

Short reports

Linkage analysis of two Canadian families segregating for X linked spondyloepiphyseal dysplasia

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Abstract

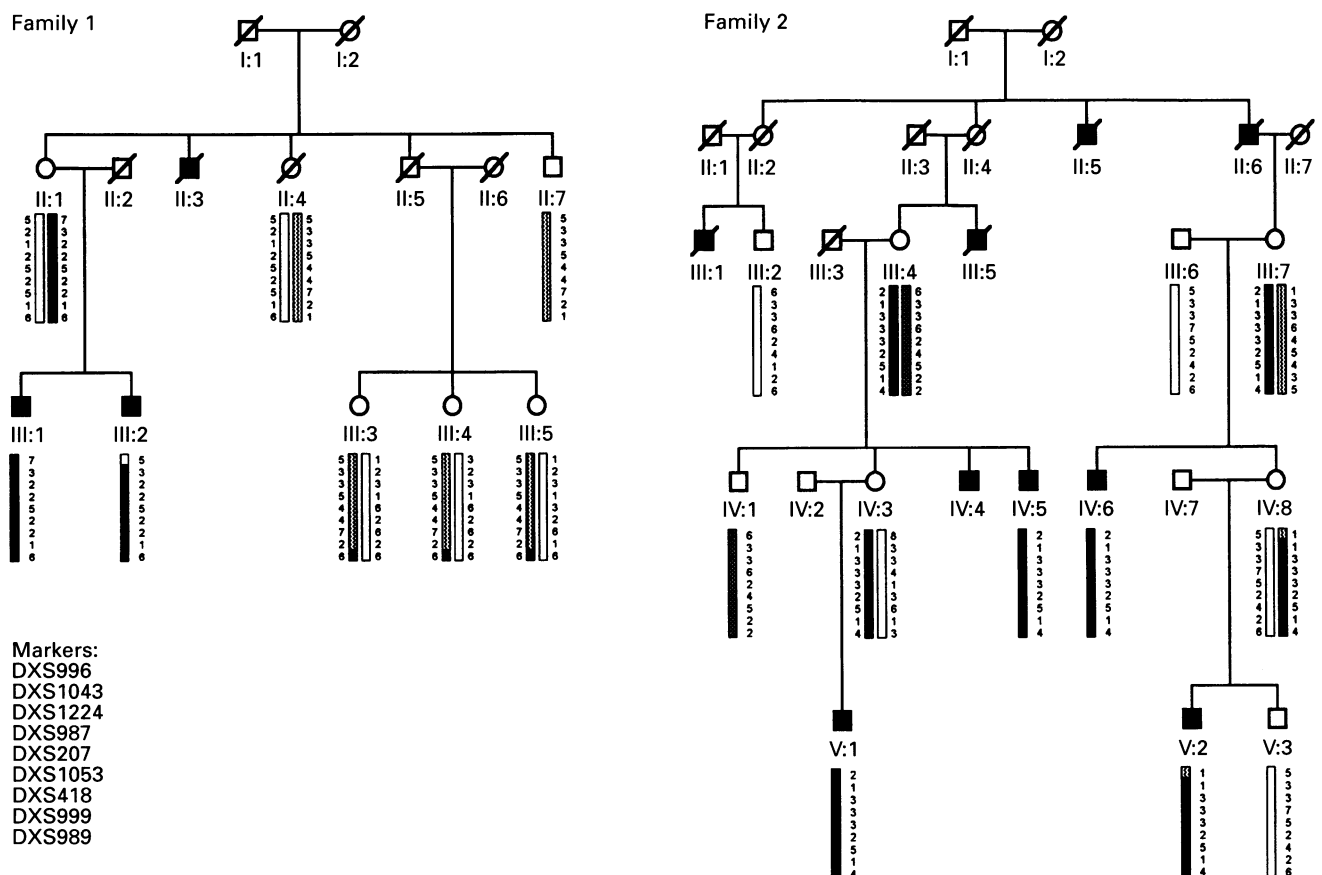
X linked spondyloepiphyseal dysplasia (SED) is caused by a growth defect of the vertebral bodies leading to characteristic changes in the vertebral bodies and a short trunk. The gene responsible for this disorder has previously been mapped to Xp22, with a maximum likelihood location between markers DXS16 and DXS92. We present linkage data using microsatellite markers on two Canadian X linked SED families, one of Norwegian descent and the other from Great Britain. In the Xp22 region, three recombination events have occurred in these families, two between

markers DXS996 and DXS1043 and one between DXS999 and DXS989. One family shows a maximal lod score of 3.0 at $\theta=0$ with marker DXS1043 and the other family has a maximal lod score of 1.2 at $\theta=0$ with markers DXS1224 and DXS418. Both families therefore support the previously reported gene localisation.

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Key words: linkage; X linked spondyloepiphyseal dysplasia.

X linked SED is characterised by a growth defect of the vertebral bodies, which are



Families segregating for X linked SED. Affected subjects are indicated by darkened symbols. Haplotypes are shown below the individual symbols. Marker order is indicated in the bottom left section of the figure.

Two point lod scores calculated using the MLINK and ILINK options of the LINKAGE program package version 4.7

Marker and family	Z at $\theta =$							Z	θ
	0	0.01	0.05	0.1	0.2	0.3	0.4		
DXS996									
1	-2.80	-0.81	-0.19	0.02	0.12	0.09	0.03	0.12	0.21
2	-0.81	0.85	1.35	1.41	1.19	0.83	0.41	1.41	0.09
Total	-3.61	0.04	1.16	1.43	1.31	0.92	0.44	1.44	0.12
DXS1043									
1	0.16	0.16	0.14	0.12	0.07	0.03	0.00	0.16	0
2	3.01	2.95	2.74	2.47	1.90	1.30	0.66	3.01	0
Total	3.17	3.11	2.88	2.59	1.97	1.33	0.66	3.17	0
DXS1224									
1	1.20	1.18	1.09	0.97	0.72	0.46	0.21	1.20	0
2	Not informative								
DXS987									
1	0.60	0.58	0.53	0.46	0.31	0.16	0.05	0.6	0
2	2.62	2.57	2.36	2.09	1.53	0.94	0.39	2.62	0
Total	3.22	3.15	2.89	2.55	1.84	1.10	0.44	3.22	0
DXS207									
1	0.60	0.58	0.53	0.46	0.31	0.17	0.05	0.6	0
2	2.24	2.19	1.97	1.71	1.14	0.59	0.18	2.24	0
Total	2.84	2.77	2.50	2.17	1.45	0.76	0.23	2.84	0
DXS1053									
1	0.08	0.08	0.06	0.05	0.03	0.01	0.00	0.08	0
2	1.98	1.94	1.77	1.55	1.10	0.64	0.23	1.98	0
Total	2.06	2.02	1.83	1.60	1.13	0.65	0.23	2.06	0
DXS418									
1	1.20	1.18	1.09	0.97	0.72	0.46	0.21	1.2	0
2	2.05	2.01	1.86	1.66	1.27	0.86	0.44	2.05	0
Total	3.25	3.19	2.95	2.65	1.99	1.32	0.65	3.24	0
DXS999									
1	0.60	0.58	0.53	0.46	0.31	0.17	0.05	0.60	0
2	2.37	2.32	2.13	1.88	1.36	0.83	0.33	2.37	0
Total	2.97	2.90	2.66	2.34	1.67	1.00	0.38	2.96	0
DXS989									
1	-1.80	-1.26	-0.69	-0.43	-0.19	-0.07	-0.02	0	0.5
2	2.93	2.88	2.67	2.41	1.85	1.25	0.63	2.93	0
Total	1.13	1.62	1.98	1.98	1.66	1.18	0.61	2.00	0.07

flattened with central and posterior humping.¹ These vertebral changes first become evident between 10 and 14 years of age, and form the basis of the clinical diagnosis in adults. The growth defect leads to the shortened trunk seen in these patients. Degenerative hip disease may also occur because of changes of the femoral head which lead to secondary osteoarthritis.

Linkage between Xp22 markers and X linked SED in six families was first reported in 1988.² In 1993 linkage to Xp22 was confirmed using an additional nine families, and the maximum likelihood location of the disease gene was narrowed to the approximately 11 cM interval between DXS16 and DXS92.³

We report linkage data involving two Canadian families segregating for X linked SED (figure). These two families include seven patients with clinical and radiological findings consistent with a diagnosis of SED. Family 1 was originally from Great Britain and family 2 originated from Norway. The previously reported families were all white and were from Denmark, Great Britain, The Netherlands, France, and the United States.³

DNA samples from family members were typed using microsatellite markers in the Xp22 region. Markers used include DXS996, DXS1043, DXS1224, DXS987, DXS207, DXS1053, DXS418, DXS999, and DXS989. The figure shows marker haplotypes assigned assuming a minimum number of recombination events. Three recombination events were detected in the Xp22 interval, two between DXS996 and DXS1043 and one between DXS999 and DXS989. The order of markers in the Xp22 region is as follows^{4,5}: Xpter-DXS996-DXS1043-DXS1224-DXS16-DXS987-DXS207-DXS1053-DXS418-DXS999-DXS92-DXS989-Xqter. The recombinational

events observed in our families are therefore consistent with the previously reported gene localisation between DXS16 and DXS92.

Two point linkage analysis was performed using the MLINK and ILINK options of the LINKAGE program package version 4.7.⁶ The frequency of the disease allele was estimated to be 1/100 000 and penetrance was assumed to be complete in affected males. Marker allele frequencies were obtained using the on line Genome Data Base. The table shows the results of the two point analyses and maximal two point lod scores obtained for each of the families. For family 1, the maximal lod score was 1.2 obtained at $\theta = 0$ from DXS1224 and DXS418. The maximal lod score obtained for family 2 was 3.0 at $\theta = 0$ from DXS1043. The disease gene is therefore highly likely to be linked to this region in both families. The maximum combined lod score was 3.2 at $\theta = 0$ with markers DXS987, DXS418, and DXS1043. A formal assessment of heterogeneity was carried out using the HOMOG program.⁷ DXS987, DXS418, and DXS1043 showed no evidence for heterogeneity in our families ($\chi^2 = 0$, $\alpha = 1$ at $\theta = 0$).

Our results further support both the previously reported localisation of the gene for X linked SED to Xp22 and the genetic homogeneity of this condition.

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