

Progressive Patterned Scalp Hypotrichosis, with Wiry Hair, Onycholysis, and Intermittently Associated Cleft Lip and Palate: Clinical and Genetic Distinction from Marie Unna

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Marie Unna hereditary hypotrichosis has been described in over a dozen families since 1924. Features include scant or no eyebrows at birth, the development of firm wiry hair in the first few years of life followed by a progressive patterned scalp alopecia in the second or third decade. This is associated with generalized hypotrichosis of the body and the condition is nonsyndromic. We have identified a novel form of autosomal dominant ectodermal dysplasia that resembles Marie Unna hereditary hypotrichosis in a family of 23 members over four generations. Affected individuals have patterned hair loss and associated hair shaft dystrophy similar to that seen in Marie Unna hereditary hypotrichosis. It differs from Marie Unna hereditary

hypotrichosis by an absence of signs of affectation at birth, relative sparing of body hair, distal onycholysis, and intermittent cosegregation with autosomal dominant cleft lip and palate. Linkage studies to the known Marie Unna locus at 8p21 near the *Hairless* gene were performed. Linkage analysis using markers D8S298, D8S560, D8S258, and D8S282 revealed significant exclusion of this locus ($Z = -2.0$ or lower) at $\theta = 0.1$. This demonstrates that this novel ectodermal dysplasia is both phenotypically and genetically distinct from Marie Unna hereditary hypotrichosis. **Key words:** alopecia/atricia/genetic/hair loss/hairless/universalis. *JID Symposium Proceedings* 8:121–125, 2003

Marie Unna, a German dermatologist first reported a novel condition in 27 affected individuals in a family living in northern Germany as hypotrichosis congenita hereditaria (Unna, 1925). It subsequently became eponymously associated with her name.

Since then, there have been multiple Caucasian families reported in the literature, mainly from Europe but also the United States (Ullmo, 1944; Borelli, 1954; Kemeny and Csontos, 1967; Stevanovic, 1970; Peachey and Wells, 1971; Solomon *et al*, 1971; Wakkers-Garritsen, 1974; Hutchinson and Wells, 1975; Spiegl and Hundeiker, 1979; Chlebarov, 1985; Wirth *et al*, 1985; Lalevic-Vasic *et al*, 1992; Marren *et al*, 1992; Souied *et al*, 1995; Argenziano *et al*, 1999; Roberts *et al*, 1999). Recently, there has been one report in an Asian family (Kim *et al*, 2001), but there have been no previous reports from Australia. All families described have an autosomal dominant pattern of inheritance. Clinically, they have all displayed similar features. These include the onset of wiry hair in the first few years of life and a progressive patterned alopecia commencing in the second or third decade. The hair loss begins initially in patches in the parietal scalp and the vertex and thereafter slowly progresses over decades to resemble a Hamilton VIII pattern.

Previous reports have consistently noted marked reduction or absence of hair from the trunk and limbs, as well as scant or absent eyebrows, beard, axillary, and pubic hair in postpubertal subjects. While there has been reported association with wide spacing of the front incisor teeth, Marie Unna hereditary hypotrichosis (MUHH) is considered to be nonsyndromic. No other problems of tissues derived from ectoderm have been reported.

Several genetic linkage studies have mapped MUHH to chromosome 8 p21.

We studied a family of 22 members over four generations (**Fig 1**) with wiry hair and a similar pattern of hair loss and found them to be phenotypically and genetically distinct from the previously described families with MUHH.

MATERIALS AND METHODS

Ethics committee approval was provided by the St Vincent's Hospital Ethics Committee, Protocol Number: 032/00.

Clinical Twenty-two members of this family were identified. A history and examination were performed. Information regarding now deceased members of the family was obtained from questioning older members of the family.

Light and scanning electron microscopy At least 20 hairs were cut from the occiput of those members in the family resident in Australia and examined under light microscopy for previously described features of Marie Unna.

Histopathology Scalp biopsies were taken from individuals V:2, V:5, VI:6, and VII:4. In the three adult members two 4 mm punch biopsies

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Abbreviations: MUHH, Marie Unna hereditary hypotrichosis; *Hr*, Hairless gene.

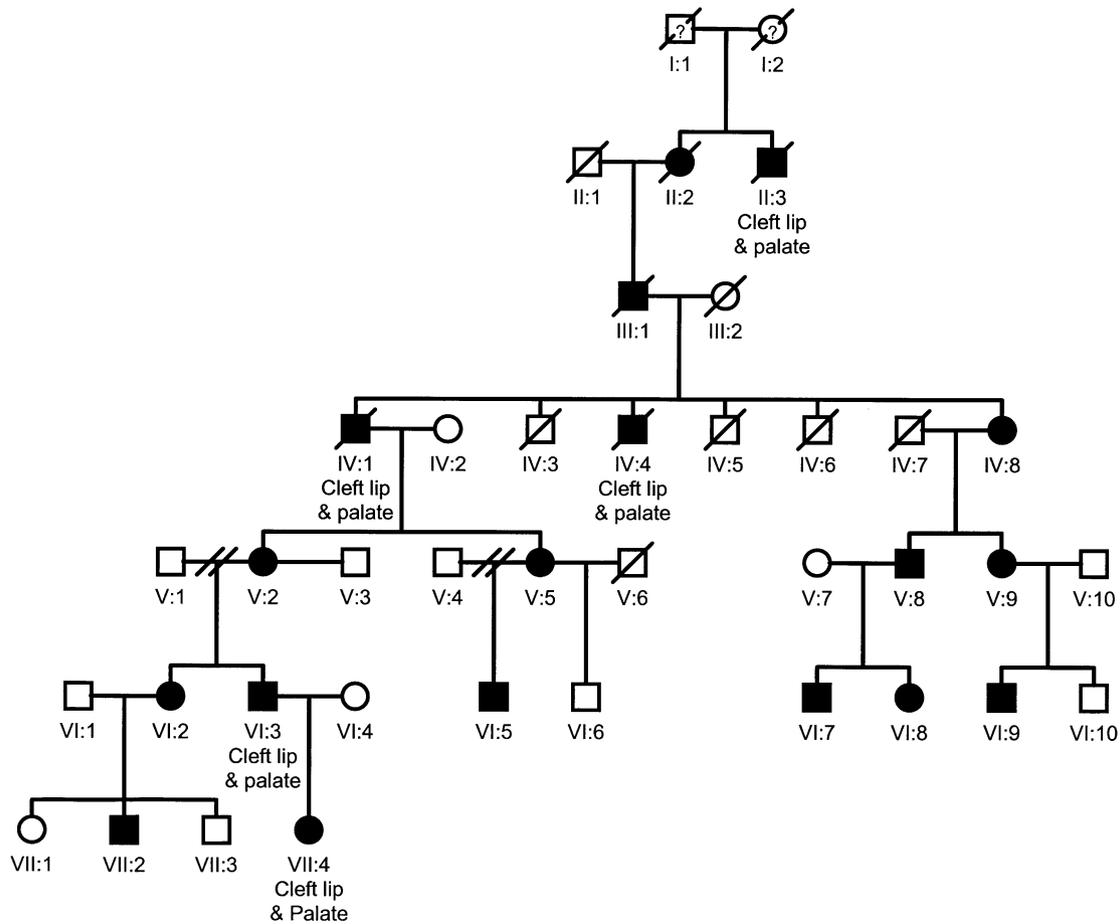


Figure 1. Family pedigree demonstrating autosomal dominant inheritance and intermittent cosegregation with cleft and palate.

were taken. The specimens were fixed in 10% formalin overnight and then one was processed for horizontal section and the other for vertical sections. In the youngest affected member, a single biopsy was taken from the occiput under general anesthetic during a dental procedure.

Sample collection and DNA extraction Genomic DNA was isolated from peripheral blood using the Nucleon BACC2 DNA extraction kit (Amersham Life Sciences, Little Chalfont, UK) or from buccal cells. Buccal cells were removed from a mouthwash of 10 ml of distilled water by centrifugation 290 (1200 r.p.m.), the cells were then lysed and digested with Proteinase K. After digestion, proteins were precipitated in high concentrations of NaCl spun at 14,000 r.p.m. (21,952) and the supernatant removed. DNA was then precipitated from the supernatant in ethanol and resuspended in sterilized Tris ethylenediamine tetraacetic acid.

Genotyping Microsatellite markers D8S1733, D8S298, D8S560, and D8S282 (GDB) at 8p21 flanking the Marie Unna locus and *Hairless (Hr)* gene were genotyped in this family. Polymerase chain reactions were carried out in 20 μ l volumes containing 1 \times Biotech polymerase chain reaction buffer (Fischer Biotech International Ltd, Belmont, Western Australia, Australia), 2.5 mM MgCl₂, 0.2 mM deoxyribonucleoside triphosphate, 100 ng each of forward and reverse primer, 50 ng genomic DNA, 0.5 U Taq DNA Polymerase (Boehringer Mannheim, Mannheim, Germany) and 1 μ Ci γ 33P-deoxycytidine triphosphate. A Corbett polymerase chain reaction cyclor was used. Polymerase chain reaction conditions were: 1 min hot start at 95 $^{\circ}$ C, then 35 cycles of 95 $^{\circ}$ C for 30 s, between 51 $^{\circ}$ C and 57 $^{\circ}$ C for 30 s, 72 $^{\circ}$ C for 45 s. Samples were separated on a 6.5% denaturing polyacrylamide gel and transferred to Whatman paper for drying. The gel was exposed to Kodak AR film overnight at room temperature.

Linkage analysis A two-point analysis was done using the MLINK program (version 5.1) of the LINKAGE package (Lathrop and Lalouel, 1984). An autosomal dominant model was used, with a disease allele frequency of 1 in 50,000; a disease penetrance of 100%, and equal allele frequencies.

Karyotyping Routine blood karyotyping using standard blood lymphocyte culture techniques and GTL (Giemsa Trypsin Lieshman's) banding in individual VII:3 was normal.

RESULTS

Hair

History In no individual was his or her affectation status known at birth. Subjects were born with either normal hair or no hair. At an average age of 2 y (range 6 mo–5 y) the hair became increasingly coarse, wiry, and difficult to manage. It was at this stage that the parents first became aware that the child was affected. Onset of alopecia varied from 15 to 23 y. The pattern of alopecia was fairly consistent between family members. Most often, alopecia commenced as patches in the parietal area on one side. The other side then developed patches of alopecia within a year or two. All affected individuals subsequently had progression of their alopecia in an anterior to posterior direction reminiscent of the pattern described by Hamilton in male androgenetic alopecia. This is similar to the final pattern seen in MUHH. Among older affected females, wig wearing had commenced between ages 25 y and 52 y.

One older male individual sported a beard from his later teenage years. Despite the onset of his scalp alopecia at age 17 y with rapid progression to involve most of his vertex by age 23 y, his beard remained full. Ten years ago in his early forties, however, a patch of alopecia slowly developed to the right of the anterior neckline of his beard and has since slowly extended proximally to now create a 3 cm \times 4 cm area of hair loss extending to the right submandibular area. The skin is normal at the sites of alopecia.

Examination Examination of affected individuals revealed that they all had coarse, tough, wiry hair that were well anchored, except at the edge of alopecia patches in individuals VI:2 and VI:5. Progression of alopecia was consistent with age. This varied from biparietal loss in younger subjects (**Fig 2**) to a Hamilton VIII pattern in older individuals (**Fig 3**). Alopecic areas tended to have a lower than normal number of hair follicles with generally no clinical signs of scarring or erythema.

The majority of hairs obtained on hair pull test were in telogen, although a minority were normal anagen or dystrophic anagen hairs.

Only two individuals had sparse eyebrows. In the other affected patients, eyebrows were within normal limits, although

compared with nonaffected family members, the outer third was thin. Two individuals had sparse eyelashes. In the other affected subjects, eyelashes were normal. Body hair was within normal limits.

Nails Affected individuals had a history of easily breakable and brittle nails that grew slowly. On examination distal onycholysis of the fingernails (**Fig 4**) was found in all but two affected individuals. It was most marked at the thumbnails and less obvious towards the smaller fingers of the hands. The distribution was generally symmetrical. Individual V:8 described a progression of nail pathology with onycholysis occurring initially in the thumbnails then, over many years progressing laterally to increasingly involve successive digits. Several affected subjects were noted to have soft nails. Koilonychia of at least one nail was present in four individuals. Seven of the affected individuals also displayed onycholysis of the toe nails, most commonly the great toe.

Cleft lip and palate Of the 13 affected individuals examined, cleft lip and palate was present in two: a father and daughter. Cleft lip and palate was also present in three now deceased affected members. No unaffected members, either alive or now deceased, had cleft lip or palate (**Fig 1**).

Hair microscopy Hairs from the Australian arm of the family were examined with light and scanning electron microscopy. Similar features to those that have previously described for MUHH were found. Hairs were flat, had irregular changes in contour and bore as well as various degrees of indentations of the hair shaft (**Fig 5**). The cuticle was normal in all hairs.



Figure 2. Bilateral parietal alopecia in VI:2.

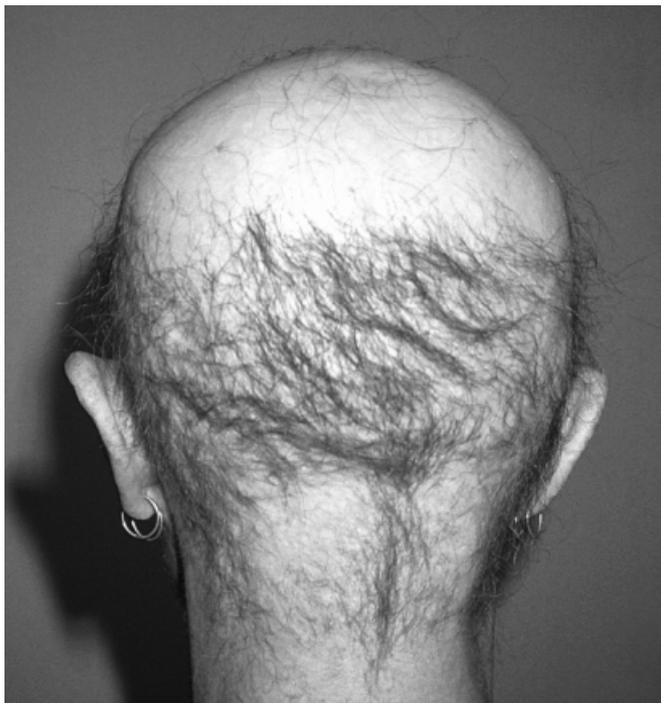


Figure 3. Hamilton-like alopecia in V:2.

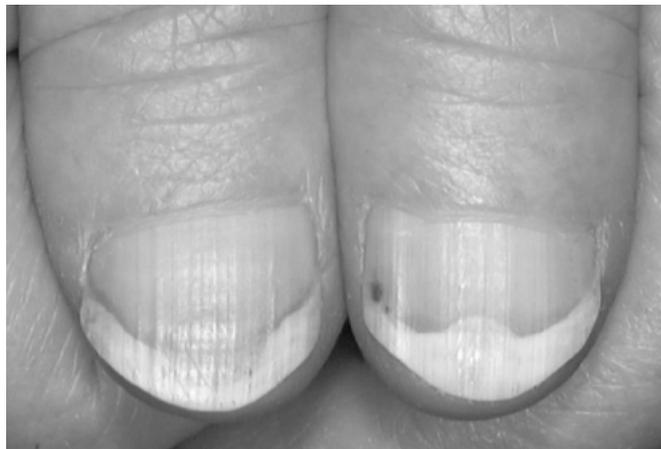


Figure 4. Distal onycholysis.

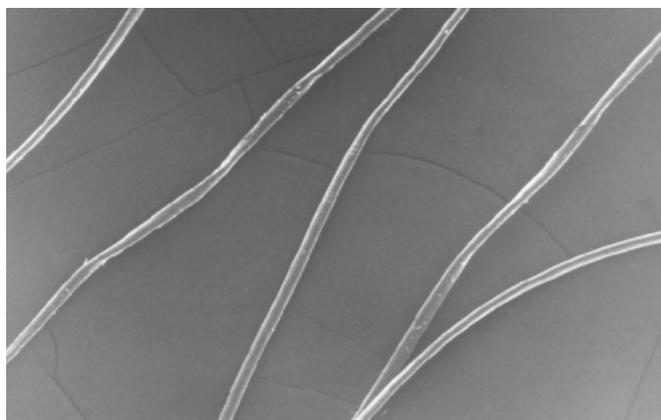


Figure 5. Scanning electron microscopy of hairs.

Table I. LOD score results of linkage analysis

Marker	Recombination fraction (θ)						
	0	0.01	0.05	0.1	0.2	0.3	0.4
D8S298	-8	-8.38	-4.32	-2.69	-1.24	-0.54	-0.17
D8S560	-8	-8.75	-4.66	-2.98	-1.45	-0.68	-0.25
D8S258	-8	-12.56	-6.99	-4.73	-2.37	-1.18	-0.45
D8S282	-8	-3.56	-1.64	-0.89	-0.31	-0.12	-0.06

Scalp biopsies Biopsies were taken from four individuals across three generations in order to capture alopecia at different stages. Horizontal sectioning of biopsy from VIII:4 who was 4 y old at the time and had no alopecia revealed normal follicular density with 50 follicles counted of which 10 were vellus. There were three or four telogen hairs. Mild perifollicular lymphocytic inflammation was seen but there was no fibrosis representing a generally nonscarring process.

A horizontal section of a biopsy from a patch of alopecia from VII:3 showed a marked decrease in follicular density with four to five follicles counted. Many sebaceous glands were present without accompanying follicles. One hair shaft seen appeared enlarged measuring 0.14 mm (normal approximately 0.06 mm). On vertical sectioning, no scarring was noted. Horizontal sections of the biopsies from individuals V:2 and V:5, aged 56 y and 53 y, respectively, in which the alopecia was advanced revealed persistence of low follicular density with six follicles seen in each subject. In both subjects there was also relative preservation of sebaceous glands with mild perifollicular lymphocytic inflammation and no perifollicular dermal fibrosis.

Genotyping Twenty-two individuals were genotyped using the markers D8S258, D8S282, D8S560, and D8S298 spanning the known Marie Unna locus and *Hr* gene on chromosome 8p21. Linkage analysis revealed significant exclusion of this locus [LOD score (Z) = -2.0 or lower] in three of four of these markers at a recombination fraction (θ) of 0.1 (Table I).

DISCUSSION

This pedigree displays many similarities to previously described families with MUHH. They all show an autosomal dominant pattern of inheritance, which is also present in this pedigree. There are three descriptions of abnormal hair at birth. Unna's original paper (Unna, 1925) describes woolly hair at birth, which falls out during the first year, and Solomon *et al* (1971) mentions frizzy, sparse course hair present at birth, and Roberts *et al* (1999) reports a combination of both normal and course hair at birth. All other papers describe no hair or normal hair present at birth. Onset of coarse wiry hair occurs in infancy (Roberts *et al*, 1999) the first few years of life (Stevanovic, 1970) or between a few months of life up to age 6 y (Peachey and Wells, 1971). In our family the age range for the development of coarse hair is between 1 y and 5 y.

Unna describes mothers knowing the affectation status of their child at birth. Presumably this would be the case in most of the other reported families where affected children were born with scant or absent eyebrows and eyelashes. In this family, however, it was unclear whether children would be affected or not until the onset of coarse wiry hair in the first few years of life as the eyebrows are normal or near normal. This has not been described in association with MUHH.

Unna describes two forms of alopecia. In the more severe form the child's hair is always sparse and then progresses to advanced alopecia by puberty; however, in the milder form, the hair is initially thick with alopecia commencing in the second or third decade. This milder form is consistent with the course of the alopecia we have described, which is similar to other reports

(Stevanovic, 1970; Peachey and Wells, 1971; Roberts *et al*, 1999); however, unlike MUHH, body hair in this pedigree is normal.

The appearance of the hair shaft both clinically and under light microscopy are similar to those seen in MUHH. VIII:4 has coarse hair that is similar to various previous descriptions of the hair as being similar to a horse's tail (Borelli, 1954) or, resembling a clown's wig (Kemeny and Csontos, 1967).

In the adults, histopathology was similar to previous reports of MUHH with decreased follicular density, a nonscarring process, increased hair shaft diameter, and preservation of sebaceous glands. The biopsy from the 4 y old affected subject showed normal hair density with an increased percentage of miniaturized follicles with normal to decreased hair shaft diameters. This histology looked most like androgenetic alopecia.

There seems to be an incomplete association with cleft lip and palate in this pedigree with its presence in three now deceased and two presently living affected members but not found in unaffected individuals. This has not been previously described in MUHH. The only dental association is with wide spaced central incisors (Solomon *et al*, 1971; Hutchinson and Wells, 1975; Roberts *et al*, 1999). Other previously described associations include juvenile macular degeneration (Marren *et al*, 1992), widespread facial milia at birth (Solomon *et al*, 1971), and keratosis pilaris with mental retardation (Ullmo, 1944).

Many reports, including Unna's original paper, report normal nails; however, in our family, the majority of those affected displayed abnormal nails. In addition to a history of slow growing brittle nails, affected members had distal onycholysis most notable in the fingernails and more severe in the thumbs than in the other digits. One individual noted the slow progression of the onycholysis to include eventually the more medial fingernails.

The resemblance of the hair phenotype and alopecia in this pedigree to MUHH lead to individual V:9 being mistakenly diagnosed as having MUHH and she was included in a previous study (Lefevre *et al*, 2000) (as patient B3) where the hairless gene was screened for mutations and was found to be normal.

MUHH has now been linked to a 2.4 cM region on chromosome 8p21 (van Steensel *et al*, 1999). Linkage to this region has been confirmed by other studies (Cichon *et al*, 2000; Lefevre *et al*, 2000; Sreekumar *et al*, 2000). The *Hr* gene, which is in this area, has been excluded as a cause of MUHH in these other studies.

Our pedigree represents the first description of a novel hair disease similar to but distinct from MUHH. There is a combination of hair shaft morphology and alopecia similar to MUHH with associated ectodermal defects of the nails and intermittently, of the lip/palate. The existing MUHH locus at chromosome 8p21 does not harbor the gene causing this disease. This demonstrates more than one genetic cause for the combination of wiry hair and progressive patterned scalp hypotrichosis.

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