# Clinical and Pathologic Correlations in Genetically Distinct Forms of Atrichia

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## ABSTRACT

Background  The genetic basis of 2 distinct forms of atrichia with papules has recently been defined at the molecular level. In atrichia with papular lesions (APL; Online Mendelian Inheritance in Man [OMIM] 209500), mutations in the hairless gene on chromosome 8p21 have recently been identified. Atrichia with papules also occurs in the clinical setting of vitamin D–dependent rickets type IIA (VDDR IIA; OMIM 277440), resulting from mutations in the vitamin D receptor gene on chromosome 12q12-q14. Despite the distinct genetic basis for both forms of atrichia, the clinical findings are strikingly similar and exhibit classic pathognomonic features unique to this phenotype. We sought to document the clinical and molecular features of APL and VDDR IIA.

Observations  Molecular analysis of the hairless and vitamin D receptor genes was performed on genomic DNA from probands and family members from 3 families with APL and 2 with VDDRIIA. We present a clinical and histologic comparison of atrichia in patients with APL and VDDR IIA and highlight the genetically heterogeneous basis of atrichia by identification of pathogenetic mutations.

Conclusions  Increased awareness of these diseases will allow early diagnosis and potential therapeutic intervention for the rickets in VDDR IIA and avoidance of treatment of the atrichia in both APL and VDDR IIA. Their phenotype similarities suggest the possibility of a functional relationship between HR and VDR.

## INTRODUCTION

The terms alopecia, hypotrichosis, and atrichia are frequently used interchangeably in the literature. However, their strict definitions are quite distinct. Alopecia can be defined as thenoncongenital process of hair loss, which may progress to partial or complete baldness. These forms of pattern alopecia may be permanent or reversible, whereas hypotrichosis is a term meaning the diffuse (congenital or acquired) forms of extensive hair loss leading to paucity of hair.1

In contrast, the term atrichia is reserved for the most dramatic and severe forms of hair loss, in particular, those that are characterized by an absence of hair follicles. Atrichia is manifested by congenital or early-onset hair loss, which ends rapidly in a completely smooth bald scalp.1 These

conditions are extremely rare, and, in fact, only very few disorders typified by absence of hair (and hair follicles) have been described. Two such conditions are atrichia with papular lesions2-4 (APL; Online Mendelian Inheritance in Man [OMIM] 209500) and atrichia in the setting of vitamin D–dependent rickets or rickets-alopecia syndrome5-6 (VDDR IIA; OMIM 277440).

In APL, a rare autosomal recessive disease characterized by early onset of atrichia followed by a papular eruption, mutations in the hairless gene (HR) on chromosome 8p21 have recently been identified. 7-18 Atrichia also occurs in the clinical setting of VDDR IIA due to mutations in the vitamin D receptor gene (VDR) on chromosome 12q12-q14.5-6 Patients with recessively inherited mutations in the VDR gene (vitamin D–dependent rickets type II, VDDR II, OMIM 277440) display several phenotypic characteristics that can be attributed to defective mineral metabolism, including hypocalcemia, hyperparathyroidism, rickets, and osteomalacia.5-6,19-21 Each of these features is also observed in patients with dietary vitamin D deficiency or in patients with vitamin D-dependent rickets type I (VDDR I), who have 25-hydroxyvitamin D 1α hydroxylase deficiency. Complete early-onset atrichia is a feature of only a subset of patients with VDDR II, therefore designated VDDR IIA.

Despite the distinct genetic basis for both forms of atrichia, the clinical findings are strikingly similar and exhibit features unique to this phenotype. In this study, we document a detailed clinical and histopathologic comparison of the progression of atrichia in patients with APL and VDDR IIA. Furthermore, we underscore the genetically heterogeneous basis of atrichia by identification of several pathogenetic mutations. Increased awareness of these diseases will allow early diagnosis and adequate therapeutic intervention for the rickets in VDDR IIA and, importantly, the avoidance of treatment of the atrichia in APL and VDDR IIA.

## METHODS

### HUMAN SUBJECTS

Three families with APL (families 1, 2, and 3) and 2 with VDDR IIA (families 4 and 5) were studied. Genomic DNA was isolated from peripheral blood collected in edetic acid (EDTA)–containing tubes according to standard techniques.22 All samples were collected after informed consent and in accordance with the rules of the local institutional review board.

### MOLECULAR ANALYSIS OF THE HR AND VDR GENES

To search for mutations in the human HR and VDR genes, all exons and splice junctions were amplified via polymerase chain reaction from genomic DNA and sequenced directly in an ABI

Prism 310 Automated Sequencer, using the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit (PE Applied Biosystems, Foster City, Calif) following purification in Centriflex Gel Filtration Cartridges (Edge Biosystems, Gaithersburg, Md) as described previously.10, 21 The mutations were identified by visual inspection and comparison with control sequences generated from unrelated, unaffected individuals.

## HISTOPATHOLOGIC ANALYSIS

Biopsies were performed in the third proband of the VDDR IIA family 4 to confirm the diagnosis of atrichia. Specifically, two 3-mm punch biopsy specimens were taken from the left parietal region of the scalp and the arm under local anesthesia. The samples were fixed in 4% paraformaldehyde and embedded in paraffin. The 4-µm sections were processed and stained with hematoxylin-eosin according to standard protocols.

## RESULTS

## CLINICAL FINDINGS IN APL

### Family 1

The proband in family 1 was a 21-year-old Jewish Israeli woman, the only affected daughter of first-cousin parents (Figure 1A, C, and E). She was born with hair, most of which she shed within the first 3 days of life, and which she completely lost by age 7 months. The progression of hair loss was from front to back, while the last hairs remained on the posterior vertex of the scalp. The hair never regrew, except for a few waxing and waning hairs in the eyebrows. Papules started to appear at age 4 years, and are now more pronounced on the elbows and knees. The proband's medical history is significant only for hyperthyroidism since age 10 years. However, dysregulated thyroid status seems to be unrelated to APL in this family, since her father and older brother have hypothyroidism, and her younger sister has borderline hyperthyroidism.

On physical examination, complete scalp atrichia and sparse eyebrows and eyelashes were noted. The scalp showed only a few papular lesions, mainly on the posterior aspect. The papules were more prominent under and mainly lateral to the eyes. Many papules were noted on the arms and around the elbows, on the thighs and around the knees. The papules around the elbows and knees were notably larger than on other body sites.

### Family 2

The proband in family 2 was a 13-year-old boy, the only affected son of his first-cousin Arab-Israeli parents. He was born with hair, but it was completely shed by age 1 year. Papules started to appear on the face and knees at age 11 years. Complete scalp atrichia and an almost complete lack of eyebrows and eyelashes with no bodily hair were noted on physical examination. Papules were found on the cheeks, above and below the eyes, on the arms, forearms, and around the elbows, on the ear, chest, abdomen, thighs, and around the knees.

**Family 3**

The proband in family 3 was a 2-year-old girl, the only affected daughter of her first-cousin Arab-Palestinian parents. She was born with hair, but it was almost completely shed by age 1 year. The progress of hair loss occurred in a frontal to posterior direction. Complete scalp atrichia, with only few hairs left on the vertex, and an almost complete lack of eyebrows and eyelashes were noted on physical examination. Only few papules were found on the scalp and face.

**CLINICAL FINDINGS IN VDDR IIA**

**Family 4**

We present in family 4 the clinical history of 4 probands from a large family with VDDR IIA. The first and second probands were dizygotic twin girls, age 3 years, both affected with VDDR IIA, and born to first-cousin Arab-Israeli parents (Figure 1B). They were born with only a few fine scalp hairs that started to fall out by age 2 months and were completely shed within the subsequent 2 to 4 months. Notably, the progression of the hair loss occurred in a frontal to posterior wave. Papules began to appear on the scalp, face, and knees at age 2 years.

On examination, we noted only 6 scalp hairs and sparse eyelashes and eyebrows. Papules in one of the twins numbered approximately 80 and were distributed on the posterior scalp, forehead, arms, forearms, thighs, and shins. Papules in the other twin numbered approximately 15 and were distributed on the posterior scalp, cheeks (lateral to the eye), and arms.

The third patient was a 25-year-old man born with hair that shed from age 1 month to age 12 months. On examination, we noted complete atrichia, sparse eyebrows, normal eyelashes, and a few hairs on his mustache. Papules were present mainly on the lateral cheeks, neck, back, elbows, arms, forearms, buttocks, knees (Figure 1 F), thighs, and shins. Notably, papules around the elbows were larger in size, and there was obvious pitting and regression of papules mainly below the knees and around the elbows.

The fourth patient in family 4 was a 13-year-old boy born with hair that began to shed immediately after birth; he became atrichic within 3 months. The hair fell out in a frontal to posterior direction. On examination, we observed approximately 50 hairs on the top posterior scalp along with a few hypopigmented marks. The eyebrows were sparse, but the eyelashes were almost completely normal. Papules were found lateral to the eyes and on the cheeks, lateral to the nose, on the arms and forearms, around the elbows, back, neck, thighs, and shins, and large papules around the knees.

**Family 5**

The proband in family 5 was a 47-year-old man, the only affected son of Italian parents with no known consanguinity (Figure 1D). He had hair at birth, which was shed by age 2 months. Facial cysts were first noticed during his teen years and progressively increased. He had from rickets since age 18 months.

Complete scalp atrichia, almost complete lack of eyebrows, sparse hairs on the upper lip, between the lower lip and chin, and inside the ears, and no bodily hair were noted on physical examination. The eyelashes were essentially normal. Papules were found on the cheeks, above and below the eyes, arms, forearms, around the elbows, on the ear, chest, abdomen, thighs, and around the knees. Numerous yellow to white papules measuring 3 to 8 mm were found on the face, especially lateral to the eyes, and on the forehead and cheeks. Smaller papules were also found on the forearms, thighs, and legs.

## HISTOPATHOLOGIC ANALYSIS OF SCALP SKIN IN FAMILY 4

A skin biopsy specimen was taken from the shoulder and scalp of the third proband (25-year-old man) in VDDR IIA family 4. Analysis revealed several features similar to APL, including the presence of only a few abnormal follicles represented by the remaining parts of the upper portion, including the hair canal and sebaceous gland, and a large keratinous cyst with a thin epithelium filled with lamellated keratin masses.

## MUTATIONS IN THE HR GENE IN APL

**Family 1**

Direct sequence analysis of each exon of the HR gene in the proband revealed a homozygous frameshift 11–base pair (bp) deletion in exon 2, designated 177del11, which resulted in a premature

termination codon 183 bp downstream (Figure 2). The parents were both heterozygous carriers, whereas the proband's older unaffected brother was genotypically normal.

**Families 2 and 3**

The probands in families 2 and 3 were both homozygous for a previously identified 1-bp deletion in exon 9, designated as 2147delC, leading to a frameshift and premature termination codon 554 bp downstream in exon 12. This mutation has been described in several families of Arab-Palestinian origin.9

**MUTATIONS IN THE VDR GENE IN VDDR IIA**

**Family 4**

The genetic basis of VDDR IIA in family 4 has been previously described in detail.21, 23 The affected individuals in family 4 were homozygous for a nonsense mutation (Y292X) in the ligand-binding domain of VDR, which was shown to result in the complete loss of functional messenger RNA (mRNA) encoding the VDR protein.21, 23

**Family 5**

Molecular analysis of the VDR gene in the proband of family 5 revealed a homozygous nonsense mutation, designated R30X, within the first zinc finger of the DNA-binding domain of VDR (data not shown). This same mutation has been previously reported in 2 independent cases of VDDR IIA.24-25 The mutation R30X is predicted to result in the absence of functional VDR protein due to degradation of the nonsense-bearing transcripts via nonsense-mediated mRNA decay.26-27

**COMMENT**

Despite the different molecular causes of APL and VDDR IIA, there is a major similarity in the clinical picture of these 2 autosomal recessive diseases. Both diseases share early onsetwith hair shedding during the first year and the frontal to posterior progression of scalp hair loss. Examination in the present cases revealed a completely smooth scalp with a few hairs remaining on top, a lack of body hair, and sparse eyebrows. Generally, complete absence or almost complete absence of a mustache is apparent in patients with APL, while normal eyelashes, a sparse mustache, and few hairs in other locations (under the lower lip and on the ear) are seen in patients with VDDR IIA.

The appearance of papules at age 2 to 5 years, their locations (mainly scalp, face, elbows, and knees), and the pitting that results from improvement with time and involution of papulesare striking. It is of interest that the number and age of onset of papules in affected individuals in this study and in previous work9 exhibit interfamilial and intrafamilial variation among family members with APL and VDDR IIA or in patients with the same mutation in different families with APL. These differences may be due to partial improvement with time, disappearance of lesions with or without pitting, late appearance of papules, and/or potential modifying factors. Also of interest is the fact that some patients with APL as well as some with VDDR IIA may retain a few hairs on the top of scalp for years. The hypopigmented lesions of the scalp seen in many (but not all) patients with APL are seen also in some patients with VDDR IIA. The histologic findings in the third patient with VDDR IIA of family 4, including the lack of mature hair follicles and presence of dermal cysts, are similar to the biopsy findings for patients with APL in previous studies.9-10, 16 Patients with VDDR IIA share the full range of symptoms of vitamin D deficiency, including hypocalcemia, osteomalacia, and rickets. Skeletal abnormalities have been rarely described in patients with APL, but the 3 cases reported include a retarded ossification of bone in affected individuals manifesting as a decrease in ossification centers in the wrist and hands.12, 28-30 All patients with APL in the present study showed normal growth.

We have identified a novel HR mutation in family 1 and a recurrent mutation in families 2 and 3, all with APL. The deletion 177del11 in family 1 represents half of a tandem duplication 22 bp in length (the first 11 bp capitalized and italicized; the second 11 bp capitalized only: . . . gactccTGGCTTCCCCCTGGCTTCCCCCagggcc . . . ). This sequence contains a long run of pyrimidines known as a homocopolymers, which are known to be sites of slippage and mispairing of repeated sequences at the replication fork during DNA replication, resulting in a deletion.31-33 The mRNA transcribed from this allele would be degraded by nonsense-mediated mRNA decay26-27 and lead to the absence of functional hairless protein in the homozygous proband.

In families 2 and 3, we found the recurrent deletion mutation 2147delC, which leads to a frameshift and premature termination codon 554 bp downstream in exon 12. This mutation was first identified in the homozygous state in 5 Arab-Palestinian families.9 Four of these families lived in the same village east of Jerusalem, while the fifth resided approximately 48 km (30 miles) away. Families 2 and 3 in the present study and the previously reported 5 families resided within 240 km (150 miles) of each other. Given the relatively restricted geographical region and the nature of the mutation, it is highly likely that 2147delC isa "founder" mutation.

Finally, in families 4 and 5, we identified 2 previously described nonsense mutations in the ligand-binding and DNA-binding domains of the VDR, respectively.21, 23-25 While both mutations occur within critical functional domains, it is likely that they lead to the degradation of nonsense-containing transcripts via nonsense-mediated mRNA decay rather than truncated proteins.26-27

Despite the obvious genetic heterogeneity underlying APL and VDDR IIA, the clinical phenotypes with respect to atrichia are essentially identical. In this study, we show clinical and histologic support for the argument that the atrichia of patients with VDDR IIA and VDR mutations and that of patients with APL and HR mutations is clinically almost indistinguishable, 34 raising the possibility of a functional relationship between these 2 proteins. These findings also extend the observations made in the hairless 35 and VDR null-mutant 36-37 mouse models, which correspond to APL and VDDR IIA, respectively. Interestingly, it has been noted in the VDR null mutant that normalization of the mineral imbalance by a diet high in calcium can reverse the bony phenotypes but does not correct the alopecia. 38

Patients with VDDR IIA are treated with intravenous infusion of calcium because they characteristically do not respond to even high doses of vitamin D or calcium, which distinguishes this form of rickets from VDDR I. Similar to the VDR null mice, this treatment leads to correction of mineral and bone abnormalities but not to the restoration of hair growth. 39 Similarly, there is no effective treatment for hair regrowth in patients with APL. The parents of the patients with VDDR IIA in the present study were able to recognize the new patients in the family by the hair loss, which appears prior to the bony abnormalities. At present, molecular diagnosis may also contribute to the recognition of new patients. However, it is important to recognize the atrichia component in these 2 diseases, which may be mistaken for alopeciauniversalis and therefore lead to unnecessary treatment.

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**FIGURES**

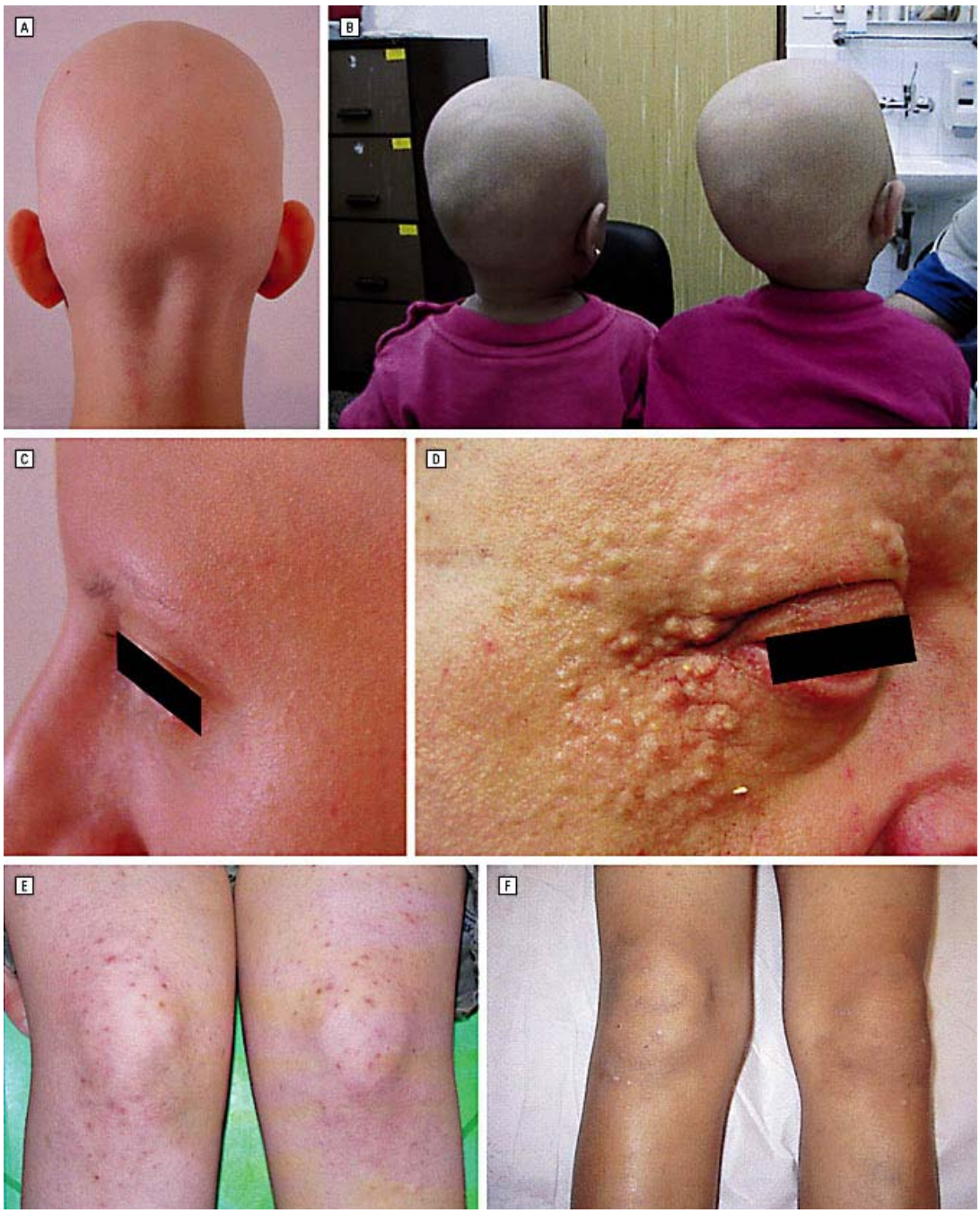


**Figure 1**. A, C, and E, Clinical presentation of atrichia with papular lesions (APL); B, D, and F, clinical presentation of vitamin D–dependent rickets IIA (VDDR IIA). Both conditions cause complete atrichia (A and B), sparse eyebrows and eyelashes (C and D), and papular eruptions around and under the eye (C and D) and around the knees (E and F). Key to the photographs: A, C, and E, proband from APL family 1, a 21-year-old woman; B, the first and second probands of VDDR IIA family 4, twin 3-year-old girls; D, the proband from VDDR IIA family 5, a 47-year-old man; and F, the third proband of VDDR IIA family 4, a 25-year-old man.

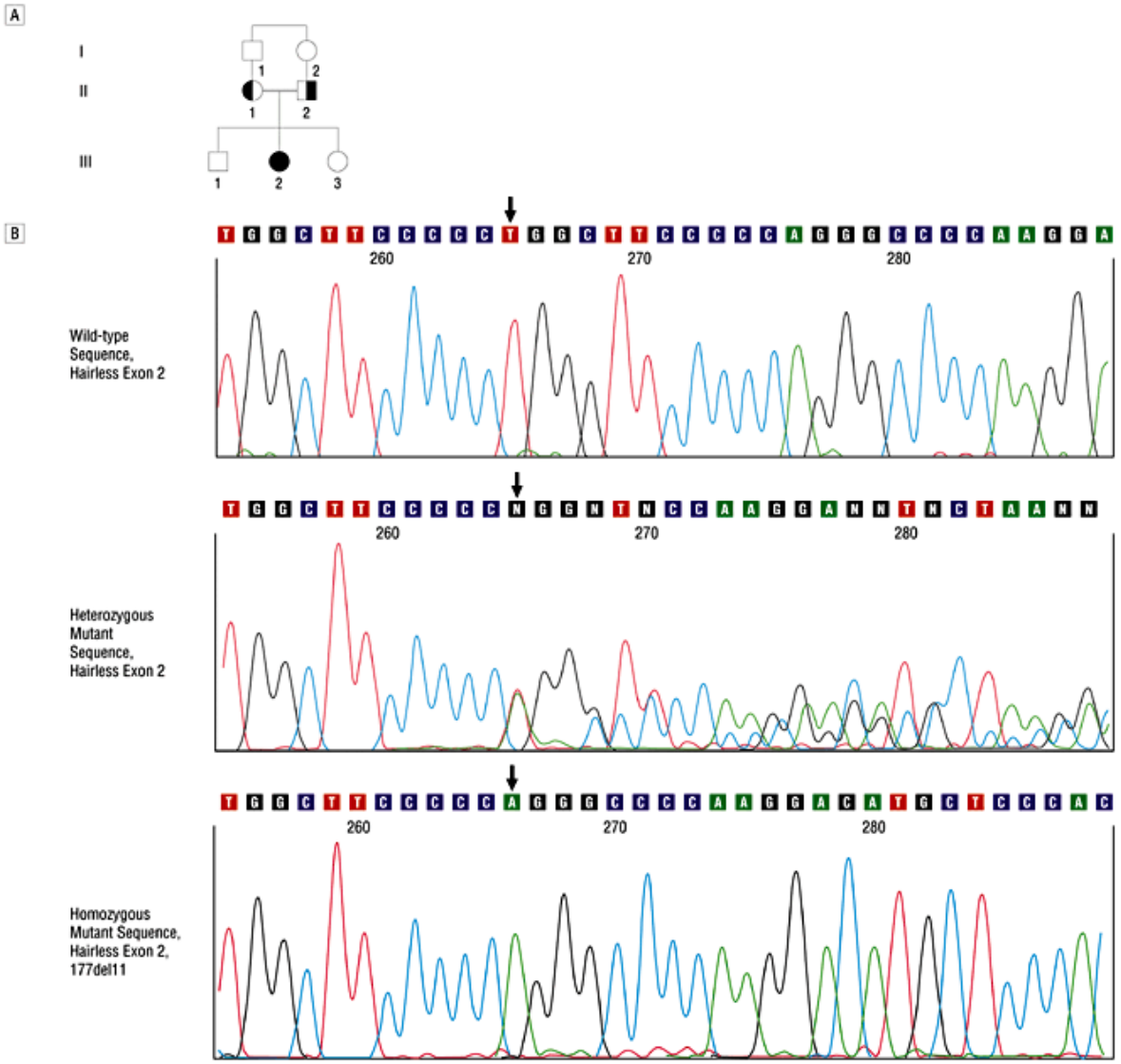


**Figure 2.** Mutation analysis in family 1. A, Pedigree of the nuclear family: the proband, individual III:2, is indicated by a solid circle, and the unaffected carrier parents by half-solid/half-open symbols. B, Sequence analysis of exon 2 of the hairless (HR) gene revealed a homozygous 11–base pair (bp) deletion in the proband (lower panel, arrow), designated 177del11. The mutation was carried in the heterozygous state in both parents (middle panel) compared with the control sequence (upper panel). Note the tandem duplication of 11 bp (TGGCTTCCCCC/TGGCTTCCCCC) and the absence of 1 block of 11 bp in individual III:2.