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A Gene for an Autosomal Dominant Scleroatrophic Syndrome Predisposing to Skin Cancer (Huriez Syndrome) Maps to Chromosome 4q23

To the Editor:

Huriez syndrome (MIM 181600), also referred to as "sclerotylosis," is an autosomal dominant genodermatosis, characterized by the triad of congenital scleroatrophy of the distal extremities, palmoplantar keratoderma (PPK), and hypoplastic nail changes, that was first described in two large pedigrees from northern France (Huriez et al. 1968). Several additional families have since been described (Lambert et al. 1977; Fischer 1978; Shaw et al. 1978; Hamm et al. 1996; Kavanagh et al. 1997). The development of aggressive squamous cell carcinoma (SCC) of the affected skin is a distinctive feature of the syndrome, occurring in ~15% of affected individuals. SCC in Huriez syndrome is characterized by early onset, mostly in the third to fourth decade of life, and by early metastasis formation (Hamm et al. 1996). The pathogenetic mechanism of tumorigenesis in Huriez syndrome is unknown.

Linkage to the MN–blood-type locus on chromosome 4q28-q31 was reported initially and has subsequently been refuted (Delaporte et al. 1995; Kavanagh et al. 1997). We therefore embarked on a linkage analysis for Huriez syndrome with highly polymorphic microsatellite markers, beginning on chromosome 4. After informed consent was obtained, 22 affected and 35 unaffected members of one of the families first described by Huriez (family A) and a second family originating from the same region of northern France (family B) were included in the analysis. We calculated two-point LOD scores between each marker locus and Huriez syndrome, under the assumption of autosomal dominant inheritance with complete penetrance, a frequency of .0005 for the disease allele, and equal allele frequencies for each marker allele, using the LINKAGE version 5.21 software (Lathrop et al. 1984). With reference to the Human Gene Map (Schuler et al. 1996), we identified marker D4S424 within 2 cM of the glycophorin A gene (GYPA), which is the erythrocyte membrane protein that encodes the MN–blood-group receptors. D4S424 yielded a LOD score of -10.7 at recombination fraction (θ) 0.01. In the families under investigation, the MN–blood-type locus was therefore excluded as a candidate region for Huriez syndrome. Our finding is consistent with the exclusion of the MN locus in the first English family with Huriez syndrome (Kavanagh et al. 1997). In contrast, marker D4S1560 gave evidence for linkage, with a LOD score of 4.4 at $\theta = 0$. Subsequent analysis of additional flanking markers confirmed localization of the Huriez locus to this region, with the highest LOD score (Z_{max}) of 12.22 at $\theta = 0$, with D4S2380 (table 1). For fine mapping of the candidate region, additional microsatellite markers were selected and mapped on the high-resolution Stanford Human Genome Center TNG radiation hybrid panel. Relative distances in centirays (fig. 1) were determined with reference to the Stanford G3 panel (Stewart et al. 1997).

Under the more conservative assumption of incomplete penetrance, the candidate interval is defined by two recombination events in one affected individual (family A, member 6.1). Here, the 17-cM region is delimited centromerically by D4S395 and distally by D4S411. Under the assumption of complete penetrance, two additional recombination events in two unaffected probands further limit the Huriez locus (fig. 2): one in family A (member 4.11), localizing the gene telomeric to D4S1544, and the other in family B (member 2.5), localizing the gene centromeric to D4S2966. The Huriez locus is thus confined to an 8-cM region between D4S1544 and D4S2966. Haplotypes were constructed for both families by use of 16 markers between D4S2963 and D4S1564. Comparison between the disease alleles of the two families revealed three adjacent markers identical by state (IBS) (fig. 1). For two of these markers, D4S2973 and D4S1559, the shared allele is the most common allele found among all individuals, with relative frequencies of .87 and .58, respectively. There is no known relationship between the two families investigated. However, in view of the rarity of the condition

Table 1

Combined Pairwise LOD Scores for Families A and B between Huriez Syndrome and Markers on Chromosome 4q

Marker	cM from ptel	LOD Score at θ = .0	.01	.05	.1	.2	.3	.4	Z_{max}	θ_{max}
D4S1544	97.9	−∞	6.36	6.55	6.16	4.93	3.35	1.52	6.55	.05
D4S414	99.2	6.99	6.87	6.39	5.76	4.40	2.97	1.26	6.87	.0
D4S2909	100.0	8.41	8.27	7.66	6.87	5.17	3.29	1.35	8.41	.0
D4S2380	101.0	12.22	12.02	11.19	10.10	7.75	5.16	2.39	12.22	.0
D4S2973	103.1	.86	.85	.78	.70	.51	.31	.13	.86	.0
D4S1559	103.1	3.69	3.59	3.21	2.76	1.91	1.08	.32	3.69	.0
D4S1578	103.1	6.67	6.55	6.04	5.40	4.08	2.71	1.29	6.67	.0
D4S1560	103.1	4.40	4.32	3.99	3.56	2.64	1.63	.60	4.32	.0
D4S2986	104.6	9.96	9.81	9.19	8.36	6.53	4.45	2.12	9.81	.0
D4S2966	107.8	−∞	8.48	8.51	7.93	6.30	4.32	2.09	8.51	.01
D4S424	146.4	−∞	−10.73	−3.60	−1.02	.73	.92	.40	.92	.3

Note.—Marker coordinates are noted according to the final Généthon linkage map (Dib et al. 1996). The coordinate of D4S2380 is noted with reference to the Marshfield Comprehensive Human Genetic Maps (Broman et al. 1998). D4S424 maps within 2 cM of the glycophorin A gene (GYPA, MN–blood-group receptors).

and the fact that both families originate from neighboring villages in northern France, we inferred that the IBS status of three adjacent markers in the candidate region reflects the existence of a common founder haplotype. If the common haplotype is verified, this would indicate that the Huriez gene is located in a 3.1-cM interval between D4S2909 and D4S1578. Further markers must be investigated to substantiate this finding, although we have exhausted all known microsatellite markers in this region. In both families, Huriez syndrome is linked to markers on chromosome 4q some 30 cM centromeric of D4S424. Epidermal growth factor (EGF) was a potential candidate gene that has been mapped to chromosome 4q21-24 on a human-rodent somatic cell hybrid panel (Brissenden et al. 1984). EGF induces cellular proliferation and differentiation of various epidermal and epithelial tissues and is a potent mitogen (Carpenter and Cohen 1979). Increased levels of the EGF receptor are associated with malignant transformation of squamous cells (Lee et al. 1997) and are observed in SCC of the skin (Springer and Robinson 1991), esophagus (Yano et al. 1991), head and neck (Lee et al. 1997), cervix (Kim et al. 1996), and lung (Pfeiffer et al. 1998). According to the gene map of the human genome (Schuler et al. 1996), the EGF gene is located between D4S411 and D4S1564. Haplotype analysis for both families A and B revealed recombination events in individuals 6.1 and 2.5, respectively, that exclude EGF as a candidate gene for Huriez syndrome.

Affected patients with sclerotylosis have a greatly increased risk of cutaneous SCC. The clinical presentation of patients with sclerotylosis strongly indicates that this disorder is a precancerous condition. Affected individuals carry a >100-fold higher risk for the development of aggressive SCC of the skin (Levi et al. 1995; Gray et al. 1997), the age at onset of skin cancer is much lower than in the general population, and tumors arise in areas of affected skin. Sclerosis (Nachbar et al. 1993; Ozturk et al. 1998), atrophy, and scarring (Hagiwara et al. 1996) are well-recognized risk factors for the development of SCC of the skin. Clinically, the development of SCC in Huriez syndrome bears striking similarity to Marjolin's ulcer, which refers to malignancies arising in chronic ulcers of the skin, scar tissue, and burn scars (Fleming et al. 1990). The skin fragility found in Huriez syndrome leads to scarring, and the scleroatrophic changes may represent a process similar to scarring, thus predisposing to skin cancer. In addition, the exposure to exogenous mutagens such as arsenic (Jackson and Grainge 1975) have been recognized as risk factors for the development of SCC of the skin. The atrophic changes in skin anatomy observed in this type of PPK may disturb the barrier function of the skin, thus facilitating the penetration of putative physical, chemical, and infectious mutagens. However, most PPKs are not associated with an increased risk of skin cancer (Stevens et al. 1996). In addition, there is no evidence that sclerotylosis is associated with an increased risk of skin tumors other than SCC, which one would expect to observe if the development of local malignancies were solely attributable to the defective barrier function and the increased exposure to exogenic carcinogens.

It is noteworthy that loss of heterozygosity of 4q has been reported in 81% of squamous cell neoplasms of the head and neck (Pershouse et al. 1997) and in 46% of cervical carcinoma (Mitra et al. 1994). In SCC of the head and neck with deletions on 4q, the region that was consistently involved extends distal of the Huriez gene

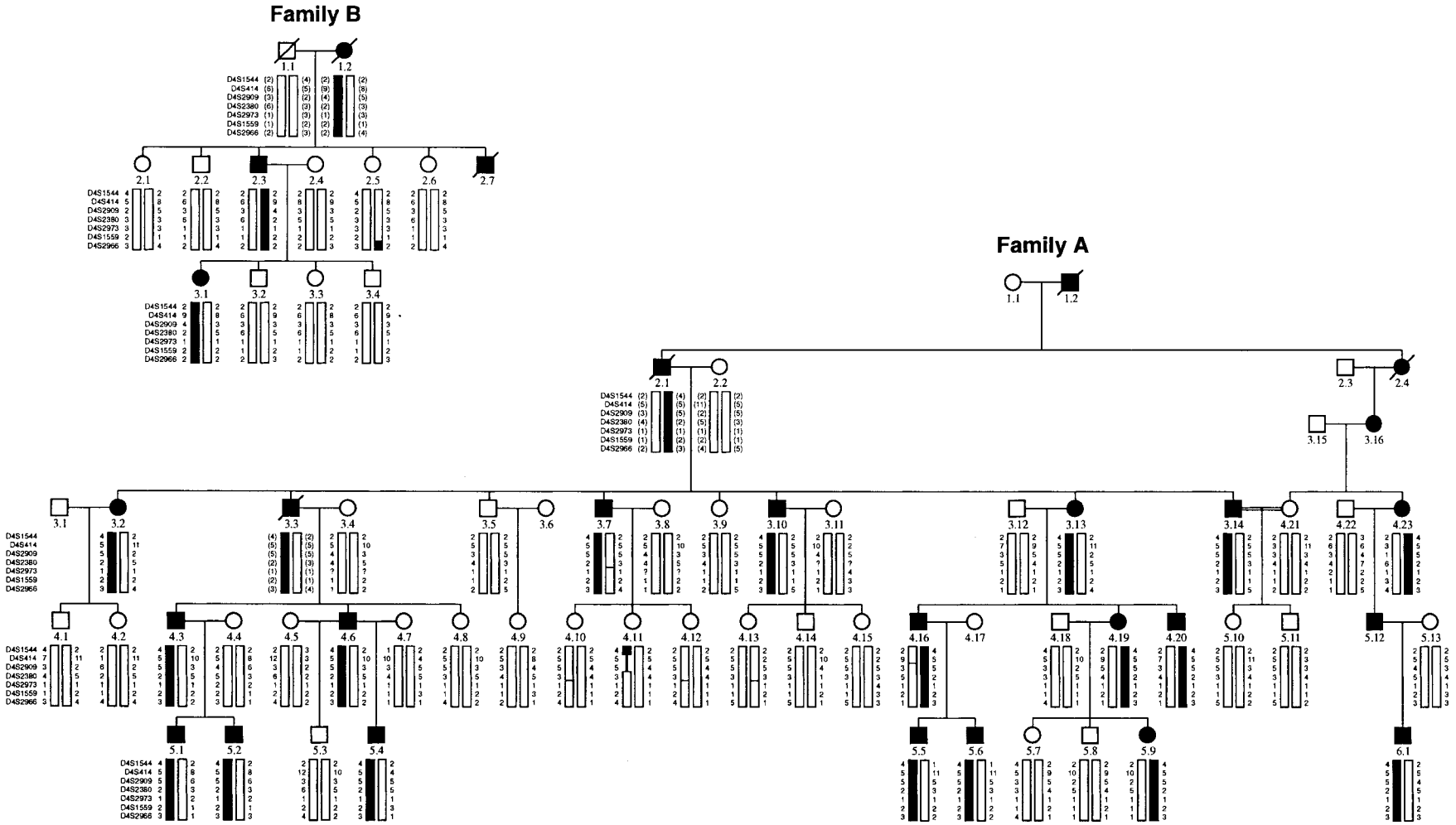

Figure 1 Pedigrees of families A and B with Huriez syndrome. Affected family members are denoted by blackened symbols. The most likely haplotype for seven markers from an 8-cM interval between D4S1544 and D4S2966 is shown below each individual.

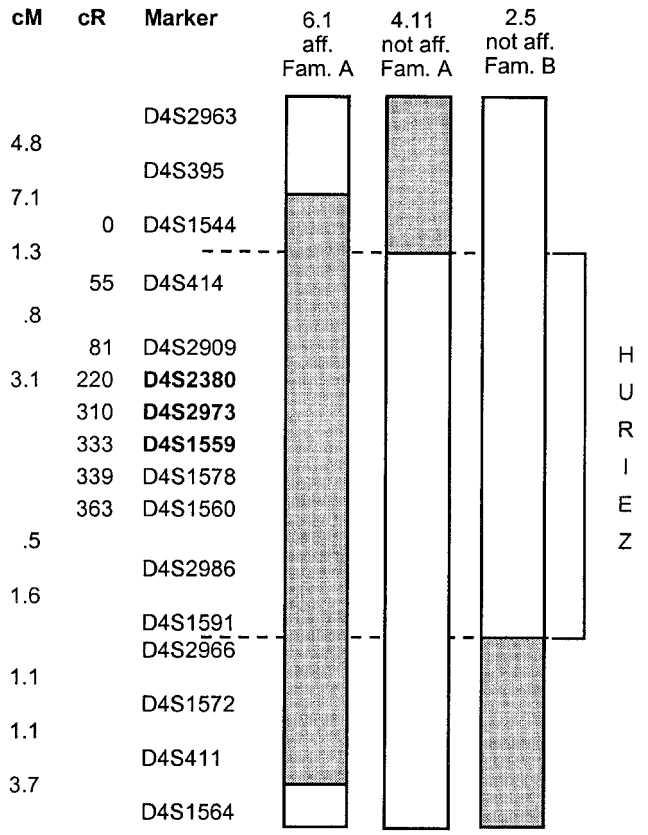

Figure 2 Linkage map of microsatellite markers from chromosome 4q23. Genetic distances are indicated in centimorgans. Markers are arranged in map order according to the final Généthon human linkage map (Dib et al. 1996). In the candidate region, markers are ordered according to their score on the TNG radiation hybrid panel. Here, relative positions are noted in cR after assigning 0 cR to marker D4S1544. The wild-type allele is represented by a white bar, the mutated allele by a gray bar. In the candidate region, markers IBS are noted in boldface type. The recombination events in members 4.11 and 6.1 of family 1 and 2.5 of family 2 are shown. The minimal candidate region for Huriez syndrome is marked. "aff." indicates affected; "not aff.," not affected.

locus and possibly overlaps with it on its centromeric end. A tumor-progression model for SCC of the skin has been proposed in which serial mutagenesis exceeds a threshold level, leading to tumor growth (Grossman and Leffell 1997). The gene mutation underlying Huriez syndrome may represent a first event in that series. Identification and characterization of the gene causing Huriez syndrome may provide important insights into the pathogenesis of skin cancer.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Généthon, http://www.genethon.fr/
Human Gene Map, The, http://www.ncbi.nlm.nih.gov/SCIENCE96/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Huriez syndrome [MIM 181600])

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Transmission-Ratio Distortion at Xp11.4-p21.1 in Type 1 Diabetes

To the Editor:

Naumova et al. (1998) reported a deviation from the expected Mendelian 1:1 ratio of grandpaternal/grandmaternal alleles at loci in Xp11.4-p21.1 in the children of 47 families not selected on the basis of the disease status of the children. The transmission-ratio distortion (TRD) was found only among male offspring and was manifested as a bias in favor of the inheritance of the alleles of the maternal grandfather. The critical region, containing the putative TRD locus, named "*DMS1,*" was mapped to an interval bounded by DXS538 and DXS7 and peaking at DXS1068.

These observations might have an impact on the results of a study in which we have provided evidence of linkage to type 1 diabetes mellitus (MIM 222100), in the same region of chromosome X (Cucca et al. 1998). The possibility of TRD at chromosome Xp gives rise to the question of whether the diabetes-linkage results are indeed disease specific. The following evidence suggests that it is highly unlikely that the *DMS1* locus is responsible for the chromosome Xp linkage to type 1 diabetes.

We genotyped DXS1068 (a marker that was at the peak of our linkage curve) in two sample sets of control families not ascertained on the basis of the disease status of the children. These control families were from the Centre d'Etude du Polymorphisme Humaine (Fondation Jean Dausset/CEPH) and from a population-based sam-