority of families. Chromosomes 3, 5, 10, 11, 15, and 19 remain largely unexcluded. Concentration on the highlighted areas of the genome should facilitate the identification of the site of the FSHD gene.

Facioscapulohumeral (Landouzy-Déjérine) muscular dystrophy (FSHD) is one of the more common autosomal dominant disorders in man with variable penetrance and severity. Clinical signs of facial weakness in childhood, with shoulder-girdle weakness and atrophy in the second decade of life or early adulthood are usual, but asymptomatic cases are also common and can be found at any age. The condition may be confused with other syndromes, such as the spinal muscular atrophies and mitochondrial myopathies.¹ Chromosomal localisation of FSHD would help in the differential diagnosis and could resolve the question of genetic heterogeneity, while close linkage would facilitate genetic counselling, prenatal diagnosis, and eventual understanding of the molecular defect.

In order to achieve these goals more rapidly, an international collaboration of groups involved in the linkage analysis of FSHD was organised, as described by Lunt² in this issue. At this meeting it was decided that by pooling the linkage data previously published and those presented at this meeting a significant advance towards the mapping of the gene

would be made. In particular, this would avoid unnecessary reduplication of negative results and would highlight those areas of the genome not yet studied.

We have used the program EXCLUDE³ on the combined data of previously published reports, and on the data provided by the participating groups. The individual data sets from these groups are given in full in the subsequent papers in this issue of the Journal,⁴⁻⁶ while the theoretical background of the EXCLUDE program and the description of it have been given by Edwards³ and Sarfarazi *et al.*⁷

Linkage data

More than five groups^{4-6 8-11} have undertaken genetic linkage studies to map the locus of the FSHD gene, but none has detected a significant linkage between a marker and the disorder. A total of 57 markers on the various autosomes has been tested for possible linkage to FSHD.

All the linkage data from previously published and unpublished work were pooled to be used with the program EXCLUDE. When the lod score was uniformly negative for all values of recombination fraction (θ), the lod score (Z) at $\theta=0.10$ was used. For positive values of lod score ($Z>0$) the maximum value of lod ($Z_{\max}$) and the value of θ at which it

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TABLE 1 Combined linkage data used to obtain the FSHD exclusion map. The first five columns of data were used as input to the EXCLUDE program.

Position on the chromosome	Locus	Data type	θ (cM)	Lod score	r	s	Localisation	Source of data
1-05	PGD	1	0-10	-0-825	1-9	3-7	1p36.2-p36.13	Leiden*
1-08	Rh	1	0-10	-8-386	18-9	37-8	1p36.2-p34	Leiden, Durham
1-31	PGM1	1	0-10	-1-079	2-4	4-9	1p22.1	Leiden, Durham
1-37	AMY1	1	0-10	-0-835	1-9	3-8	1p21	Leiden
1-64	FY	1	0-10	-3-935	8-9	17-7	1q22-q23	Leiden, Durham
2-06	ACPI	1	0-10	-1-745	3-9	7-9	2p25 or 2p23	Leiden
2-34	KM	1	0-10	-0-956	2-2	4-3	2p12	Leiden
3-65	TF	1	0-10	0-071	***	***	3q21	Leiden
4-10	D4S10	1	0-10	-2-750	6-2	12-4	4p16.3-p16.2	Cardiff
4-24	GC	1	0-10	-3-218	7-3	14-5	4q12-q13	Leiden, Durham
4-57	EGF	1	0-00	0-180	0-0	0-6	4q25	Durham†
4-70	FGFB	1	0-10	-0-200	0-5	0-9	4q21-qter	Durham
4-77	MNS	1	0-10	-2-162	4-9	9-7	4q28-q31	Leiden, Durham
5-56	D5S37	1	0-22	0-347	1-1	4-8	5q21	Cardiff‡
5-58	D5S71	1	0-10	-1-717	3-9	7-7	5q21-q22	Cardiff
6-16	HLA-A	1	0-10	-4-120	9-3	18-6	6p21.3	Leiden
6-16	HLA-B	1	0-10	-6-721	15-1	30-3	6p21.3	Leiden
6-16	HLA-C	1	0-10	-5-179	11-7	23-3	6p21.3	Leiden
6-16	HLA-D	1	0-10	-3-892	8-8	17-5	6p21.3	Leiden
6-17	GLO1	1	0-10	-3-861	8-7	17-4	6p21.31-p21.1	Leiden
7-76	MET	1	0-10	-6-190	14-0	27-9	7q31-q32	Cardiff
8-88	GPT	1	0-10	-1-542	3-5	7-0	8q23-qter	Leiden
8-93	TG	1	0-10	-1-410	3-2	6-4	8q24	Cardiff
9-93	ABO	1	0-10	-3-496	7-9	15-8	9q34.1-q34.2	Leiden, Durham
9-93	AKI	1	0-10	-0-321	0-7	1-4	9q34.1-q34.2	Leiden
11-02	HRAS1	1	0-30	0-494	4-2	13-8	11p15.5	Cardiff
11-84	ETS1	1	0-31	0-347	3-3	10-8	11q23.3	Cardiff
12-80	PAH	1	0-10	-3-215	7-2	14-5	12q22-q24.2	Cardiff
13-38	ESD	1	0-10	-3-261	7-3	14-7	13q14.1-q14.2	Leiden, Durham
14-93	PI	1	0-10	-5-715	12-9	25-8	14q32.1	Leiden
14-95	IGHG1	1	0-10	-1-629	3-7	7-3	14q32.3	Cardiff
14-98	AM	1	0-10	-0-282	0-6	1-3	14q32.3	Leiden
14-98	GM	1	0-40	0-225	10-3	25-8	14q32.3	Leiden, Cardiff
14-98	D14S1	1	0-10	-7-488	16-9	33-8	14q32.1-q32.2	Leiden
16-14	HBA1	1	0-10	-11-852	26-7	53-4	16pter-p12	Cardiff, Paris
16-77	APRT	1	0-10	-3-762	8-5	17-0	16q24	Cardiff
16-80	HP	1	0-10	-3-262	7-4	14-7	16q22.1	Leiden, Durham
17-31	D17S71	1	0-10	-3-475	7-8	15-7	17p11-q11	Cardiff
17-66	D17S36	1	0-35	0-212	3-7	10-7	17q	Cardiff
18-06	D18S3	1	0-10	-5-899	13-3	26-6	18p11.3	Cardiff
18-32	D18S7	1	0-35	0-395	7-0	19-9	18q11.1-q11.2	Cardiff
18-33	JK	1	0-10	-1-808	4-1	8-1	18q11.1-q11.2	Leiden, Durham
18-71	D18S8	1	0-38	0-300	9-0	23-8	18q21.3	Cardiff
18-96	D18S11	1	0-10	-6-777	15-3	30-5	18q23	Cardiff
19-14	C3	1	0-10	-0-887	2-0	4-0	19p13.3-p13.2	Leiden, Paris
19-41	LU	1	0-10	0-016	***	***	19q12-q13	Leiden
19-57	APOC2	1	0-20	-0-193	1-0	2-0	19q12-q13.2	Cardiff, Paris
19-70	D19S9	1	0-15	0-667	0-9	5-7	19q12-q13.2	Cardiff
20-22	D20S6	1	0-10	-2-455	5-5	11-1	20p12	Cardiff
20-19	D20S5	1	0-10	-2-100	4-7	9-5	20p12	Cardiff
20-94	ADA	1	0-10	-2-920	6-6	13-2	20q13.2-qter	Leiden
21-43	D21S11	1	0-20	0-185	0-4	2-2	21q11.2-q21	Cardiff, Paris
21-57	APP	1	0-10	-0-380	0-9	1-7	21q21	Paris§
21-96	D21S3	1	0-10	-0-380	0-9	1-7	21q22.3	Paris
22-48	IGLV	1	0-28	0-117	0-8	2-7	22q11.1-q11.2	Cardiff
22-71	PI	1	0-10	-0-308	0-7	1-4	22q11.2-qter	Leiden, Durham
22-73	SISR12	1	0-10	-0-847	1-9	3-8	22q12.3-q13.1	Cardiff

r=equivalent number of recombinants. s=equivalent number of informative meioses. ***Too little information; data not included in the exclusion map.

*For Leiden data see references 10 and 11. †For Durham data see reference 5. ‡For Cardiff data see reference 4. §For Paris data see reference 6.

occurred were used. The overall linkage data available on FSHD are summarised in table 1. The chromosomal position in table 1 is denoted by the chromosome number, a full stop, and the location of the marker on that chromosome expressed as % of pter to qter. For example, the value of 1.08 for *Rh* means that this marker is on chromosome 1 at an approximate position of 8% from the telomere. When the localisation of a marker on the chromosome is expanded over a region of that chromosome, the location of that marker is taken to be in the middle of that region, and then the percentage of position is calculated. For two markers where too little information was available (*TF* on chromosome 3 and *LU* on chromosome 19) the data were excluded from the map.

Input to program EXCLUDE consists of chromosomal position, locus name, a number defining the types of data (1 for this data set), followed by the linkage data given in the form of θ and Z (first five columns of table 1). Each of these fields is separated by a few spaces. As the program starts to read each of the data sets on a separate line, it calculates the equivalent number of informative meioses (s), number of recombinants (r), and the ratio r/s (table 1). For a given value of recombination fraction (θ) and the corresponding value of lod score (Z), the equivalent number of informative meioses (s) is obtained from:

$$s = Z / \{ \theta * \log(2\theta) + (1-\theta) * \log(2(1-\theta)) \}$$

and the equivalent number of recombinants will be:

$$r = s * \theta.$$

The program then accesses an internal file which contains the approximate genetic length of each of the human chromosomes given in centimorgans for both male and female chromosomes. The program

FIGURE The exclusion map for FSHD. The shaded area of the chromosome shows the possible location of the disease gene and the white area the excluded zones.

TABLE 2 Results from program EXCLUDE, showing the most likely location of the FSHD gene.

Chromosome No	Length (cM)	No. of loci	Chromosomal probability		Maximum likelihood for FSHD location
			Relative (%)	Maximum (%)	
1	250	5	8.67	1.68	1.00
2	225	2	7.80	7.28	1.00
4	180	5	6.24	0.58	1.08
5	180	2	6.24	9.73	2.22
6	170	5	5.89	2.14	0.97
7	160	1	5.55	2.83	0.90
8	150	2	5.20	4.73	0.98
9	150	2	5.20	4.62	0.97
11	140	2	4.85	27.60	6.47
12	140	1	4.85	3.19	0.92
13	100	1	3.47	0.73	0.53
14	100	5	3.47	0.91	1.06
16	90	3	3.12	0.00	0.29
17	80	2	2.77	0.20	0.40
18	80	5	2.77	0.00	1.25
19	70	3	2.43	2.96	2.67
20	70	3	2.43	0.00	0.52
21	50	3	1.73	1.09	1.53
22	50	3	1.73	0.52	1.25

Maximum chromosomal probability 27.60%.
Maximum likelihood for FSHD location 6.47 (lod=0.81).

TABLE 3 Exclusion area for each individual chromosome.

Chromosome	Length (cM)	Maximum chromosomal probability (%)	Total area of chromosomes			
			Not excluded		Excluded	
			(cM)	(%)	(cM)	(%)
1	250	1.68	4.2	0.15	245.8	8.52
2	225	7.28	16.4	0.57	208.6	7.23
3	200	100.00	200.0	6.93	0.0	0.00
4	180	0.58	1.0	0.04	179.0	6.20
5	180	9.73	17.5	0.61	162.5	5.63
6	170	2.14	3.6	0.13	166.4	5.77
7	160	2.83	4.5	0.16	155.5	5.39
8	150	4.73	7.1	0.25	142.9	4.95
9	150	4.62	6.9	0.24	143.1	4.96
10	150	100.00	150.0	5.20	0.0	0.00
11	140	27.60	38.6	1.34	101.4	3.51
12	140	3.19	4.5	0.15	135.5	4.70
13	100	0.73	0.7	0.03	99.3	3.44
14	100	0.91	0.9	0.03	99.1	3.43
15	100	100.00	100.0	3.47	0.0	0.00
16	90	0.00	0.0	0.00	90.0	3.12
17	80	0.20	0.2	0.01	79.8	2.77
18	80	0.00	0.0	0.00	80.0	2.77
19	70	2.96	2.1	0.07	67.9	2.35
20	70	0.00	0.0	0.00	70.0	2.43
21	50	1.09	0.6	0.02	49.4	1.71
22	50	0.52	0.3	0.01	49.7	1.72
Totals	2885		559.1	19.38	2325.9	80.62

calculates the positional likelihood of the disease locus on each chromosome, and also the percentage probability of any locus being on any of the 22 autosomes (table 2). The last two columns of table 2 give the maximum values of likelihood and probability of FSHD being on that chromosome. The figure is the graphical representation of these values. Table 3 complements the exclusion map by showing the exact area and the percentage of each chromosome being excluded as a likely position of the FSHD gene. As this table shows, more than 80% of the genome has already been excluded as a likely site for the FSHD gene.

Results and discussion

The additional data presented in this volume of the Journal provide the means of constructing an exclusion map for the FSHD locus. Before the workshop, data on a total of 29 linkage markers previously published were available. These loci were spread over 14 chromosomes. Now that the linkage data on FSHD have been expanded to 57 loci, more areas of the genome have been excluded as the likely site of the FSHD gene. There were no linkage data available for chromosomes 10 and 15, and the only data on chromosome 3 had to be excluded owing to the low lod score, these taken together representing about 16% of the genome. The overall data show that the most likely location for the FSHD gene is on chromosome 11 with a likelihood of 6.47 times more likely than being on any other chromosome. Other possible chromosomes are 19 (likelihood of 2.67) and 5 (likelihood of 2.22). Other areas of the genome that still need more linkage data are 2q, 6q, 7p, 8p, 9p, 12p, and 21p. As this exclusion map clearly shows, the chance of the disease gene being on any other chromosome is very remote.

The indication from the exclusion map that the FSHD gene lies on one of the chromosomes 3, 5, 10, 11, 15, or 19 will give impetus to the use of markers

on those chromosomes and to the search for new informative polymorphisms in this area of the genome. The possibility must also be considered, however, that genetic heterogeneity might mask a positive result. While the existence of a number of large individual kindreds in the various studies makes this unlikely, a careful analysis for heterogeneity would be required in the event of negative results for those chromosomes not currently excluded.

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