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A linkage map of 10 loci flanking the Marfan syndrome locus on 15q: results of an International Consortium Study

This paper is dedicated to the memory of Dr David Hollister, a physician, scientist, and friend, whose seminal contributions in connective tissue research, and Marfan syndrome in particular, have shaped the field.

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Abstract

Members of an International Consortium for Linkage Analysis of the Marfan Syndrome (MFS1) have pooled data for joint analysis in an attempt to determine the precise location of the MFS1 gene and the order of 10 DNA markers on 15q. Five laboratories performed a total of 2111 genotypes in 22 families consisting of 225 affected and 248 normal subjects. For each marker a mean of 98 meioses was informative. *D15S48* and *D15S1* were identified as the closest linked markers with 99% upper confidence intervals of 12% and 13% respectively. We have used the CRI-MAP program to construct the most likely order as: *D15S24-D15S25-D15S1-MFS1-D15S48-D15S49-(D15S45/S51)-(D15S29/S38)*. Placement of *D15S2* in relation to *-D15S1-D15S48-* cannot be determined with certainty. The genetic map of these markers extends 53·6 cM in males and 65·0 cM in females with a sex averaged map of 60·7 cM. The sex difference was statistically significant ($p = 0·005$). Linkage heterogeneity between 22 MFS1 families was documented ($p = 0·009$) necessitating the exclusion of one family from the analysis. However, comparison of the remaining 21 families for two point and multipoint lod scores showed no evidence for linkage heterogeneity of the MFS1 locus.

Marfan syndrome (MFS1) is an autosomal dominant connective tissue disorder with an estimated prevalence of about 4 to 6 per 100 000 persons.[1] The diagnosis of Marfan syndrome is entirely dependent on internationally agreed clinical criteria.[2] The lack of a specific genetic or biochemical test compounded by the presence of significant variability of clinical expression between subjects and families gave impetus to an active search for the localisation, identification, and characterisation of the MFS1 gene. In response to this need, an International Consortium for MFS1 linkage was organised to expedite this process by sharing DNA probes, exchanging information on research techniques, and by pooling data. From the combined results of genetic linkage presented at the first meeting of the Consortium[3] or subsequently sent to one of us (MS), an initial exclusion map of this condition was constructed.[4] Other exclusion maps for the MFS1 locus were produced periodically. The last map constructed in May 1990 was based on more than 140 markers.

Shortly after this the MFS1 locus was assigned to chromosome 15 by positional mapping in five Finnish families[5]; confirmation of this location has followed in other families and with additional probes.[6–8] Rapid progress has since been made in the fine mapping of this locus. In this paper we report the combined two point and multipoint linkage analyses of *MFS1* and 10 DNA markers on the 15q15–q21 region from analysis of the pooled data from all participating groups. This has allowed an accurate ordering of the DNA markers, improved the estimates of genetic distances, and determined the exact location of the MFS1 locus, which was not necessarily discernible in each individual dataset. Five members of the MFS1 Consortium submitted their pedigrees and genotypic data for use in a combined genetic analysis.

Methods

THE FAMILY PANEL

The Consortium members contributed a total of 22 autosomal dominant MFS1 families for the joint analyses. All pedigrees and their genotypic data were transferred into the DBLINK database[9] and subsequently plotted using the dedicated pedigree drawing program PLOT2000.[10] Pedigrees were then screened for incompatibilities, structural, genotypic, coding, and typing errors both manually and by an initial screening of recombinants. Any discrepancies were resolved through discussion with the contributing investigator and by resampling and retyping those subjects concerned. The composite clinical phenotype of each family studied was consistent with the diagnosis of MFS1 according to diagnostic criteria previously established and widely accepted.[2]

Table 1 DNA markers used in this study.

Locus	Probe	Enzyme	Allele frequency*	H†	PIC‡	Reference
D15S24	CMW1	*Eco*RI	0·19§	0·74	0·69	Rich *et al*[11]
D15S25	pTHH114	*Rsa*I	0·41	0·49	0·37	Nakamura *et al*[12]
D15S2	pDP151	*Eco*RI	0·29	0·41	0·33	Brissenden *et al*[13]
D15S1	pMS1-14	*Msp*I	0·39	0·48	0·36	Barker *et al*[14]
D15S48	CRI-L442	*Msp*I	0·16‖	0·73	0·69	Donis-Keller *et al*[15]
D15S49	CRI-L1204	*Msp*I	0·38	0·47	0·36	Donis-Keller *et al*[15]
D15S51	CRI-P452	*Msp*I	0·26	0·39	0·31	Donis-Keller *et al*[15]
D15S45	pEFZ33	*Hin*dIII	0·29	0·41	0·33	Fujimoto *et al*[16]
D15S29	pEFD49.3	*Taq*I	0·28	0·41	0·33	Fujimoto *et al*[17]
D15S38	pEFD49.2	*Taq*I	0·29	0·49	0·37	Fujimoto *et al*[18]

* The least frequent allele. Allelic frequencies, H, and PIC values are based on our sample. † H = heterozygosity. ‡ PIC = polymorphic information content. § Multiallelic system. ‖ Haplotyped frequency.

Table 2 Summary of the pedigrees and their genotypic data.

Centre	No of families	No of affected/totals	No of genotypes
Farmington	13	123/241	1273
Birmingham	5	41/75	238
Edinburgh	2	19/35	111
Dundee	1	14/33	241
Paris	1	28/89	248
Totals	22	225/473	2111

The 22 pedigrees combined a total of 478 subjects with an average number of 22 persons per pedigree (16 children and six sets of parents). The dataset included 225 affected and 248 unaffected subjects, as well as five of unknown clinical status whose genotypic data were useful in ordering the DNA markers, but were not used to determine the location of *MFS1*. The DNA markers used in this study are listed in table 1. A total of 2111 genotypes was performed by the participating laboratories using 10 DNA markers (table 2).

Linkage analysis

A total of five laboratories has contributed genotypic data on 10 DNA markers. One of the markers, *D15S48*,[15] is polymorphic for more than one enzyme so the genotypic data of this marker have been haplotyped in all subsequent analyses. Table 3 summarises the genetic linkage data contributed by the Consortium members on the MFS1 locus and the DNA markers. There is a total of 317 informative meioses for the MFS1 locus of which 235 are potentially phase known. The largest number of subjects was genotyped for *D15S1* (170) and the smallest number for *D15S51* and *D15S38* (24 and 25 respectively), with an average of 98 meioses per marker.

Table 3 Summary of linkage data for the combined dataset.

	Total No of informative			
	Families	Phase known	Phase unknown	Meioses
MFS1	22	235	82	317
D15S24	8	7	61	68
D15S25	12	5	76	81
D15S2	15	4	94	98
D15S1	18	9	161	170
D15S48	17	11	144	155
D15S49	10	6	91	97
D15S51	5	0	24	24
D15S45	10	3	96	99
D15S29	8	8	104	112
D15S38	1	0	25	25

The two point univariate linkage analyses between the MFS1 locus and the DNA markers and between the markers themselves were carried out with the MLINK program of the LINKAGE package[19] (v 5·03). The Marfan locus was defined as having full penetrance and a population frequency of 0·0001. The sex specific and sex averaged analyses were carried out with CRI-MAP (v 2·4·2) program (P Green, personal communication).[15 20] The heterogeneity testing was carried out with both the HOMOG (v 3·0) and HOMOG2 (v 2·75) programs.[21] The multipoint analysis was performed using the CRI-MAP program.

In order to construct a more accurate map, we first used the available genotypic data from version 4 of the CEPH database[22] and built a framework map[23] of all the markers in the region of the interest. Sex specific and sex averaged maps were then generated for this map. The estimated recombination fractions between the loci obtained by the multipoint linkage analysis were converted to centimorgans using the Kosambi mapping function.

Results

Initial examination of recombinants between the MFS1 locus and the marker loci identified one family (French pedigree) as being different from the remaining 21. Affected members of this family had typical skeletal and cardiovascular manifestation but none had ectopia lentis after careful slit lamp examination.[24 25] This family is only informative for *D15S1*, *D15S48*, *D15S49*, and *D15S38*. Multipoint linkage analysis of this family and the fixed order of *D15S1-MFS1-D15S48-D15S49-D15S38* produced a location score of −0·463. For this order, three subjects (two normal males and one affected female) showed double crossovers with *MFS1* and the four DNA markers (out of a total of 14 recombinants). The highest location score (1·482) for this family was obtained when *MFS1* was placed distally to *D15S38*. Under this assumption the three double crossovers can be explained by a single crossover event. Analysis of heterogeneity testing with the HOMOG program and for *D15S1* showed that this family is significantly different from others ($p = 0·009$, table 4). Because of this observation we decided to exclude this family from further analysis. All the data presented in tables 5, 6, 7, and 8 exclude this family and are only based on the remaining 21 families.

Table 4 Result of MFS1 heterogeneity testing with marker loci using the HOMOG program.*

Locus	Including the French family				Excluding the French family			
	No	χ^2_1	p	L(R)	No	χ^2_1	p	L(R)
D15S24	8	0·00	0·500	1·00	8	0·00	0·500	1·00
D15S25	12	0·00	0·500	1·00	12	0·00	0·500	1·00
D15S1	18	5·44	0·009	15·16	17	0·00	0·500	1·00
D15S2	15	2·41	0·060	3·34	15	2·41	0·060	3·34
D15S48	17	0·00	0·500	1·00	16	0·00	0·500	1·00
D15S49	10	0·00	0·500	1·00	9	0·00	0·500	1·00
D15S51	5	0·00	0·500	1·00	5	0·00	0·500	1·00
D15S45	10	0·39	0·265	1·22	10	0·39	0·265	1·22
D15S29	8	0·00	0·500	1·00	8	0·00	0·500	1·00
D15S38	1	Not done			0	Not done		

* HOMOG assumes that there are two family types, one with linkage ($\theta < 1/2$) and one without linkage ($\theta = 1/2$).
No = number of families tested.
L(R) = likelihood ratios in favour of heterogeneity.

The results of pairwise analyses between each of the 10 DNA markers and the MFS1 locus obtained by using the CRI-MAP program are presented in table 5. Since the algorithms incorporated in CRI-MAP do not carry out a full likelihood calculation (which may lead to the loss of some available information),[15 20] we also used the MLINK program to confirm and compare the estimated values of recombination fractions between *MFS1* and the marker loci. The summary of pairwise lod scores of *MFS1* versus each marker locus, using both CRI-MAP and LINKAGE programs, is shown in table 6. Two of the markers, *D15S48* and *D15S1*, are closely linked to *MFS1* ($\theta = 0{\cdot}03$). The upper 99% confidence limits (-2 lods of Zmax) for these two markers are 12% and 13% respectively. All the other markers showed looser linkage to the MFS1 locus in both males and females. There are only two phase known recombinants (excluding the French family) between *D15S1* and *MFS1* in a total of 134 informative meioses scored. One of these recombinants is in a 12 year old affected female.[8] The second recombinant is in an 8 year old affected male with Marfanoid habitus and dilatation of the aortic root. The original typing of these two subjects and their immediate relatives has been confirmed after the resampling and retyping of those subjects concerned. The two recombinants for *D15S1* are the only ones reported so far. In the original Finnish families[5] (L Peltonen, personal communication) and the four families reported by Dietz *et al*[6] there are no recombinants between *MFS1* and *D15S1*. Out of a total of 124 informative meioses scored in 16 pedigrees, there were only two phase unknown recombinants between *MFS1* and *D15S48*. Other recombinants for *D15S48* have also been reported previously.[6] Application of the χ^2 test[26] for sex specific and sex averaged lod scores obtained by the CRI-MAP program (table 6) showed significance for the *MFS1-D15S45* interval ($\chi^2_1 = 5{\cdot}57$, $p = 0{\cdot}018$).

There is a total of 64 recombinant events (40 maternally and 24 paternally derived) in the 21 families studied here. Examination of those crossovers showed that they involved 53 subjects. Some subjects were crossed over for more than two markers while others showed crossovers in both maternal and paternal chromosomes. Given the order of loci obtained in this study (table 8), six subjects were scored as possible double crossovers. The phase of parental chromosome in five of these subjects was unknown and, additionally, four of the crossovers occurred in the unaffected spouse's chromosome. The only phase known double crossover was scored in an affected male whose affected mother was only informative for *D15S25* and *D15S49*. All affected members of this family have skeletal, cardiovascular, and ocular manifestations. The confirmed crossover was *D15S25-X-MFS1-X-D15S49*. Since the genetic distance between *D15S25* and *D15S49* in the CEPH families is estimated to be around 15 cM (table 7), the observation of this double crossover could be explained given the estimated map distances between the two loci.

The sex averaged results of the two point linkage obtained from the MLINK program

Table 5 Two point linkage between the MFS1 locus and the marker loci (results are from CRI-MAP program).

Locus		0·001	0·05	0·10	0·15	0·20	0·25	0·30	0·35	0·40	0·45
D15S24	F	−12·04	−2·11	−0·59	0·17	0·60	0·85	0·97	1·00	0·96	0·90
	M	−2·54	0·60	0·93	1·00	0·96	0·86	0·72	0·55	0·38	0·24
	M+F	−15·58	−2·51	−0·66	0·17	0·56	0·71	0·69	0·55	0·35	0·14
D15S25	F	1·52	4·46	4·57	4·41	4·12	3·75	3·31	2·83	2·33	1·87
	M	4·58	4·42	4·26	4·09	3·90	3·71	3·51	3·30	3·10	2·92
	M+F	1·51	4·30	4·25	3·92	3·45	2·89	2·27	1·61	0·96	0·39
D15S2	F	0·70	2·01	1·91	1·67	1·40	1·11	0·84	0·59	0·39	0·23
	M	−4·38	0·57	1·31	1·66	1·86	1·96	2·00	2·01	1·99	1·96
	M+F	−5·69	0·56	1·20	1·32	1·24	1·06	0·83	0·59	0·37	0·18
D15S1	F	7·20	6·68	6·13	5·55	4·96	4·34	3·71	3·09	2·49	1·96
	M	3·93	6·98	7·21	7·17	7·02	6·79	6·52	6·20	5·86	5·50
	M+F	3·92	6·44	6·12	5·51	4·77	3·94	3·08	2·20	1·37	0·62
D15S48	F	9·63	12·10	11·70	11·01	10·17	9·23	8·20	7·11	5·96	4·85
	M	12·09	11·68	11·24	10·79	10·31	9·81	9·29	8·77	8·25	7·76
	M+F	9·63	11·68	10·85	9·72	8·43	7·03	5·56	4·04	2·52	1·12
D15S49	F	−3·08	1·68	2·26	2·45	2·48	2·40	2·26	2·06	1·82	1·53
	M	2·48	2·41	2·33	2·24	2·15	2·05	1·94	1·83	1·70	1·56
	M+F	−2·99	1·70	2·16	2·23	2·14	1·93	1·66	1·32	0·93	0·49
D15S51	F	0·22	0·23	0·23	0·19	0·19	0·14	0·13	0·09	0·07	0·03
	M	0·10	0·08	0·06	0·04	0·02	0·01	0·00	0·00	0·00	0·00
	M+F	0·32	0·31	0·28	0·23	0·21	0·15	0·14	0·08	0·07	0·02
D15S45	F	−0·58	4·26	4·89	5·12	5·20	5·17	5·09	4·96	4·81	4·66
	M	5·19	4·75	4·29	3·80	3·28	2·75	2·21	1·67	1·17	0·76
	M+F	−0·59	3·81	3·97	3·72	3·28	2·73	2·11	1·47	0·86	0·35
D15S29	F	−5·60	1·29	2·38	2·90	3·17	3·30	3·34	3·32	3·27	3·20
	M	2·02	3·34	3·23	2·98	2·65	2·28	1·87	1·43	1·00	0·60
	M+F	−8·21	1·28	2·33	2·60	2·53	2·26	1·87	1·39	0·89	0·40
D15S38	F	0·00	0·00	0·00	0·00	0·00	0·00	0·00	0·00	0·00	0·00
	M	−1·20	0·35	0·49	0·49	0·44	0·36	0·26	0·17	0·08	0·02
	M+F	−1·20	0·35	0·49	0·49	0·44	0·36	0·26	0·17	0·08	0·02

Table 6 Comparison of two point lod scores from CRI-MAP and LINKAGE programs.

	CRI-MAP					LINKAGE		
	Sex specific			Sex averaged		Sex averaged		−1 lods confidence interval
Loci pair	θ_m	θ_f	Lods	θ	Lods	θ	Lods	
MFS1-D15S24	0·15	0·34	1·00	0·27	0·72	0·21	1·48	0·09→0·40
MFS1-D15S25	0·00	0·09	4·58	0·07	4·34	0·04	7·53	0·00→0·13
MFS1-D15S2	0·33	0·05	2·01	0·15	1·32	0·08	4·31	0·02→0·21
MFS1-D15S1	0·11	0·00	7·21	0·05	6·44	0·03	12·73	0·00→0·09
MFS1-D15S48	0·00	0·04	12·10	0·03	11·79	0·03	17·24	0·00→0·09
MFS1-D15S49	0·00	0·18	2·48	0·14	2·24	0·15	2·87	0·05→0·33
MFS1-D15S51	0·00	0·01	0·32	0·00	0·32	0·00	0·31	0·00→0·50
MFS1-D15S45	0·00	0·21	5·20*	0·09	3·99*	0·08	5·85	0·02→0·19
MFS1-D15S29	0·05	0·31	3·34	0·15	2·60	0·26	1·29	0·13→0·46
MFS1-D15S38	0·13	0·00	0·50	0·13	0·50	0·38	0·05	0·00→0·50

* Test for $\theta_m = \theta_f$ is significant ($\chi^2_1 = 5·57$, $p = 0·018$).

were used to test for homogeneity of the MFS1 family panel with regard to the DNA markers studied by the members of the Consortium (table 4). In order to conduct a more accurate test, we also calculated the multipoint linkage likelihoods for each family, assuming the most likely order as obtained from the CEPH dataset (table 7) and by placing the *MFS1* locus between the *D15S1* and *D15S48*. Following the conversion of these likelihoods into their equivalent lod scores they were used in the HOMOG program to test for heterogeneity of *MFS1* with respect to the marker loci. As shown in table 4, by excluding the French family the likelihood ratios in favour of heterogeneity of the MFS1 locus do not reach the 5% level of significance for any of the markers tested or for the multipoint lod scores (with a likelihood ratio of 1·00). Thus, *MFS1* is linked to chromosome 15 markers in all of the 21 families studied here.

The estimated genetic distance between most of the markers in the present sample is larger than those estimated in the CEPH panel (data not shown). This is mainly because most typings in the Marfan families have been performed selectively, so that not all of the families are genotyped for all of the 10 DNA markers. Because of this, we have decided to construct the 10 point map of markers using both the CRI-MAP program and the CEPH family panel as described before. We first made an initial framework map[23] with likelihood ratios of $\geq$1000:1 (lods of $\geqslant$3·00) and subsequently inserted other loci into it. Every time a new marker was inserted into the map and a new order was obtained, all the loci were permutated to check the validity of the map. Since there are no recombinants in the interval of *D15S29-D15S38* in the CEPH families (Z = 12·33) and, additionally, they are known to be from the same cosmid clone,[17 18] these two markers were haplotyped while building up the map. Similarly, since there are no recombinants between *D15S51* and *D15S45* in the CEPH family panel (Z = 4·92), they were always kept together (haplotyped, but distances not forced to 0·0) for further analysis. This process was continued until the following most likely order was obtained: *D15S24-D15S25-D15S1-D15S48-D15S49-(D15S45-*S51)-(*D15S29*/S38).

When all the loci within this map were permutated two to three loci at a time, only two orders out of a total of 21 tested had likelihood ratios of < 1000:1. The first of these orders inverts the position of *D15S25* and *D15S1* (145 times less likely); the second order inverts the position of *D15S1* and *D15S48* (71 times less likely). The sex specific and sex averaged genetic maps for the above order are shown in table 7. Distances in each interval were computed from the maximum likelihood estimates of recombination fractions using the Kosambi mapping function and are measured in cM. The overall length of this map is 53·6 cM in males and 65·0 cM in females with an averaged map distance of 60·7 cM. Comparison of the likelihood for sex specific and sex averaged maps is statistically significant ($\chi^2_7 = 20·17$, $p = 0·005$). We have not been able to position *D15S2* in relation to the *D15S1-D15S48* interval. However, all other odds against the location of *D15S2* in any other position of this map were > 1000:1.

We then used this map and attempted to insert the MFS1 locus using all the 21 families (excluding the French family) that were contributed by the Consortium members. The evidence for the location of *MFS1* is summarised in table 8. The most likely location for *MFS1* is between *D15S1* and *D15S48*. The second best location is between *D15S25* and *D15S1* (odds against it being 676:1). All other locations had odds of greater than 1000:1 against that order.

Table 7 Ten point linkage map of loci on 15q15→q21 region. Map is generated using the CEPH genotypic data.

	Sex averaged	Sex specific		Odds against inversion of adjacent loci
	θ cM	θ_m	θ_f	
D15S24				
	23·6	25·7	20·6	10^{15}:1
D15S25				
a	7·6	10·0	4·6	145:1
D15S1				
D15S2 b	1·1	0·0	2·7	71:1
D15S48				
c	5·3	3·6	6·5	10^4 :1
D15S49				
	14·0	12·2	15·1	10^{15}:1
D15S51 — *D15S45**				
	9·2	2·2	15·6	10^5 :1
D15S38 — *D15S29*†				
	60·7	53·6	65·0	

The likelihood comparison for sex averaged and sex specific is statistically significant ($\chi^2_7 = 20·17$, $p = 0·005$).
[a] Odds for placement of *D15S2* = 1:9·57 (least likely).
[b] Odds for placement of *D15S2* = 1:1 (most likely).
[c] Odds for placement of *D15S2* = 1:1·02.
* Haplotyped system (distances not forced to 0·0).
† Haplotyped system (distances forced to 0·0).

Table 8 Evidence supporting the location of the MFS1 locus.

Insertion of MFS1 locus into the fixed map	Location score	Odds against the location of the MFS1 locus
MFS1—S24—S25—S1—S48—S49—S45—(S29,S38)	5·028	10^{15}:1
S24—*MFS1*—S25—S1—S48—S49—S45—(S29,S38)	15·970	10^{4}:1
S24—S25—*MFS1*—S1—S48—S49—S45—(S29,S38)	17·366	676:1
S24—S25—S1—*MFS1*—S48—S49—S45—(S29,S38)	20·191	Best order
S24—S25—S1—S48—*MFS1*—S49—S45—(S29,S38)	16·680	10^{4}:1
S24—S25—S1—S48—S49—*MFS1*—S45—(S29,S38)	14·924	10^{5}:1
S24—S25—S1—S48—S49—S45—*MFS1*—(S29,S38)	11·340	10^{9}:1
S24—S25—S1—S48—S49—S45—(S29,S38)—*MFS1*	10·109	10^{10}:1

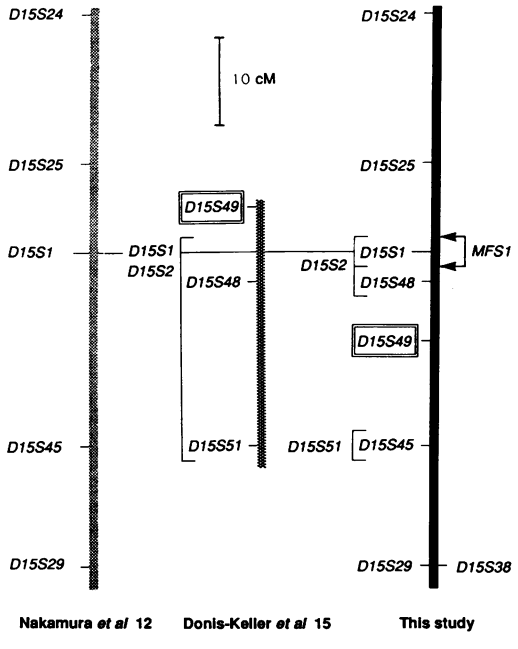
Discussion

Genetic linkage analysis of 2111 genotypes with 10 DNA markers in 22 families contributed by five members of the MFS1 Consortium provided the means for an accurate estimate of recombination fraction and confidence intervals. Initial analysis of recombinants identified one family as being different from the others. Since the heterogeneity testing for this family as compared with the others was significant, this family was excluded from further analysis. The two markers *D15S1* and *D15S48* showed close linkage to the MFS1 locus ($\theta = 0{\cdot}03$). Sex averaged and sex specific lod scores computed between all the markers and the MFS1 locus confirm linkage of all DNA markers both in males and in females (tables 5 and 6). However, there is a significant excess of recombination in females for the *MFS1-D15S45* ($p = 0{\cdot}018$) interval (table 6). The overall genetic map of the DNA markers in the CEPH families is estimated to be 53·6 cM in males and 65·0 cM in females given an excess female ratio of 1·21 (table 7). The overall sex difference in the estimated maps was tested by comparing the likelihood values for the sex specific and sex averaged maps. Application of χ^2 approximation to the generalised likelihood ratio test yielded a χ^2_7 of 20·17 which has an associated p value of 0·005.

When the two likelihood ratios of heterogeneity versus homogeneity of *MFS1* were estimated (using both two point and multipoint lod scores of all the DNA markers), no significance was detected at the 5% level (table 4). This either indicates that MFS1 is a homogeneous disorder, or the present sample size is not sufficient to detect genetic heterogeneity. However, as mentioned above, one of the families showed significant heterogeneity for only *D15S1* ($p = 0{\cdot}009$) but not for *D15S48* and other markers (table 4). This family was excluded from all subsequent analyses.

Our newly generated map for this region of chromosome 15 integrated the two previously reported maps[12 15] in which *D15S1* was the only common marker (figure). The order of the loci in our map is in agreement with each of the two published maps with the exception of *D15S49* which was previously positioned proximal to *D15S48* by Donis-Keller *et al*[15] (that is 15 136 times less likely in our map). The orientation of *D15S24* and *D15S1* in our map is also consistent with the results of cytogenetic localisation.[11 13]

The genetic linkage map of *MFS1* and the DNA markers can be moderately constructed with relative odds of at least 676:1 for the best order against the next alternative one (table 8). As is shown in table 8, the most likely location for the MFS1 gene is between *D15S1* and *D15S48*. Odds against the MFS1 locus being in any other location is of a magnitude of 10^4 to 10^{15}.



Comparison of the female map generated in this study with those published previously. Only the relevant portion of DNA markers in the two published maps that are common to this study is shown. The order of loci obtained in this study is consistent with the order of two published maps with the exception of D15S49. D15S1 was the only common marker between the two previously published maps.

The combined effort of the Consortium in pooling genotypic data brought about a common goal of defining a fine map of the *MFS1* region. As a result of this effort the assignment of *MFS1* to the 15q15–q21.1 region in a total of 21 families is now established. We have also been able to identify two closely linked markers, *D15S48* and *D15S1*. Owing to the large number of meioses studied for these markers, we can now define 99% upper confidence intervals of 12% and 13% for these two markers respectively.

Recently, the gene encoding fibrillin has been isolated and localised to chromosome 15.[27 28] Genetic linkage studies using fibrillin specific DNA markers established linkage of Marfan syndrome to this gene[27 29] and additionally identified mutation[29] in the fibrillin gene in two isolated Marfan patients. These

markers can now be used for diagnostic purposes in subjects at risk for this condition.

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