Letters to the Editor

Am. J. Hum. Genet. 64:651–653, 1999

Both Recessive and Dominant Forms of Anhidrotic/Hypohidrotic Ectodermal Dysplasia Map to Chromosome 2q11-q13

To the Editor:

Ectodermal dysplasias (EDs) are a group of conditions characterized by the abnormal development of ectodermal-derived structures including teeth, hair, and eccrine sweat glands. EDs may be either isolated or associated with other clinical manifestations. Hitherto, >100 ED syndromes have been delineated (Freire-Maia and Pinheiro 1988). Whereas the X-linked form of anhidrotic/hypohidrotic ED is well characterized (MIM 305100), the existence of autosomal dominant (MIM 129490) or recessive forms (MIM 224900) has long been discussed. Partial resolution of this controversy was provided when an autosomal dominant form of hypohidrotic ED in a six-generation family was mapped to chromosome 2q11-q13 (Ho et al. 1998). Clinical features included smooth dry skin, hypotrichosis, decreased sweating, and dental anomalies in most affected individuals in that family. The existence of autosomal recessive anhidrotic/hypohidrotic ED is supported by the occurrence of the disease in several families, including a large inbred Moroccan kindred (Munoz et al. 1997; Kabbaj et al. 1998). Here we show that a gene for autosomal recessive ED maps to 2q11-q13, suggesting that dominant and recessive ED may be allelic disorders.

In a large inbred Moroccan kindred, all 14 individuals affected with autosomal recessive ED presented with hypotrichosis, hypodontia, and anhidrosis (Kabbaj et al. 1998). Six of the affected children died in early childhood, probably as a result of dehydration episodes. After obtaining informed consent, we collected blood samples from a total of 32 family members, including 8 affected children. DNA was prepared by standard methods and genotyping was done as reported elsewhere (Belin et al. 1998). After the exclusion of several chromosomal regions encompassing candidate genes, we tested polymorphic markers in the chromosome 2q11-q13 region in which a gene for dominant ED has been mapped (Ho et al. 1998). LOD scores were computed with the LIPED program, version 5.0, under the assumption of autosomal recessive inheritance with complete penetrance and a disease allele frequency of .001 (Ott 1974). Positive two-point LOD scores were obtained with several markers in the region 2q11-q13, with a maximum LOD score of 7.4, at a recombination fraction of zero, with D2S293 (table 1). The allele shared by all the patients at D2S293 was not found on the normal chromosomes of 11 obligatory ED carriers, which suggests the existence of a linkage disequilibrium.

A common haplotype between D2S113 and D2S2269 was identified in six of seven parents of the patients, with an apparent ancestral recombination at the locus D2S135 in individual 21 (fig. 1). Recombination events were observed in patients 24, 25, and 44, at loci D2S373, D2S1895, and D2S121, respectively, which made it possible to locate the disease locus in the 7.47-cM interval between loci D2S135 and D2S121. In all the patients, homozygosity for each of the markers was present in this interval.

During the mapping of a gene for dominant ED, Ho et al. (1998) found several discrepancies in the marker order, throughout the 2q11-q13 region, between the Marshfield genetic map and the Whitehead physical YAC contig sequence-tagged site (STS) content map. In their analyses, which were consistent with the marker order in the Whitehead physical STS content map, they delineated recombinant haplotypes and defined the proximal flanking boundary for the gene for dominant ED (*ED3,* previously known as "EDA3" [Ho et al. 1998]) at D2S1321 and the distal flanking boundary at D2S308. This region entirely contains the interval in which we mapped a gene for recessive ED (fig. 2).

The possibility that affected individuals might be ho-

Table 1

LOD Scores for Linkage of the Locus for the Autosomal Recessive Form of Anhidrotic ED to Chromosome 2q11-q13 Markers

	LOD Score at Recombination Fraction of					
Marker	.00	.05	.10	.20	.30	. 40
D2S373	−∞	−2.82	−.94	−.08	.09	.07
D2S293	7.40	6.86	5.78	4.14	2.53	1.04
D2S1890	5.81	5.39	4.57	3.30	2.04	.89
D2S160	6.33	5.84	4.97	3.59	2.24	.99
D2S121	.34	2.52	2.69	2.03	1.29	.58
D2S1895	−∞	2.89	3.34	2.57	1.61	.68

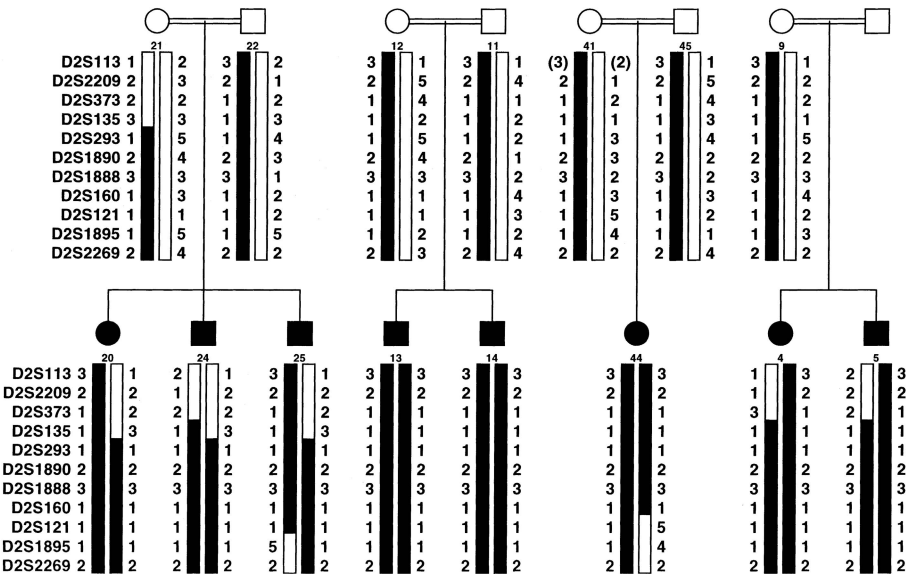

Figure 1 Haplotypes of the chromosome 2q11-q13 region of the patients and their parents. The haplotypes were inferred on the basis of the analyses of additional family members examined but not shown. A complete pedigree of the family appears elsewhere (Kabbaj et al. 1998).

mozygous for a dominant allele with very mild expression in heterozygote carriers was considered. However, the obligate carriers were reexamined and none of them presented any sign of ED. Two main explanations can account for the localization of dominant and recessive ED to the same chromosomal region. First, one can hypothesize that a cluster of genes with related function maps to chromosome 2q11-q13. The existence of gene clusters coding for related proteins such as collagens or keratins is well known, and linked genes may encode various subunits of a single multimeric complex. For instance, mutations in either SUR1 or KIR6.2, which are tightly linked genes on chromosome 11p15.1, result in persistent hyperinsulinemic hypoglycemia of infancy. Alternatively, autosomal recessive and dominant ED might be allelic disorders, as previously shown in several diseases. For instance, collagen gene mutations may cause either dominant or recessive disorders, depending on their nature. Indeed, mutations in COL11A2 cause either Stickler syndrome, a dominant disorder, or OSMED, a recessive bone dysplasia (Vikkula et al. 1995).

As mentioned by Ho et al. (1998), the candidate region contains several genes and anonymous expressed sequences, none which seem to be reasonable candidates by their function or by homology with mouse mutant phenotypes. The study of additional families of both recessive and dominant ED should allow reduction of the interval, toward the cloning of the gene or genes involved in these disorders.

Acknowledgments

We thank Anna Pelet and members of the family for their participation in this study. This work was supported in part by grants from the "coopération Franco-Marocaine dans le domaine de la santé," the Association Française contre les Myopathies (AFM), and the Institut National de la Santé et de la Recherche Médicale (INSERM).

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Electronic-Database Information

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

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.marshmed.org/genetics (for marker order in the 2q11-q13 region)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for X-linked anhidrotic/hypohidrotic ED [MIM 305100], autosomal dominant ED (MIM 129490], and autosomal recessive ED [MIM 224900])

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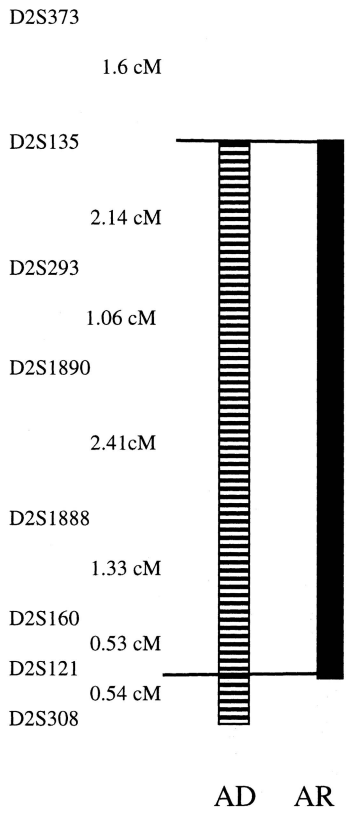

Figure 2 Comparison of the candidate regions on chromosome 2q11-q13 for autosomal dominant (AD) and recessive (AR) ectodermal dysplasia. The order of the principal markers used in the study and the distances are those of the Marshfield sex-averaged chromosome 2 linkage map. Since loci D2S135 and D2S1321 are very close to each other, only D2S135 appears in the figure.

Genome Research, http://www-genome.wi.mit.edu (for marker order in the 2q11-q13 region)

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0002-9297/99/6402-0037$02.00

Am. J. Hum. Genet. 64:653–658, 1999

Mosaicism and Sporadic Familial Adenomatous Polyposis

To the Editor:

Familial adenomatous polyposis (FAP [MIM 175100]) is an autosomal dominant heritable disorder caused by germ-line mutations in the APC gene (M74088 [GenBank]). There is a high new-mutation rate, with ~25% of all cases being sporadic (Bisgaard et al. 1994). Parental mosaicism can explain new mutations in genetic disorders (Hall 1988), whereas germ-line and/or somatic mosaicism has been described in genes associated with tumors such as p53 (Kovar et al. 1992), Rb1 (Greger et al. 1990; Lohmann et al. 1997), NF1 (Lázaro et al. 1995), and NF2 (Bourn et al. 1994). We were interested to determine whether APC-gene mutational mosaicism could account for some of the apparentlynew" APC mutations. Systematic studies of our registry identified five in which a germ-line mutation was established (Prosser et al. 1994), parental leukocyte DNA was available, and paternity was assured. These five patients were the subjects of detailed studies to determine the level of parental APC mutational mosaicism (table 1).

During S^{35} sequencing of parental blood-leukocyte DNA samples from the first sporadic FAP case, we noted a faint mutant allele that was reproducible on repeated analyses. The clinical history of this sporadic FAP patient (patient 17) is noteworthy. Dense distal colonic polyposis was diagnosed at age 22 years, with three distinct carcinomas and myriads of smaller polyps, many of which showed carcinomatous change. Mastectomy was required for breast carcinoma when the patient was age 37 years, and disseminated ovarian cancer resulted in death at age 44 years. Her mother (patient 16) had a mastectomy for breast carcinoma at age 46 years, was negative in a screen for colonic polyps when she was