

Keratosis follicularis spinulosa decalvans: confirmation of linkage to Xp22.13-p22.2

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Abstract

Keratosis follicularis spinulosa decalvans (KFSD) is a rare, X linked disorder with skin and eye involvement (MIM 308800). We have studied a large British family with KFSD using polymorphic markers from Xp21-p23 and obtained a lod score of 2.056 at $\theta=0$ with markers proximal and distal to the KFSD candidate region

Xp22.13-p22.2 identified by Oosterwijk *et al.* Our data confirm the linkage to Xp22.13-p22.2 observed in the previously reported Dutch family, but fail to narrow the candidate interval for the KFSD locus. (*J Med Genet* 1998;35:336-337)

Keywords: KFSD; X linked; Xp22.13-p22.2

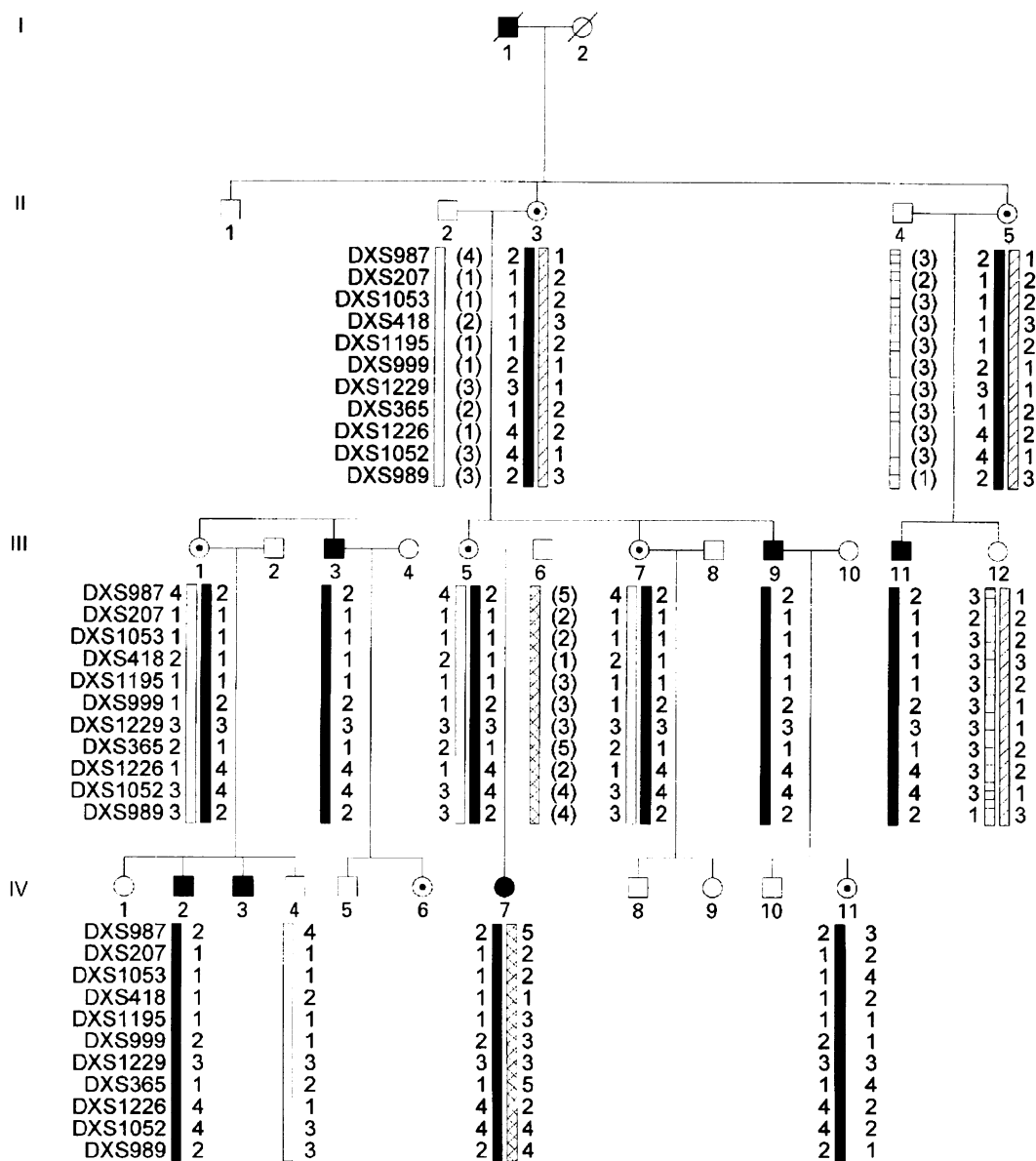


Figure 1 Pedigree of KFSD family. III.3: follicular hyperkeratosis, photophobia, III.9: follicular hyperkeratosis, photophobia, III.11: follicular hyperkeratosis, photophobia, entropion, recurrent blepharitis, IV.2: keratosis pilaris, IV.3: keratosis pilaris, IV.7: keratosis pilaris, calcaneal hyperkeratosis, photophobia, IV.11: follicular hyperkeratosis, photophobia. Haplotypes are shown for (telomere to centromere) DXS987, DXS207, DXS1053, DXS418, DXS1195, DXS999, DXS1229, DXS365, DXS1226, DXS1052, and DXS989, a distance of 16.2 cM.

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Table 1 Results of two point linkage analysis

Locus	Recombination fraction (θ)						
	0	0.01	0.05	0.1	0.2	0.3	0.4
DXS987	2.056	2.023	1.888	1.709	1.315	0.866	0.384
DXS207	1.153	1.333	1.052	0.943	0.702	0.428	0.147
DXS1053	1.153	1.333	1.052	0.943	0.702	0.428	0.147
DXS418	1.153	1.333	1.052	0.943	0.702	0.428	0.147
DXS1195	1.153	1.333	1.052	0.943	0.702	0.428	0.147
DXS999	1.755	1.722	1.587	1.408	1.014	0.575	0.163
DXS1229	1.028	1.011	0.938	0.841	0.623	0.376	0.126
DXS365	1.755	1.722	1.587	1.408	1.014	0.575	0.163
DXS1226	2.056	2.023	1.888	1.709	1.315	0.866	0.384
DXS1052	2.056	2.023	1.888	1.709	1.315	0.866	0.384
DXS989	1.755	1.722	1.587	1.408	1.014	0.575	0.163

Keratosis follicularis spinulosa decalvans (KFSD) is a rare, X linked genodermatosis characterised by generalised follicular hyperkeratosis, scarring alopecia involving the scalp, eyebrows, and eyelashes, and corneal dystrophy. Symptoms develop in early childhood with photophobia and keratosis pilaris followed by progressive scarring alopecia. The symptoms diminish with age and the long term prognosis for vision is good. Female carriers show a milder version of the phenotype in about 50% of cases.¹ KFSD was first described by Lameris in 1905² with a more detailed phenotype in the same large Dutch family being defined by Siemens in 1926.³ In 1992 this family was reassessed clinically⁴ and in 1995 the KFSD locus was mapped to Xp22.13-p22.2 with a maximum lod score of 12.07 for DXS365 at $\theta=0$.⁵ Further refinement of the candidate interval placed the KFSD locus between DXS7161 and DXS1226, a map distance of 1-2 Mb.⁶

Materials, methods, and results

DNA was collected from members of a large British family (fig 1) with characteristic clinical features of KFSD. The family had been previously reported as part of a clinical study.⁸ Genomic DNA was extracted from EDTA blood samples by protease K treatment followed by salt extraction.

Eleven microsatellite markers covering a region 5.1 Mb telomeric to and 1.7 Mb centromeric to the candidate interval defined in the Dutch KFSD family were chosen. Primer sequences and cycling conditions for the markers were obtained from the Genome database (GDB) and one primer of each pair was fluorescein labelled at the 5' end during synthesis. PCR reactions were carried out in 50 μ l volumes and contained 10 mmol/l Tris-HCl (pH 8.3), 50 mmol/l KCl, 1.5 mmol/l MgCl₂, 200 μ mol/l dNTPs, 0.1 μ mol/l each primer, 250 ng genomic DNA, and 5 U *Taq* polymerase. PCR products were analysed on an automated laser fluorescent sequencer (ALF, Pharmacia).

Two point linkage analysis was performed using the MLINK program version 5.2⁹ assuming a gene frequency of 0.00001, X linkage, and a penetrance of 0.5 in female gene carriers. Penetrance in males was assumed to

be complete. Allele frequencies were assumed to be equal.

No recombination between the KFSD locus and the marker set was observed. The haplotypes obtained are shown in fig 1. Markers DXS987, DXS418, and DXS989 were all fully informative and showed tight linkage to the KFSD locus with a maximum lod score in each case of 2.056 at $\theta=0$ (table 1).

Discussion

To our knowledge, this family in which KFSD is segregating is only the second of appropriate size and structure for linkage analysis. Our linkage data confirm the previous finding of a locus for KFSD in the region of Xp22.13-p22.2 bounded by DXS7161 and DXS1226. The marker DXS989 is centromeric to DXS274 while DXS987 is telomeric to DXS418. The lack of recombination observed in our family with these markers prevents any further narrowing of the candidate interval for the KFSD locus.

Because of the variability of the clinical phenotype in carrier females, some authors have suggested that KFSD is a sex limited, autosomal dominant disease.^{10,11} Our family has a severely affected female member (IV.7), but linkage analysis is strongly suggestive of a KFSD locus in the same region of the X chromosome as that found in the large Dutch family. KFSD has features in common with both ulerythema ophryogenes (UO) and ichthyosis follicularis (IF), but neither disorder has photophobia as a significant feature. However, in small families with skin manifestations resembling KFSD, diagnostic difficulties can occur. To our knowledge, male to male transmission has not been documented in a proven case of KFSD, and we conclude that evidence to date is consistent with one X linked locus in this disorder.

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