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Linkage data for Marfan syndrome and markers on chromosomes 1 and 11

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Abstract

Six large families with classical Marfan syndrome were studied using markers on chromosomes 1 and 11. Two of three families tested showed negative scores using *D1S7* but a third family gave a positive score (0·92) at θ=0·1. The other chromosome 1 markers typed (*MUC1*, *NGFB*, *D1S8*) excluded close linkage. Negative lod scores with two chromosome 11q22 markers (*D11S84*, *D11S148*) excluded at least 20 cM in this area (Z=<−2), which was chosen for study as two enzymes responsible for collagen degradation (collagenase and stromelysin) are localised to this region.

Marfan syndrome is a dominantly inherited connective tissue disorder affecting primarily the skeletal, ocular, and cardiovascular systems. The estimated prevalence is 6/100 000, with 25% of cases resulting from new mutations.[1] The gene shows a high penetrance. The condition is heterogeneous[2] and shows great intrafamilial variability of expression.

A typical Marfan syndrome patient is characterised by an asthenic build, being unusually tall with a high arched palate, long thin extremities, arachnodactyly, chest wall deformities (pectus carinatum, excavatum), scoliosis, and joint hypermobility. Common ocular abnormalities range from myopia to bilateral lens dislocation and retinal detachment. Eighty percent have cardiovascular involvement ranging from mitral valve prolapse to aortic root dilatation and aneurysm. Most of the premature deaths result from aortic dissection, although beta blocker therapy decreases the rate of dilatation of the aortic root, while elective surgical replacement prolongs life, with an 87% five year postoperative survival rate.[3]

The primary defect of Marfan syndrome remains unknown, and no laboratory or prenatal diagnostic test is available. Although many abnormalities of connective tissue have been reported,[4–7] none of the putative genes coding for major connective tissue fibrillar components has been found to be linked in family studies.[8–12]

To date, however, the following loci have been excluded in the families studied: *COL1A1*, *COL1A2*, *COL2A1*, *COL3A1*, *COL6A1*, *COL6A2*, *COL6A3*, and tentatively, elastin.

In 1979, Mace's study of 17 families with 15 conventional markers yielded a maximum lod score of 1·38 at θ=0·25 between the rhesus blood group locus on chromosome 1 and Marfan syndrome.[13]

In our present study, we report exclusion data for four loci on chromosome 1 and two loci on chromosome 11. Linkage studies were performed for six families with classical Marfan syndrome, that is members classically affected in at least two out of three major systems (table 1) with a pedigree showing autosomal dominant inheritance.

The two main enzymes responsible for collagen degradation are collagenase (localised to 11q21–q22.3) and stromelysin (11q22.2–q22.3).[14] It is possible that excessive degradation of collagen (and other components of connective tissue) could be the primary cause of Marfan syndrome. A regulatory gene for collagenase or stromelysin or both becomes a new

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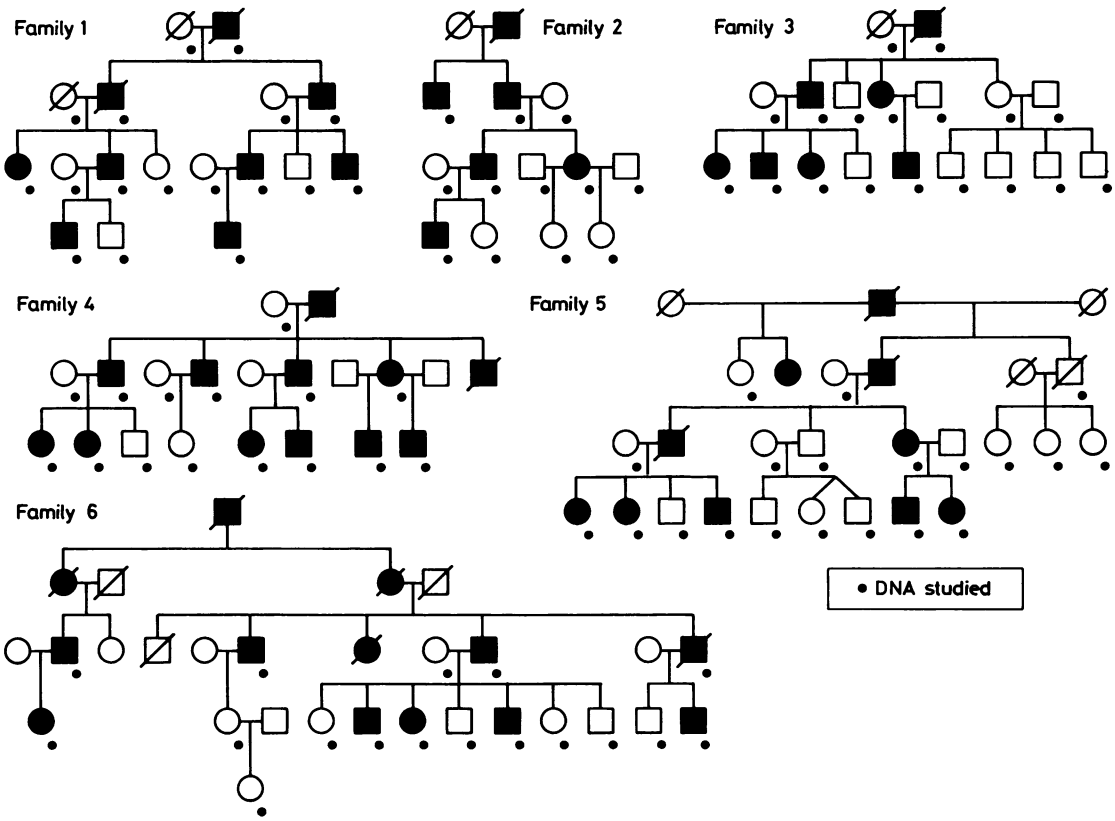

Family pedigrees.

Table 1 Cumulative phenotype of six families studied.

	Family					
	1	2	3	4	5	6
Ocular	+	+	+	+	+	+
Ectopia lentis						
Unilateral	+	−	+	+	−	−
Bilateral	+	++	+	+	+	+
Myopia	+	+	+	+	++	+
Retinal detachment	−	−	−	−	−	−
Skeletal	+	+	+	+	+	+
Excessive height	+	+	+	+	+	+
Arachnodactyly	+	++	+	+	++	−
Chest deformities	+	+	+	++	++	+
Pectus excavatum	+	+	−	+	+	−
Pectus carinatum	+	+	+	+	+	+
Scoliosis	++	+	+	+	+	+
Cardiovascular	+	+	+	+	+	+
Aortic root dilatation	++	+	++	+	++	+
Aortic valve regurgitation	+	+	+	+	+	+
Mitral valve prolapse	−	+	+	+	+	+
Aortic dissection	+	+	+	+	+	−

+Some of the affected members.
++All affected members.

putative gene. Therefore, two probes assigned to 11q22 were used for linkage analysis.

Materials and methods

Six families with classical Marfan syndrome were studied (table 1). The cumulative phenotype of each family includes classical involvement of all three major systems. The difficulty of finding large families with this potentially fatal disease was overcome through international collaboration. Each family was personally examined by one of the authors: family 1 (JWO), family 2 (AdeP), family 3 (NCN), family 4 (JdeG), families 5 and 6 (AHC).

Ophthalmological and echocardiographic examinations were performed and necropsy reports confirmed where necessary. All children were beyond the stage of expression of the familial phenotype when examined and so were assigned affected or unaffected status. Neither of the two UK families had been included in Mace's original linkage study.

Extraction of DNA from peripheral blood, preparation of probes, and characterisation of RFLPs were performed using standard techniques. Lod scores were calculated by LIPED[15] assuming full penetrance.

Results

Sex averaged lod scores for markers that were informative and whose results were available when the exclusion map (Blanton *et al*, this issue) was compiled are shown in table 2. None of the combined lod scores was indicative of linkage ($Z_{max} > 3{\cdot}0$), although family 4 showed a score of 0·92 at $\theta = 0{\cdot}1$ with *D1S7*.

Discussion

It is probable that Marfan syndrome is heterogeneous. To minimise the likelihood of including several subtypes in this study, only fully examined classically affected families were studied.

The highly polymorphic locus *D1S7* was selected because of the previously reported positive lod scores between Marfan syndrome and *Rh*. *D1S7* has been shown[16] to be linked to *Rh* at $\theta m, \theta f = 0{\cdot}15$, $Z_{max} = 4{\cdot}24$. Two of the three families tested showed negative scores, but a third family gave a positive score (0·92) at $\theta = 0{\cdot}1$. Further families and probes are being typed. The other chromosome 1 markers typed (*MUC1, NGFB, D1S8*) all excluded close linkage. A hypothetical putative gene, whose function would be to regulate one or both of the two main enzymes involved in collagen degradation located

Table 2 Lod scores for linkage between Marfan syndrome and six markers.

	Lod scores (Z) for recombination fraction (θm=θf)						
	0·001	0·01	0·05	0·1	0·2	0·3	0·4
Family							
	Marker: *D1S7* (1p35–p33)						
3	−6·90	−3·92	−1·91	−1·12	−0·45	−0·16	−0·04
4	−0·67	0·29	0·83	0·92	0·78	0·47	0·16
2	−7·50	−4·51	−2·46	−1·63	−0·86	−0·46	−0·20
Total	−19·56	−10·90	−4·97	−2·71	−0·92	−0·30	−0·11
	Marker: *MUC1* (1q21–q24)						
3	−6·90	−3·92	−1·91	−1·12	−0·45	−0·16	−0·04
2	−4·57	−2·59	−1·25	−0·73	−0·29	−0·10	−0·02
5	−9·29	−5·31	−2·60	−1·52	−0·57	−0·16	0·01
Total	−25·55	−15·55	−8·12	−4·90	−2·02	−0·71	−0·12
	Marker: *NGFB* (1p22.1)						
2	−1·87	−1·00	−0·26	0·04	0·25	0·26	0·16
5	−7·97	−4·97	−2·89	−1·99	−1·12	−0·61	−0·26
Total	−9·84	−5·97	−3·15	−1·95	−0·87	−0·35	−0·10
	Marker: *D1S8* (1q42–q43)						
2	−4·57	−2·58	−1·25	−0·73	−0·29	−0·11	−0·02
	Marker: *D11S84* (11q22)						
3	−0·42	−0·38	−0·26	−0·16	−0·06	−0·02	−0·005
4	−2·09	−1·35	−0·70	−0·43	−0·18	−0·07	−0·02
2	−2·27	−1·35	−0·68	−0·42	−0·19	−0·08	−0·03
5	−4·80	−2·81	−1·44	−0·89	−0·39	−0·15	−0·04
6	−2·28	−1·29	−0·63	−0·37	−0·14	−0·04	−0·003
Total	−13·66	−8·02	−3·99	−2·39	−0·99	−0·37	−0·10
	Marker: *D11S148* (11q22)						
4	−4·50	−2·77	−1·46	−0·93	−0·46	−0·23	−0·10
1	−1·77	−0·94	−0·31	−0·08	0·06	0·07	0·03
6	−6·74	−3·77	−1·78	−1·01	−0·39	−0·13	−0·03
Total	−13·01	−7·48	−3·55	−2·02	−0·79	−0·29	−0·10

on the long arm of chromosome 11, has not been shown to be linked to the disease.

Negative lod scores with two chromosome 11q22 markers, (*D11S84, D11S148* (pYNB)) exclude at least 20 cM in this area ($Z=<-2$) and perhaps more, although the physical relationships both between the markers and between them and collagenase and stromelysin are uncertain.

Collaboration with other groups is continuing, to avoid duplication of results and to maximise the efficiency of further linkage studies.

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