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The Gene for Hypotrichosis of Marie Unna Maps between D8S258 and D8S298: Exclusion of the *hr* Gene by cDNA and Genomic Sequencing

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Summary

Hypotrichosis of Marie Unna (MU) is an autosomal dominant hair-loss disorder with onset in childhood. A genomewide search for the gene was performed in a large Dutch family using 400 fluorescent microsatellite markers. Linkage was detected with marker D8S258, and analysis of this family and a further British kindred with additional markers in the region gave a combined maximum two-point LOD score of 13.42, with D8S560. Informative recombinants placed the MU gene in a 2.4-cM interval between markers D8S258 and D8S298. Recently, recessive mutations in the *hr* gene were reported in families with congenital atrichia, and this gene was previously mapped close to the MU interval. By radiation-hybrid mapping, we placed the *hr* gene close to D8S298 but were unable to exclude it from the MU interval. This, with the existence of the semidominant murine *hr* allele, prompted us to perform mutation analysis for this gene. Full-length sequencing of *hr* cDNA obtained from an affected individual showed no mutations. Similarly, screening of all exons of the *hr* gene amplified from the genomic DNA of an affected individual revealed no mutations. Analysis of expressed sequences and positional cloning of the MU locus is underway.

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Introduction

Alopecia is a common genetic trait in humans, primarily affecting males, in the form of male pattern baldness (Dawber 1997). Although intrinsically benign, the cosmetic effect of alopecia is considerable, and, therefore, demand for novel treatments for baldness is correspondingly large. Recently, a small number of genes have been identified in which mutations produce human hair loss, either alone or in conjunction with other ectodermal defects.

A single-gene form of baldness, congenital atrichia (MIM 203655; also called "congenital atrichia with papular lesions"), has been described in the literature. Congenital atrichia is an autosomal recessive disorder causing complete loss of all hair, beginning at an early age (Ahmad et al. 1993). Recently, the congenital atrichia gene was mapped to chromosome 8p22-p21, and mutations were reported in the human homologue of the murine hair-loss gene, hairless (*hr*), in a number of families (Ahmad et al. 1998*a*, 1998*b*; Cichon et al. 1998; Nothen et al. 1998; Zlotogorski et al. 1998). The *hr* mouse was originally described in 1926 (Brooke 1926), but it was not until recently that the murine gene was identified (Cachon-Gonzalez et al. 1994). The hairless protein is a putative transcription factor thought to be involved in the regulation of the hair cycle, although the precise molecular mechanisms have yet to be elucidated (Panteleyev et al. 1998*b*). The genomic organization of the human *hr* gene has been recently described, including an alternate transcript that shows some degree of epidermal specificity (Cichon et al. 1998; Ahmad et al. 1999). Ahmad and colleagues extensively analyzed the tissue distribution of *hr* expression (Ahmad et al. 1999).

Mutations in the hair keratins hH6b and hH1b have been shown to cause monilethrix, which is a structural

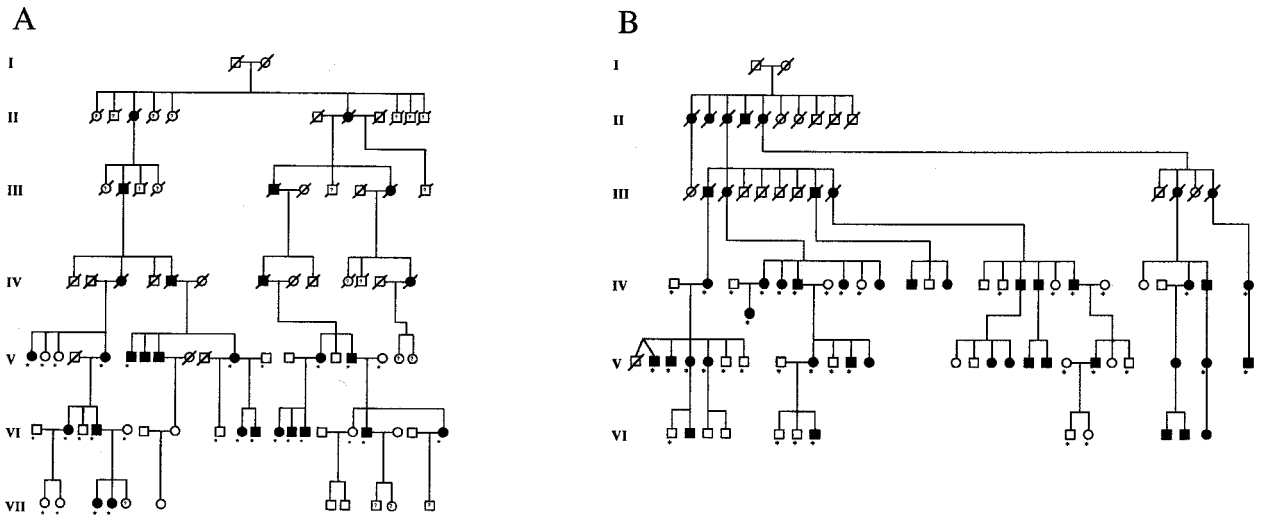

Figure 1 Pedigrees of two white families with MU that were used for linkage analysis, showing autosomal dominant inheritance. *A*, Pedigree of family 1, who are of Dutch origin. *B*, Pedigree of family 2, who are of British origin. Asterisks (*) indicate individuals from whom DNA was available for study.

disorder of the hair and often is accompanied by alopecia (Healy et al. 1995; Winter et al. 1997*a*, 1997*b*). In addition, a number of ectodermal dysplasia genes and loci have been identified in which alopecia is one of the epithelial defects. The conditions involved include X-linked ectodermal dysplasia, caused by mutations in the EDA gene (Kere et al. 1996); skin fragility/ectodermal dysplasia syndrome, caused by loss of plakophilin-1 expression (McGrath et al. 1997); Clouston syndrome, which maps to 13q11-q12.1 (Kibar et al. 1996); and Papillon-Lefevre syndrome, which has been recently mapped to 11q14 (Laass et al. 1997).

In 1925, the Hamburg-based dermatologist Marie Unna described a new type of autosomal dominant alopecia, which she had observed in an extended northern German pedigree (Unna 1925). This disorder is now known as "hypotrichosis of Marie Unna" (MU; MIM 146550). Later, Ludwig (1953) reexamined the same family, and, since these first descriptions, a number of others have appeared in the literature (Borelli 1954; Stevanovic 1970; Peachey and Wells 1971; Solomon et al. 1971; Bentley-Phillips and Grace 1979; Speigel and Hundeiker 1979; Wirth et al. 1985). MU is a rare disorder and is characterized by hair loss in a Norwood (or Hamiltonian) pattern (Dawber 1997). At birth, scalp hair is sparse, and the eyelashes and eyebrows are especially affected. During childhood, hair growth ensues, but the hairs that appear are coarse and wiry. In contrast to congenital atrichia—which appears, on the basis of the small number of cases so far studied, to result in complete hair loss in the early years of life—MU causes hair loss in the years close to the onset of puberty. Although eyebrows and body hair are somewhat affected in MU, progressive alopecia of the scalp is the main feature of the disorder. Identification of the MU gene may give a valuable insight into the molecular-genetic mechanisms underlying other types of baldness in humans and may open the door to novel therapeutic approaches. Here, we show that the MU gene maps to a locus on human chromosome 8p.

Patients and Methods

Clinical Findings

The pedigrees of families studied are shown in figure 1. Family 1 was of Dutch origin, family 2 of British origin. All kindreds examined exhibited the hallmarks of autosomal dominant inheritance, as previously described for MU. Affected persons in both families showed typical progression of alopecia, as illustrated in figure 2.

The proband in family 1, individual VI-2, a 47-year-old white female, presented to the outpatient clinic of the Department of Clinical Genetics at the Free University Hospital in Amsterdam with complaints of progressive hair loss. Apparently, hair growth had been sparse and wiry since childhood. Eyebrows and eyelashes had always been thin. Although the hair reportedly did grow during childhood, the vertex and parietal areas remained bald. At the onset of puberty, the hair loss apparently worsened. Axillary and pubic hair failed

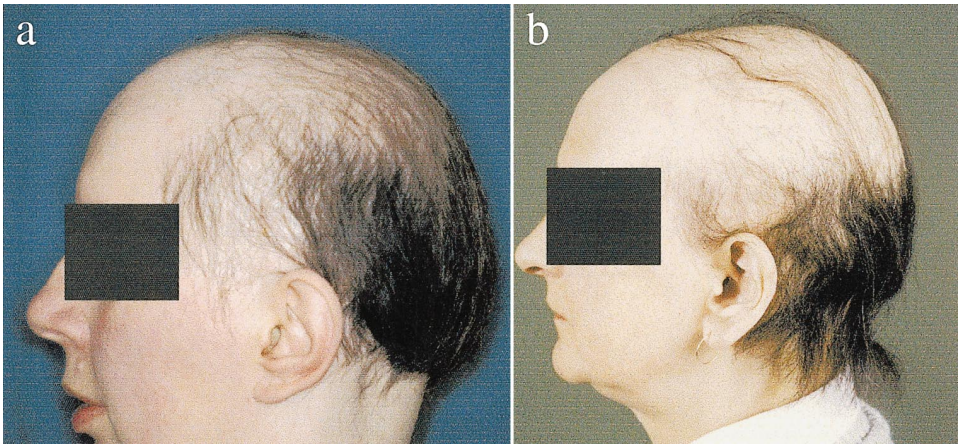

Figure 2 Clinical appearance of MU disease in similarly affected females from (*A*) family 1 (individual VI-2) and (*B*) family 2 (individual IV-25). Both show the characteristic pattern of hair loss.

to develop. After the birth of her first child, the hair loss again increased. According to the patient, her mother and several other family members had an identical disorder. The same abnormalities were found in the patient's mother, whose disease history was identical. Additional affected family members were also examined and had very similar abnormalities of the hair, as well as almost identical disease histories. The pedigree was consistent with an autosomal dominant pattern of inheritance.

On examination, the patient was found to have extensive bitemporal and parieto-occipital alopecia (fig. 2). No hair-follicle openings were evident in the bald area. The remaining hair was coarse and wiry, and some hairs showed a wavy hair shaft. Eyelashes and eyebrows, as well as terminal hair on the rest of the body, was scarce. Teeth, eyes, and nails were normal. Microscopic examination of the hair showed irregular hair shafts (not shown). Knotting the hair resulted in square knots, a diagnostic feature of MU. Identical clinical and microscopic abnormalities were found in additional family members.

Family 2 was of British origin, and affected individuals presented with clinical histories essentially identical to those of the Dutch family described above. A diagnosis of MU was made. Informed consent was obtained, and blood samples for DNA analysis were collected from members of both families.

Genotyping and Linkage Analysis

Four hundred microsatellite markers were derived from the Applied Biosystems LMS2 mapping panel (Perkin-Elmer) and were used according to the manufacturer's recommended protocol with minor modifications. The main changes were that DNA was used at a concentration of 100 ng/μl, instead of the recommended 25 ng/μl, and that 40 PCR cycles were used. In brief, markers were PCR amplified by use of a fluorescently labeled primer and Amplitaq Gold polymerase (Perkin-Elmer), in buffer containing 2.5 mM MgCl2. The resultant PCR products were analyzed on an ABI 377 automated DNA sequencer. Gel data were extracted by use of the ABI Genescan software, and microsatellite peaks were analyzed by use of the ABI Genotyper program. For the initial genome screen, 24 meioses from family 1 were used and linkage was scored by eye. Markers that showed only one recombination event or that were either partially or completely uninformative were used to analyze 30 meioses from family 2. Two-point LOD scores were computed by the MLINK algorithm of LINKAGE version 5.1, under the assumptions of a mutant-allele frequency of .001 and 99% penetrance. Marker-allele frequencies were assumed to be equal in the population.

Mutation Detection for the hr *Gene*

cDNA was prepared from primary epidermal keratinocyte cultures, as described elsewhere (McLean et al. 1995). The entire coding sequence of the human *hr* gene was amplified in a series of overlapping fragments by reverse transcription–PCR (RT-PCR) with primers derived from the published cDNA sequence (Genbank accession number AF039196; Ahmad et al. 1998*a*). RT-PCR was performed under standard conditions, and the products were directly sequenced with the ABI Prism system. Sequencing ladders were analyzed on an ABI 377 DNA sequencer. These same primers were used to amplify genomic DNA templates, by the Boehringer High Fidelity PCR system. The 3′ UTR sequence was obtained by 3′ rapid amplification of cDNA ends (RACE) PCR with the Clontech Marathon kit. The 5′ UTR sequence

Table 1

Combined LOD Scores for MU Families 1 and 2, for 8p Markers

	LOD Score at θ =						
Marker	0	.01	.05	.10	.20	.30	.40
D8S511	−27.39	−2.37	1.49	2.53	2.50	1.66	.72
D8S1827	−18.65	−1.33	1.77	2.67	2.66	1.89	.91
D8S549	−11.21	−.78	1.25	1.73	1.56	1.03	.48
D8S1731	−27.48	−1.68	2.59	3.78	3.76	2.69	1.31
D8S261	7.53	7.45	7.03	6.37	4.81	3.11	1.44
D8S1715	3.53	3.46	3.15	2.75	1.96	1.20	.54
D8S258	3.33	8.13	7.99	7.23	5.35	3.33	1.43
D8S282[a]	11.91	11.71	10.84	9.69	7.19	4.51	1.80
D8S560[a]	13.42	13.18	12.18	10.90	8.18	5.28	2.33
D8S298	6.59	10.89	10.61	9.65	7.30	4.70	2.08
D8S1786	10.48	10.28	9.46	8.42	6.27	4.07	1.92
D8S1733	9.25	9.08	9.37	7.47	5.61	3.68	1.69
D8S1752	10.96	10.78	10.04	9.03	6.84	4.50	2.12
D8S1739	−4.60	2.28	2.65	2.80	1.86	1.12	.48
D8S1771	−6.86	3.30	4.16	4.04	3.08	1.87	.74

[a] Showed no visible recombinants.

of cDNA and the genomic equivalent, which includes an intron equivalent to intron 1 in the murine sequence, was obtained by a combination of 5′ RACE and cross-species PCR with primers designed from the murine 5′ UTR sequence. Mutation detection was performed on an affected individual from family 1 by use of both the cDNA and the genomic DNA strategies, making, in each case, a comparison with cDNA or genomic DNA from a normal, unrelated individual.

Radiation-Hybrid Mapping

Exon 3 of the *hr* gene was amplified by use of primers located in the flanking introns, 2 and 3: HRe3.L (sense strand, 5′ CCC CTT CCT TCT TGC TTG TC 3′) and HRe3.R (antisense strand, 5′ ATA AAG CCT ACA GAC CCC GC 3′). This sequence tagged site was used to screen the Stanford G3 radiation-hybrid panel (Research Genetics), which gave the following data vector: *hr* 00 00000000000000000000000000000000100000100100 11000000010000000000101000000001000000. The microsatellite markers D8S258 and D8S298 were also mapped, with the published primers and conditions. Markers were used to screen the panel in triplicate to ensure accuracy, and the resultant data vectors were mapped via the Stanford radiation-hybrid website.

Results

Mapping of the MU Gene to Human Chromosome 8p

A genomewide search for the MU gene was undertaken by use of the ABI LMS2 mapping panel, which consists of 400 fluorescently labeled microsatellite markers spaced at intervals <10 cM across the genome. Initially, 24 meioses from family 1 were analyzed, and linkage was assessed by eye. Linkage was detected with markers D1S206, D4S1597, D5S400, D8S258, and D18S57. Genotyping of additional individuals from families 1 and 2 revealed that four of these linkages were false, the exception being D8S258, which is located on chromosome 8p. With the latter marker, analysis of additional meioses in family 1 and family 2 resulted in a significant combined two-point LOD score of 3.33 at recombination fraction (θ) 0, as shown in table 1. Linkage analysis was performed on both families by use of an additional 14 microsatellites in the vicinity of D8S258, to further define the locus. Two-point LOD scores obtained by genotyping both families with these markers are outlined in table 1. A highly significant maximum combined two-point LOD score of 13.42 at θ = 0 was obtained with marker D8S560.

Two critical recombinants were observed in individuals from the Dutch family (family 1; fig. 1), with markers D8S258 and D8S298, as shown in figure 3. These recombination events place the MU gene in the interval between these markers, representing a genetic distance of 2.4 cM, based on the current CEPH-Généthon Integrated Map.

Exclusion of the hr *Gene as a Candidate for MU*

The MU locus is well within the interval to which the human *hr* gene has been mapped, mutations in which cause the recessive hair-loss disorder congenital atrichia

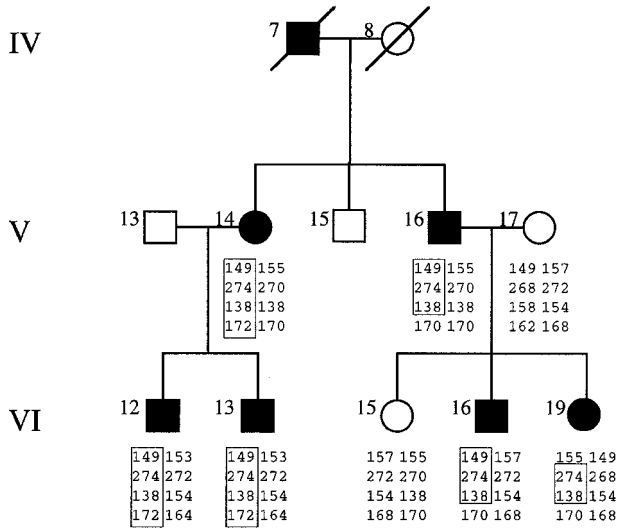

Figure 3 Haplotype analysis of part of family 1, showing the two recombinants that delineate the 2.4-cM MU critical region between markers D8S258 (distal) and D8S298 (proximal). As shown in figure 4, distances of markers from the telomere, according to the Généthon map, are: D8S258, 40.3 cM; D8S282, 41.6 cM; D8S560, 42.2 cM; and D8S298, 42.7 cM.

(Ahmad et al. 1998*a*; Cichon et al. 1998). Specifically, the previous mapping studies had placed the *hr* gene in the interval between D8S261 and D8S1771, by use of radiation-hybrid mapping (Cichon et al. 1998). Since we had critical recombinants with D8S258 and D8S298, which are 2.4 cM apart in the middle of this region, we performed radiation-hybrid mapping using the Stanford G3 panel to discover if the *hr* gene lies within this MU critical region. D8S258, D8S298, and the *hr* gene were scored in triplicate on the G3 panel. Data vectors obtained for D8S258 and D8S298 were identical to those reported by the Stanford Human Genome Center. The *hr* gene was placed 7 $cR_{10,000}$ (centiRays for a 10,000 rad radiation hybrid panel) distant from D8S298 (fig. 4). However, the G3 panel was unable to resolve the order of markers at this locus. (A description of how the G3 radiation hybrid panel was constructed and an explanation of the units of distance used can be found at the Stanford radiation-hybrid website.) Therefore, we were unable to exclude the *hr* gene from the MU interval by this means and proceeded to analyze the *hr* gene for mutations in MU. Interestingly, the order of markers on the G3 map of this region (fig. 4) is not fully consistent with the Généthon linkage map of the locus (table 1). Specifically, the positions of D8S560 and D8S1733 are reversed on these two maps. Our linkage data are consistent with the Généthon ordering of these markers, and one possibility is that the G3 data for these markers have been switched. Physical mapping of the locus should further resolve these inconsistencies.

Mutation detection for the *hr* gene was performed in two ways. First, the entire *hr* cDNA was amplified by RT-PCR using mRNA derived from skin-biopsy samples from an affected individual in family 1 and a normal unrelated individual and was fully sequenced. The UTRs of the human *hr* mRNA were not present in the GenBank entry for the gene and so were first determined by 5′ and 3′ RACE techniques. This was particularly important in the case of the 5′ UTR sequence, which contains an intron in mice and therefore might harbor splicing mutations (Cachon-Gonzalez et al. 1994). Sequencing of the cDNA revealed a number of minor sequence changes from the published human *hr* cDNA sequence (Ahmad et al. 1998*a*), as reported (Cichon et al. 1998; Ahmad et al. 1999). All changes observed were also detected in normal unrelated individuals and were therefore excluded as pathogenic mutations. Second, mutation detection was performed by use of genomic DNA. Initially, the intron-exon organization of *hr* was not available, and so we determined it independently, although these data have been recently reported by other groups (Cichon et al. 1998; Ahmad et al. 1999). We found the intron-exon organization of the gene to be identical to that published. We also cloned the 5′ UTR sequence from cDNA and genomic DNA by a combination of 5′ RACE

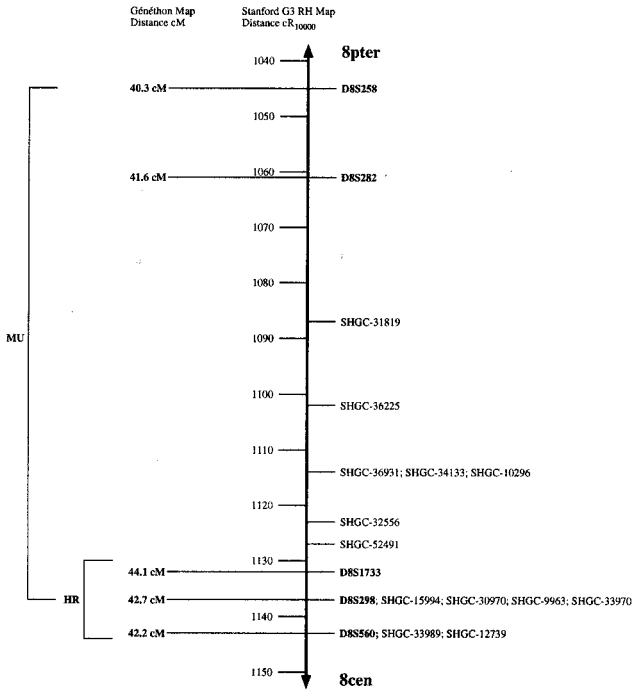

Figure 4 Radiation-hybrid map of MU locus, based on the Stanford G3 panel. Distances are in $cR_{10,000}$. On the basis of this mapping panel, the *hr* gene was located 7 $cR_{10,000}$ from marker D8S298 but could not be ordered relative to this and nearby markers. Note that the order of markers is different from that given by the Généthon linkage map (see table 1): D8S560 and D8S1733 are in reverse order. Our linkage data are consistent with the Généthon order. Physical mapping of the locus should resolve this inconsistency.

PCR and cross-species PCR, using primers derived from the murine sequence. Like the murine sequence, the human 5′ UTR of the *hr* gene contains an intron (Cichon et al. 1998; Ahmad et al. 1999). Again, no mutations at the genomic DNA level, including all intronic splicing and branch point sites, were found in an affected person from family 1.

Discussion

Here, by genomewide linkage analysis with fluorescent microsatellite markers, we have mapped an autosomal dominant gene for a human hereditary hair-loss syndrome, MU. On the basis of two critical recombination events in the Dutch family studied (family 1; fig. 1), we have shown that the gene for MU is located in a 2.4-cM region between Généthon markers D8S258 (distal) and D8S298 (proximal) on human chromosome 8p22-21 (fig. 3). A strong candidate gene in this region is the human homologue of the murine hairless gene, *hr*, which was previously mapped to the center of a region delineated by markers D8S261 and D8S1771 (Ahmad et al. 1998*a*). Homozygous mutations in this gene have

been demonstrated in families with the autosomal recessive disorder congenital atrichia. These include homozygous missense mutations (Ahmad et al. 1998*a*, 1998*b*; Cichon et al. 1998); homozygous deletion mutations (Zlotogorski et al. 1998; Ahmad et al. 1999); and a homozygous splice-donor mutation (Cichon et al. 1998). Homozygous loss-of-function mutations in the murine *hr* gene have recently been shown to underlie various rhino mouse phenotypes: $hr^{rh\text{-}8J}$ (Ahmad et al. 1998*d*); hr^{rhY} (Panteleyev et al. 1998*a*); and hr^{rhChr} (Ahmad et al. 1998*c*), in addition to the original hairless phenotype (Cachon-Gonzalez et al. 1994). The *hr* polypeptide is a putative transcription factor that may control apoptotic events in the hair cycle (Panteleyev et al. 1998*b*). Here, we have performed higher-resolution radiation-hybrid mapping of *hr* but have been unable to exclude it from the MU critical region. We have shown by radiation-hybrid mapping that *hr* lies very close to D8S298, a marker with which we observed recombination in MU (fig. 4). However, we were not able to place this gene outside the MU locus by this method.

Autosomal dominant inheritance has not been described for congenital atrichia, and the heterozygous carriers of the mutant alleles reported are apparently asymptomatic (Ahmad et al. 1993, 1998*a,* 1998*b;* Cichon et al. 1998; Zlotogorski et al. 1998). We speculated that MU might be caused by dominant-negative mutations in *hr*, whereas the mutations seen in congenital atrichia act in a recessive, loss-of-function fashion. Support for this hypothesis was gained from examination of the Mouse Genome Database. There are several independent mutant alleles of the *hr* gene in mice, such as the rhino alleles hr^{rh} (Howard 1940), hr^{rh}*-8J* (Ahmad et al. 1998*d*); hr^{rhY} (Panteleyev et al. 1998*a*), and hr^{rhChr} (Ahmad et al. 1998*c*), the bald allele hr^{ba} (Garber 1952); and the insertional mutant $hr^{TgN5053Mm}$ (Jones et al. 1993). All of these alleles are recessive; however, one mouse mutant known as "near-naked," hr^{n}, is allelic with the recessive *hr* mutations and shows semidominance, giving a milder hair-loss phenotype in heterozygotes and a more severe phenotype in homozygotes (Stelzner 1983). This evidence, combined with the close proximity of the human *hr* gene to the MU locus, led us to postulate that MU might well be a dominantly acting mutation in *hr,* and so we undertook mutation detection for this gene in our MU patients, using both cDNA and genomic DNA. However, no mutations were found by either approach.

In conclusion, the MU gene maps to a locus close to but apparently distinct from the *hr* gene on 8p22-21. There are several expressed sequence tags that map to this region, none of which represent good candidates and the vast majority of which are anonymous (NCBI Gene Map '98). Extensive BLAST analysis of these sequences (Altschul et al. 1990; Altschul et al. 1997) failed to identify any of them with homology to *hr*, to other transcription factors, or to other potential candidates. We are now constructing a physical map of the locus to allow identification of the MU gene, a gene that undoubtedly encodes a protein that plays an important role in hair development and maintenance in humans.

Acknowledgments

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Electronic-Database Information

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

CEPH-Généthon Integrated Map, http://www.cephb.fr/ceph-genethon-map.html
GenBank Entrez Browser, http://www.ncbi.nlm.nih.gov/Entrez/nucleotide.html
Mouse Genome Database, http://www.informatics.jax.org/
NCBI Gene Map '98, http://www.ncbi.nlm.nih.gov/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for MU and congenital atrichia with papular lesions)
Stanford radiation-hybrid website, http://www-shgc.stanford.edu/RH/index.html

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