Am. J. Hum. Genet. 50:801–807, 1992

Linkage Analysis of Keratosis Follicularis Spinulosa Decalvans, and Regional Assignment to Human Chromosome Xp21.2-p22.2

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Summary

Keratosis follicularis spinulosa decalvans (KFSD) is a rare X-chromosomal disorder. It consists of follicular hyperkeratosis of the skin, scarring alopecia of the scalp, absence of the eyebrows, and corneal degeneration. There is photophobia in childhood, but the symptoms tend to diminish after puberty, and prognosis for vision is good. Some heterozygotes do show clinical symptoms. In a large Dutch pedigree we performed DNA analysis in order to localize the KFSD gene. In 54 individuals, including 21 affected males, RFLP analysis was done using DNA probes covering the X chromosome. Two-point linkage analyses with 19 informative DNA markers revealed significant linkage to DNA probes on Xp21.1-p22.3. The highest lod scores of 5.70 and 4.38 were obtained with DXS41 and DXS16 at a recombination fraction of zero and 4 cM, respectively. Multipoint linkage data place KFSD between DXS16 and DXS269. Our data confirm X linkage of KFSD in this family and tentatively map the gene on Xp22.2-p21.2. Combined with clinical investigation, RFLP analysis may become an important tool in carrier detection.

Introduction

Keratosis follicularis spinulosa decalvans (KFSD; MIM 308800 [McKusick 1990]) is a rare X-chromosomal disorder. It was first described in the Netherlands by Lameris (1905) and Rochat (1906). Later Siemens (1925), Holthuis (1943), and Jonkers (1950) made further dermatological and ophthalmological investigations in the same family. Recently several patients and carriers, descendants from the same Dutch pedigree, were clinically investigated (van Osch et al., in press).

The disorder is characterized by follicular hyperkeratosis of the skin, scarring alopecia of the scalp, and absence of eyebrows and sometimes of eyelashes. There is severe photophobia in childhood, and corneal dystrophy develops later on. The symptoms tend to diminish with age, and the prognosis for vision is normal. There is no mental retardation or other nonectodermal symptoms. The etiology of the disease is unknown.

In solitary cases the clinical diagnosis may be difficult and genetic heterogeneity may exist. (Kohler et al. 1981; Rand and Baden 1983; Guillet et al. 1987). Yet in most published families with KFDS (Siemens 1925; Franceschetti et al. 1957; Waardenburg et al. 1961, pp. 517–521; Kuokkanen 1971) male-to-male transmission is absent and daughters of affected men often have affected sons themselves, which makes X-linked inheritance very likely. There was no transmission to descendants through unaffected males. Female carriers, however, frequently have mild clinical symptoms which led to the first postulation of X-linked dominant (or intermediate) inheritance in man, by Siemens (1925). Waardenburg et al. (1961, pp. 517–521) later confirmed this hypothesis for the Dutch pedigree.

Received August 28, 1991; revision received November 26, 1991.

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0002-9297/92/5004-0016$02.00

The incidence of KFSD is unknown. Families have been reported from Finland (Kuokkanen 1971), France (Guillet et al. 1987), Great Britain (Hazell and Marks 1984), Germany (Siemens 1925; Kohler et al. 1981; Happle 1982), and the United States (Rand and Baden 1983).

Although the prognosis of KFSD is good, there is a need for reliable carrier detection, since only about half of the obligatory heterozygotes have clinical symptoms. Localization of the gene might enable future mutation detection and research into the cause of the disorder. We report on the first linkage study in KFSD in the extended Dutch pedigree. Two-point linkage analysis and multipoint analysis allowed us to map the gene for KFSD in this family, on the short arm of the X chromosome.

Subjects and Methods

Patient Ascertainment

Starting from several descendants of the Dutch pedigree who were part of a clinical study (van Osch et al., in press), we ascertained as many family members as possible. The patients had been investigated formerly (Jonkers 1950; Waardenburg et al. 1961, pp. 517–521; van Osch et al., in press) or were seen by one of the authors. Since all affected males show clear signs shortly after birth that diminish but leave scars at later age, the affection state of all men in the present study could be scored with certainty.

Two branches of the same pedigree were studied (fig. 1). Blood samples were taken from 54 individuals who were 4–93 years of age and who included 21 affected males. Only women who were obligate carriers or who were clinically affected (one case; see fig. 1, VI-12) were included in this study.

DNA Analysis

Genomic DNA was isolated from white blood cells by protease K and subsequent salt extraction (Miller et al. 1988). Ten-microgram DNA aliquots were cleaved with the restriction enzymes *Taq*I, *Pst*I, *Bcl*I, *Msp*I, *Eco*RI, and *Eco*RV, respectively, and were analyzed for RFLPs according to a method described elsewhere (van Oost et al. 1991).

A total of 27 DNA probes were used to detect RFLPs. Their location on the X chromosome, the enzymes used, the fragment sizes, and allele frequencies, based on data from HGM10 and HGM10.5 (Keats et al. 1989; Kidd et al. 1989; Davies et al. 1990; Williamson et al. 1990) and on recent data from others (Del Mastro et al. 1990; Alitalo et al. 1991*a*), are listed in physical order in table 1.

Linkage Analysis

Two-point linkage analyses to determine the maximum likelihood recombination distances (θ_{max}) and the lod score (Z) at θ_{max} (Z_{max}) between the main locus (KFSD) and each of the DNA marker loci were carried out using MLINK from LINKAGE package 5.03 (Lathrop and Lalouel 1984). The gene frequency of KFSD in the general population was taken to be .0001.

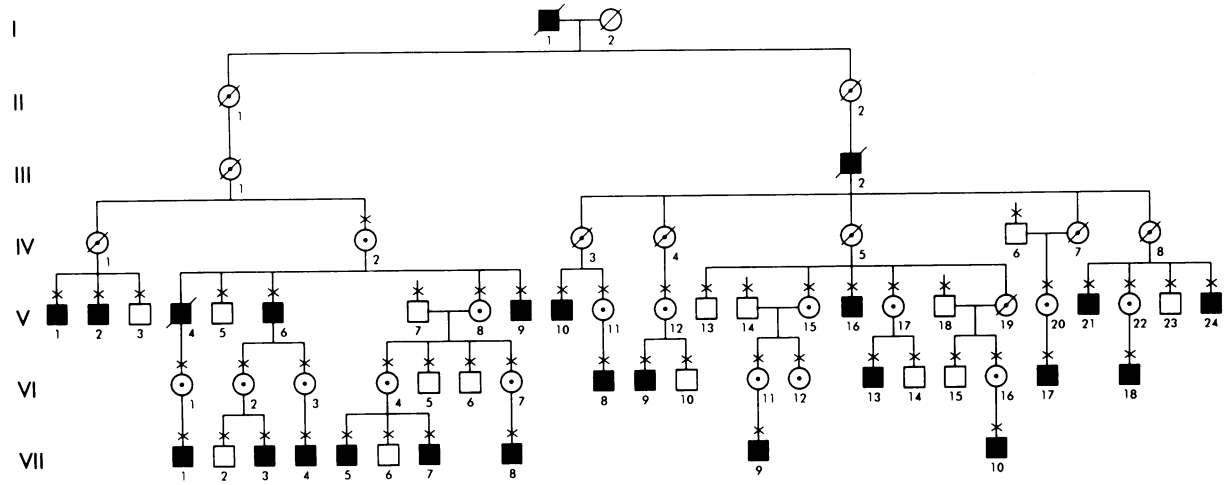

Figure 1 Part of Dutch pedigree with KFSD. Only branches that were investigated are shown. Squares denote males, and circles denote females. A blackened square denotes an affected male; a dot within a circle denotes that the female is a carrier; a diagonal line through a symbol denotes that individual is deceased; and a cross above a symbol denotes that individual was studied.

Table 1

X Chromosome Probes Used for RFLP Analysis

Locus (probe)	Location	Enzyme	Alleles (kb)	Frequencies
DXF30 (cri232)	Xp22.32	*PstI*	Multiallelic system	
DXS143 (pDIC56)	Xp22.3	*BclI*	8.9/7.4	.56/.44
DXS85 (782)	Xp22.3-p22.2	*EcoRI*	14.0/7.0	.60/.40
DXS16 (pXut23)	Xp22.2	*BclI*	2.5/2.2	.51/.49
DXS92 (XG.16)	Xp22.1	*TaqI*	7.1/3.8/3.5	.40/.50/.10
DXS41 (99.6)	Xp22.1	*PstI*	22.0/13.0	.56/.44
DXS28 (C7)	Xp21.3	*EcoRV*	8.0/7.5	.15/.85
DXS67 (B24)	Xp21.3	*MspI*	1.6/1.4	.96/.04
DXS269 (p20)	Xp21.2	*MspI*	6.0/3.5	.60/.40
DXS164 (pERT87.8)	Xp21.2	*TaqI*	3.8/2.7 and 1.1	.26/.74
DXS84 (754)	Xp21.1	*PstI*	12.0/9.0	.55/.45
MaoA (A2r/D7)	Xp11.3-p11.23	*MspI*	9.4/3.8	.67/.33
DXS7 (L1.28)	Xp11.4-p11.3	*TaqI*	12.0/9.0	.77/.23
DXS255 (M27β)	Xp11.22	*PstI*	Multiallelic system	
DXS14 (p58.1)	Xp11.21	*MspI*	4.0/2.5	.65/.35
DXYS1 (pDP34)	Xq21.31	*TaqI*	11.8/10.6	.40/.60
DXYS13 (pTak2)	Xq21.3	*MspI*	8.7/4.7	.91/.09
DXS3 (p19.2)	Xq21.3	*TaqI*	5.0/3.0 and 2.0	.38/.62
DXS17 (pS9)	Xq22	*TaqI*	2.7/2.5	.65/.35
DXS42 (p7F1)	Xq24-q25	*BclI*	5.0/4.2	.82/.18
DXS11 (22.33)	Xq24-q26	*TaqI*	20/11	.16/.84
DXS51 (52A)	Xq26.2-q26.3	*TaqI*	1.3/.7 and .6	.50/.50
DXS98 (4D8)	Xq26-Xqter	*MspI*	25/7.8	.82/.18
DXS134 (CpX67)	Xq27-Xqter	*MspI*	3.7/3.4	.42/.58
DXS304 (U6.2)	Xq27.3	*BclI*	7.0/3.3	.81/.19
DXS52 (F8.14)	Xq28	*BclI*	Multiallelic system	
F8 (F8.14)	Xq28	*BclI*	1.2/.9	.29/.71

NOTE.—For reference, see Kidd et al. (1989) and Williamson et al. (1990).

The spontaneous mutation rate was taken to be zero, and penetrance in males was assumed to be 100%.

Multipoint analyses were performed for KFSD and the marker loci by using LINKMAP and ILINK from LINKAGE package 5.03. We used a fixed order for the marker loci whenever such an order was evident from the literature (Brown et al. 1988; Keats et al. 1989; Kidd et al. 1989; Davies et al. 1990; Williamson et al. 1990; Alitalo et al. 1991*a*). In all analyses the relative likelihoods (odds) and probabilities of the alternative orders were calculated.

Results

Pedigree analysis (fig. 1) in this seven-generation family revealed that affected males within and between generations were related in a way compatible with X-linked inheritance. No male-to-male transmission was found. Only males were severely affected, but a significant number of female heterozygotes showed mild clinical symptoms (data not shown). These characteristics make X-linked inheritance highly probable.

Two-Point Linkage Analysis

A total of 27 DNA probes were used, of which 19 proved informative. Initially, one part of the pedigree (fig. 1, descendants of III-1) was studied with several of the DNA probes from table 1 distributed randomly along the long and short arm of the X chromosome. Guided by provisional linkage results, RFLP studies were extended to the other family members available, by using DNA probes on Xp: DXS143 (pDIC56), DXS28 (C7), DXS269 (p20), DXS16 (pXut23), DXS84 (L754), DXS85 (L782), DXS41 (99.6), and DXS164 (pERT 87.8). The number of informative meioses and the results of the two-point linkage analyses between the marker loci and KFSD (MLINK) are summarized in table 2.

Table 2

Two-Point Linkage Data for KFSD and Informative X Probes

Locus (probe)	Recombinations[a]	Z at θ (cM) of								Z_{max}	θ_{max}	Confidence Interval
		.00	.001	.01	.05	.10	.20	.30	.40			
DXF30 (cri232)	4/16	. . .	−9.29	−4.34	−1.10	.08	.87	.94	.62	.964	.26	.09–.50
DXS143 (pDIC56)	6/31	. . .	−8.33	−2.45	1.18	2.25	2.51	1.91	.94	2.620	.16	.07–.33
DXS85 (L782)	7/26	. . .	−13.40	−6.48	−1.98	−.39	.61	.66	.34	.702	.26	.10–.50
DXS16 (pXUT23)	1/19	. . .	3.03	3.95	4.28	4.08	3.27	2.20	1.00	4.383	.04	.00–.18
DXS41 (p99.6)	0/17	5.70	5.69	5.62	5.26	4.79	3.75	2.59	1.29	5.702	.00	.00–.11
DXS28 (C7)	0/12	4.15	4.14	4.09	3.83	3.48	2.73	1.89	.94	4.148	.00	.00–.15
DXS269 (p20)	2/21	. . .	.33	2.25	3.32	3.48	3.10	2.35	1.32	3.476	.10	.01–.28
DXS164 (pERT87.8)	2/18	. . .	−.40	1.53	2.62	2.82	2.56	1.94	1.09	2.825	.11	.01–.33
DXS84 (L754)	5/27	. . .	−7.05	−2.12	1.02	2.04	2.40	1.95	1.07	2.416	.18	.06–.36
DXS7 (L1.28)	3/10	. . .	−10.60	−5.64	−2.34	−1.09	−.13	.17	.19	.210	.35	.12–.50
MaoA (A2r/D7)	3/11	. . .	−8.33	−4.36	−1.71	−.70	.08	.31	.26	.320	.33	.10–.50
DXS255 (M27β)	5/14	. . .	−10.25	−5.30	−2.05	−.86	.00	.21	.18	.215	.33	.11–.50
DXYS1 (pDP34)	2/7	. . .	−6.54	−3.57	−1.61	−.89	−.36	−.19	−.12	−.029	.48	.09–.50
DXS3 (p19.2)	3/6	. . .	−3.31	−1.77	−.80	−.31	.05	.15	.12	.153	.31	.05–.50
DXS17 (pS9)	1/5	. . .	−9.45	−5.47	−2.80	−1.71	−.74	−.29	−.07	−.018	.48	.00–.50
DXS42 (p7F1)	2/7	. . .	−1.07	−.10	.48	.62	.58	.38	.14	.665	.15	.00–.50
DXS304 (U6.2)	5/7	. . .	−15.23	−9.25	−5.12	−3.39	−1.75	−.88	−.34	.150	.45	.26–.50
DXS52 (F8.14)	7/16	. . .	−24.58	−14.62	−7.77	−4.95	−2.35	−1.05	−.34	−.126	.45	.28–.50
F8C (F8.14)	1/4	. . .	−1.69	−.71	−.08	.13	.25	.23	.14	.252	.23	.01–.50

[a] In each entry, the first number is the number of recombinations and the second number is the total number of informative meioses.

Z values >2 are found in the region Xp22.3-Xp21.1, for DXS143, DXS16, DXS41, DXS84, DXS28, DXS269, and DXS164. The highest Z values are obtained between KFSD and DXS41 (5.70), DXS28 (4.15), and DXS16 (4.38), at θ values of .00, .00, and .04, respectively. Z values for markers on Xq and proximal and terminal on Xp were negative and/or insignificant (table 2). No structural rearrangements were detected by any of the probes used.

Multipoint Linkage Analysis

Analysis of haplotypes and recombination events locate KFSD between DXS16 and DXS269 (fig. 2). The region where the highest Z values are obtained with DXS41, DXS28, and DXS16 is limited by DXS85 distally and by DXS269 on the proximal side, since these markers both show several recombinations.

With data on the informative DNA probes on Xp, multipoint analysis was performed, which provides a more powerful means of finding the most probable location. The LINKMAP program calculates the likelihood for the position of the disease locus with respect to a fixed map of markers. The results with locus order DXS16–DXS41–DXS28–DXS269, with respective θ values of 10, 14, and 10 are given in figure 3. The highest location score (– 2 ln likelihood ratio) is 9.3 and was obtained at DXS41 and DXS28. This is about 2.2 units higher than the neighboring peaks, indicating odds of about 3:1 favoring a position of the KFSD gene between DXS16 and DXS269.

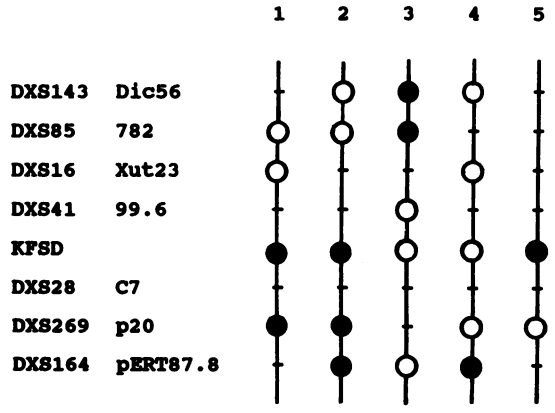

Figure 2 Meiotic crossover events in maternally derived X chromosomes, showing maternal allele at risk (●) or not at risk (○). The relative order of the polymorphic loci is shown on the left. Horizontal dashes indicate maternal homozygosity or unknown phase.

The ILINK program calculates the most probable locus order, varying the θ values for all markers involved. For all combinations with KFSD, given the order of the four marker loci, an odds ratio is calculated. The results of five-point linkage analysis with the seven most tightly linked markers are shown in table 3. The results clearly exclude the location of KFSD distal from DXS85 or proximal of DXS164 and are very suggestive for localization of KFSD between DXS16 and DXS269 (odds 45:1).

Discussion

KFSD is a rare disorder that consists of corneal abnormalities, local alopecia, and follicular hyperkeratosis of the skin (Siemens 1925; Waardenburg et al. 1961, pp. 517–521; Kuokkanen 1971). Both clinical and genetic heterogeneity have been described (Kohler et al. 1981; Rand and Baden 1983; Hazell and Marks 1984; Guillet et al. 1987). This pedigree is the largest published to date, and both pedigree analysis and linkage data clearly establish X-linked inheritance in this family.

Recombination events between KFSD and DNA probes were recorded for all except DXS41 and DXS28, both on Xp. Close linkage ($Z > 2$) was found for seven marker loci in the region Xp22.3-p21.1. Two-point linkage data give a Z_{max} of 5.70 for DXS41

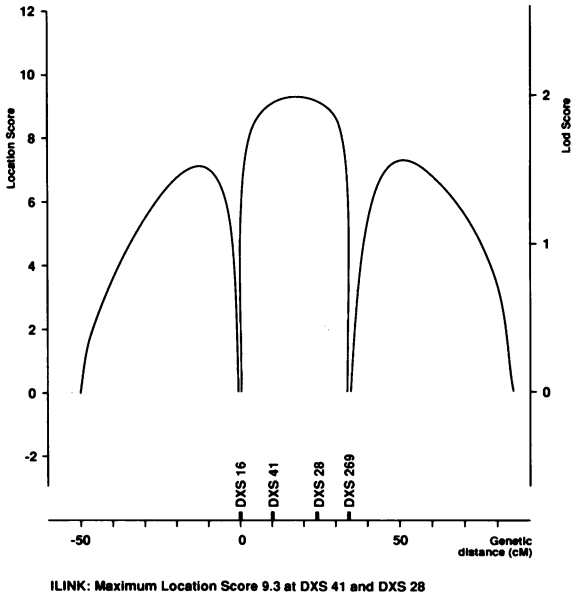

Figure 3 Genetic localization of KFSD gene by multipoint linkage mapping with LINKMAP package.

Table 3

Five-Point Linkage Analysis of KFSD and Marker Loci (ILINK)

Locus Order	Estimated Recombination Fractions Adjacent Loci				Relative Odds
KFSD–DXS85–DXS16–DXS269–DXS164	.192	.130	.186	.063	1:1,584,893.19
DXS85–KFSD–DXS16–DXS269–DXS164	.250	.036	.113	.053	1:45.71
DXS85–DXS16–KFSD–DXS269–DXS164	.186	.055	.084	.052	1:1
DXS85–DXS16–DXS269–KFSD–DXS164	.230	.069	.057	.098	1:147.91
DXS85–DXS16–DXS269–DXS164–KFSD	.230	.072	.042	.067	1:281.84
KFSD–DXS16–DXS41–DXS28–DXS269	.023	.000	.000	.089	1:11.72
DXS16–KFSD–DXS41–DXS28–DXS269	.041	.000	.000	.113	1:1
DXS16–DXS41–KFSD–DXS28–DXS269	.058	.000	.000	.099	1:1.01
DXS16–DXS41–DXS28–KFSD–DXS269	.041	.000	.000	.113	1:1
DXS16–DXS41–DXS28–DXS269–KFSD	.000	.000	.054	.053	1:7.40
KFSD–DXS143–DXS85–DXS41–DXS269	.158	.000	.194	.146	1:4,197,589.84
DXS143–KFSD–DXS85–DXS41–DXS269	.166	.202	.200	.151	$1:10^{12.8}$
DXS143–DXS85–KFSD–DXS41–DXS269	.000	.167	.000	.109	1:1
DXS143–DXS85–DXS41–KFSD–DXS269	.000	.167	.000	.111	1:1
DXS143–DXS85–DXS41–DXS269–KFSD	.000	.218	.000	.046	1:10.59
KFSD–DXS41–DXS28–DXS269–DXS164	.000	.000	.069	.069	1:1.05
DXS41–KFSD–DXS28–DXS269–DXS164	.000	.000	.081	.080	1:1.07
DXS41–DXS28–KFSD–DXS269–DXS164	.000	.000	.091	.069	1:1
DXS41–DXS28–DXS269–KFSD–DXS164	.000	.000	.055	.136	1:61.66
DXS41–DXS28–DXS269–DXS164–KFSD	.000	.000	.037	.069	1:91.20

(99.6), with no recombinations (confidence interval θ .00–.11). This means that the odds are $10^{5.7}$:1 in favor of close genetic linkage between KFSD and DXS41.

Z values for markers along Xq and on proximal Xp as well as terminal Xp were negative and/or insignificant. No other X-chromosomal regions with significant linkage ($Z > 2$) were found. This makes localization of KFSD elsewhere on the X chromosome improbable and formally excludes ($Z < -1$) large parts of Xq (table 2).

Multipoint linkage analysis (LINKMAP) places KFSD distal of DXS269 and proximal of DXS85. ILINK data show that the locus order DXS85–DXS16–KFSD–DXS269–DXS164 is at least 45 times more likely than any other order. Because of the lack of recombination events, more detailed mapping with regard to DXS41 and DXS28 was not feasible.

Our results in this large Dutch pedigree with KFSD confirm X-linked inheritance and tentatively place the gene between DXS16 (pXUT23) and DXS269 (p20), i.e., on Xp22.2-p21.2. This is in the region where the genes for X-linked juvenile retinoschisis (Alitalo et al. 1991*b*), the gene for X-linked liver glycogenosis (Willems et al. 1991), one of the X-linked retinitis pigmentosa genes (Musarella et al. 1990), and probably the gene for Nance-Horan syndrome (Zhu et al. 1990) are located.

One of the questions encountered in genetic counseling of members of this KFSD family is put forward by women wanting to know their carrier status. Until now these women could only be investigated for clinical symptoms, which are often absent. RFLP linkage analysis, in combination with clinical examination, will become an important tool in heterozygote detection.

Further RFLP studies both in this and other families are needed to confirm the provisional mapping of KFSD. This may enable a more precise localization of the gene and more detailed molecular research into the etiology of this ectodermal disorder.

Acknowledgments

We are indebted to the members of this family for their willingness to participate in this study. We thank Ton Put (Amsterdam) for drawing the pedigree and the many investigators for providing us with DNA probes.

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