Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2022;31:49-64
doi: 10.15570/actaapa.2022.7

Uncombable hair syndrome and beyond

Manahel Mahmood Alsabbagh[1] ✉

[1]*Department of Molecular Medicine, Princess Al-Jawhara Center for Molecular Medicine and Inherited Disorders, Arabian Gulf University, Manama, Kingdom of Bahrain.*

Abstract

Uncombable hair syndrome presents with frizzy hair in early childhood. Isolated hair manifestations are usually observed; however, systemic involvement of the nervous system, eyes, and ears have also been reported. The syndrome has been classified into three subtypes, correlating with the three mutated genes: peptidyl arginine deiminase, type III; transglutaminase 3; and trichohyalin. This article presents the clinical picture of uncombable hair syndrome with special attention to its systemic manifestations. It also addresses its molecular aspects. Google Scholar was used to retrieve relevant publications. Clinical and molecular data were tabulated and frequencies were calculated. At least 127 cases were identified. Congenital hair defects were reported in two-thirds of cases, in which hair texture (83%), color (52%), density (15%), and growth (11%) were impaired. Uncombable hair rarely involves the eyebrows and eyelashes, and it may co-occur with loose anagen hair syndrome, androgenic alopecia, alopecia areata, and scarring alopecia. Pathologies of the skin, nails, and teeth were reported among 63%, 28%, and 25%, respectively. Systemic abnormalities were not uncommon. Dysmorphic features (n = 8), and neuropsychiatric/developmental (n = 8), ophthalmic (n = 7), otic (n = 4), and cardiopulmonary (n = 3) manifestations were also reported. Molecular genetic analysis of all patients is recommended to identify genotype–phenotype correlation. A general pediatric review might be needed to rule out any potential systemic association.

Keywords: genetic skin disease, hair, hypohidrosis, hypotrichosis, transglutaminases

Received: 15 February 2022 | **Returned for modification:** 4 April 2022 | **Accepted:** 6 April 2022

Introduction

Uncombable hair syndrome was first reported in the medical literature in 1972 by Dupre et al. as *cheveux incoiffables*. However, the condition was described decades earlier by the German physician Heinrich Hoffmann in *Struwwelpeter* (Shockheaded Peter), a children's story published in 1845 that was later translated into English by Mark Twain as *Slovenly Peter* (1).

Uncombable hair syndrome is also known as "spun glass hair" due to its clinical appearance, whereas "pili trianguli et canaliculi" describes the hair shaft morphology under scanning electron microscopy (2). The condition was observed to be sporadic or inherited in an autosomal recessive manner. Uncombable hair may present as an isolated phenotype, or it may be syndromic.

This article reviews the available literature on uncombable hair syndrome and describes the cutaneous and systemic presentation with special reference to the underlying genetic component.

Methods

Google Scholar (scholar.google.com) was used to search for uncombable hair syndrome and its synonyms. The search was conducted on October 30th, 2021. Using the key phrases *uncombable hair syndrome*, *spun glass hair*, *pili canaliculi et trianguli*, *pili trianguli et canaliculi*, and *cheveux incoiffables*, a total of 603 results were retrieved, and each was assessed individually for both genetic and clinical aspects. Articles examining disease pathophysiology were also considered. To expand the search of related genetic aspects, ClinVar (ncbi.nlm.nih.gov/clinvar) was used to search for the aforementioned key phrases on February 28th, 2021 and repeated on October 30th, 2021. The genetic and clinical data were tabulated for each case manually and then the frequencies of reported clinical signs and symptoms were calculated.

Results and discussion

Background of patients

We were able to identify 64 reports documenting at least 127 cases. The full text of 10 publications (16% of publications; representing 17% of cases, n = 22) could not be retrieved. Supplementary Table 1 summarizes the published cases.

Where patient's sex was reported, the syndrome was found to slightly predominate among females (53%, n = 34) in comparison to males (47%, n = 30). The youngest case at the time of reporting was 1 year of age and the oldest was 56 years. Where family history was reported, it was negative in 57% (n = 26) and positive in 43% (n = 20). Where the status of parental consanguinity was reported, it was negative for 77% of patients (n = 13), among which five cases had a positive family history, suggesting a possible dominant mode of inheritance. Parental consanguinity was positive for 24% of patients (n = 4), among which only two cases had a positive family history, indicating a possible recessive mode of inheritance.

Five different genes/regions were reported in 12 cases with uncombable hair syndrome, of which three were closely related; namely, peptidylarginine deiminase 3 (PADI3; 67%, n = 8), transglutaminase 3 (TGM3; 8%, n = 1), and trichohyalin (TCHH; 8%, n = 1). The remaining two were microdeletion of 17q.11.2 and poliovirus receptor-like 1 (PVRL1). Microdeletion of 17q11.2 is associated with type-1 neurofibromatosis. Schena et al. (3) reported typical scanning electron microscopic hair findings of uncombable hair syndrome, including longitudinal groove and reniform or triangular cross-sections in a 2-year-old girl that also displayed clinical

✉ **Corresponding author: mmso80138@rcsi.com**

findings of type-1 neurofibromatosis. Likewise, the PVRL1 gene is associated with ectodermal dysplasia. Yoshida et al. (4) reported the usual scanning electron microscopic findings of hair such as pili trianguli and pili canaliculi, in addition to pili torti in a 7-year-old boy that exhibited hypohidrosis, hypodontia, and cleft lip/palate, giving a diagnosis of cleft lip/palate-ectodermal dysplasia syndrome (Fig. 1).

Clinical presentation

Where hair condition was reported at birth, one-third (32%, *n* = 7) of cases with uncombable hair syndrome had normal hair (5–9) that was straight (10, 11) with good density (8, 9) and a good growth rate (8). However, congenital hair defects were reported in 68% (*n* = 15) of cases, manifesting as light-colored hair (12–16) that was wispy (5), dry and frizzy (13, 14, 16), or woolly in texture (15) with a poor growth rate (17) and reduced density (15, 18) or even atrichia (12), improving by the age of 6 months (19). Congenital scalp abnormalities include chronic dermatitis (16) and scaly scalp (16). For patients born with normal scalp hair, the hair defect may become apparent within the first 6 months of life, the time when physiological shedding of newborn hair takes place. The earliest non-congenital hair changes were observed at the age of 3 (7) and 4 months (10), and the latest was at the age of 11 years (9).

Upon presentation, characteristics of hair were available for 52% (*n* = 66) of cases, of which 52% (*n* = 34) had an abnormal hair color. The hair color is usually light, commonly described as being blond (1, 11, 15, 20–32), reddish–blond (33), silvery-blond (10, 12, 15, 19, 22, 34), silvery (9, 35), yellowish (13), or bright gold (15) that may also glisten (3, 35, 36) and shine (6, 29, 33) due to light reflection from the uneven hair surface (37). On the other hand, the hair has also been described as dull (34) and lusterless (38).

Where hair characteristics were described, 83% (*n* = 55) reported a change in hair texture. The texture is usually described as dry (*n* = 14), coarse (*n* = 5), rough (*n* = 4), kinky (*n* = 1), wiry (*n* = 1), crimped (*n* = 2), stiff (*n* = 1), or frizzy (*n* = 5), as well as tousled (*n* = 2), wavy (*n* = 3), curly (*n* = 2), and unruly (*n* = 9), resulting in a general unusual and peculiar appearance frequently described as standing straight up from the scalp or like a hedgehog's spines. Although the hair is typically difficult to comb (*n* = 7), manage (*n* = 4), or handle (*n* = 1), fine (*n* = 2) and soft (*n* = 1) hair has also been reported. The hair fibers are brittle (*n* = 4) and fragile (*n* = 2), but non-fragile hair fibers have also been observed (*n* = 2). Patches of uncombable hair might be found concurrently with normal hair

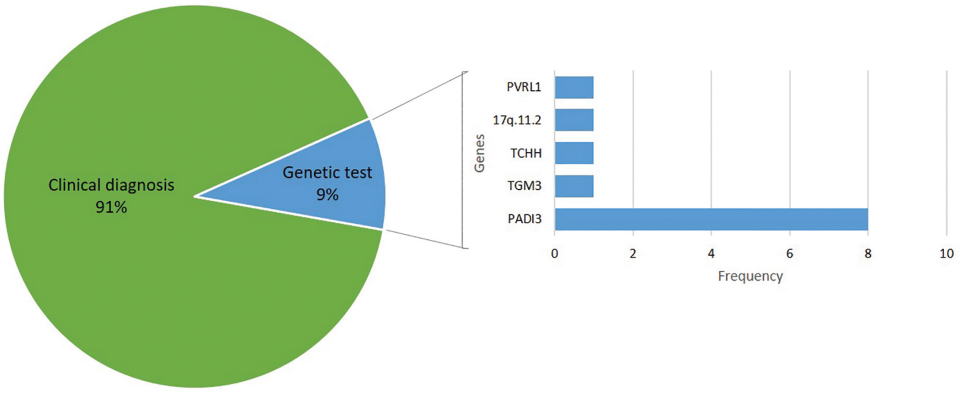

Figure 1 | Frequency of gene variants in patients with uncombable hair syndrome.

Table 1 | Genes and mutations associated with uncombable hair syndrome, summarized from the National Center for Biotechnology Information, unless stated otherwise.

Gene		Variant		
Name	**Function**	**Variant**	**Type**	**Pathogenicity**
Peptidyl arginine deiminase 3 (PADI3)	Deaminates proteins: converts arginine to citrulline in presence of calcium ions	c.C505T (p.Q169*)	SNP (nonsense)	Pathogenic
		c.T335A (p.L112H)	SNP (missense)	Pathogenic
		c.C881T (p.A294V)	SNP (missense)	Pathogenic
(OMIM * 606755)	Modulates structural hair proteins during hair follicle formation: filaggrin in hair follicle and trichohyalin in inner root sheath	c.C1372A (p.P458T) (74)	SNP (missense)	ND
		c.A1732T (p.K578*)(1)	SNP (nonsense)	ND
		c.C1813A (p.P605T)	SNP (missense)	Pathogenic
Trans-glutaminase 3 (TGM3)	Catalyzes glutamine-lysine crosslinking: involved in later stages of cell envelope formation in hair follicle	c.C1351T (p.Q451*)	SNP (nonsense)	Pathogenic
(OMIM * 600238)				
Trichohyalin (TCHH)	Mechanically strengthens hair follicle inner root sheath: forms crosslinked complexes with keratin intermediate filaments	c.C5029T (p.Q1677*)	SNP (nonsense)	Pathogenic
		c.4774del (p.E1592fs)	Deletion (frameshift)	Pathogenic
(OMIM * 190370)		c.1273_1274del (p.L425fs)	Deletion (frameshift)	Pathogenic
		c.1272_1273insGAGGA (p.L425fs)	Insertion (frameshift)	Pathogenic
		c.1255_1256del (p.L419fs)	Deletion (frameshift)	Pathogenic
		c.1237_1238del (p.L413fs)	Deletion (frameshift)	Pathogenic
		c.1236_1237insGAGGA (p.L413fs)	Insertion (frameshift)	Pathogenic
		c.C991T (p.Q331*)	SNP (nonsense)	Likely pathogenic
PVRL1	Ca^2+-independent adhesion protein involved in adherence and tight junctions in epithelial and endothelial cells	c.C400T (p.R134*) (4)	SNP (nonsense)	ND
(OMIM * 600644)				
17q.11.2/(OMIM # 613675)		Microdeletion (3)	Microdeletion	ND

OMIM = Online Mendelian Inheritance in Man, ND = not determined, SNP = single nucleotide polymorphism.

(2%, *n* = 1), and uncombable hair may extend to involve the eyebrows (17%, *n* = 2) and eyelashes (15%, *n* = 2), although the eyebrows (83%, *n* = 10), eyelashes (85%, *n* = 11), and other body hair are generally uninvolved.

Hypotrichosis, potentially progressing to alopecia, was reported among 17% (*n* = 11), probably due to slow growth of hair (11%, *n* = 7) and hair loss (3%, *n* = 2). Uncombable hair syndrome may co-occur with loose anagen hair syndrome (3%, *n* = 2), androgenic alopecia (2%, *n* = 1), alopecia areata (2%, *n* = 1), and scarring alopecia (2%, *n* = 1) resulting from a scaly scalp or scalp with erythematous crusted and pustular patches (16). These four concurrent hair disorders may contribute to hypotrichosis. However, normal hair growth has also been reported (3%, *n* = 2); see Figures 2 and 3.

Interestingly, although hair characteristics spontaneously improve with age (9, 28, 38), clinical improvement in scalp lesions, hair, and nails have also been reported upon using daily supplements of biotin (12, 16, 23, 27).

Uncombable hair under the microscope

Hair fibers collected from patients with uncombable hair syndrome were examined by Goerz et al. (30), who concluded that these hair fibers have normal thickness, strength, and tensile elongation. However, in clinical settings, hair fibers are examined by light and/or scanning electron microscopy. Routine light microscopy reveals longitudinal grooves along the hair shafts together with triangular, reniform, square (39), or oval (30) cross-sections. These findings are also detectable using frozen sections (20). Sometimes nonspecific changes are observed under light microscopy, including thin hairs (7), hairs of variable diameter (35), twists (8, 15, 33), dark bands (40), pits, and uneven distribution of pigmentation (33).

Hair shaft abnormalities might go undetected under light microscopy (5, 15, 16, 23, 24, 41, 42), mandating scanning electron microscopic examination. Scanning electron microscopy usually reveals the two main findings mentioned above: canal-like grooves and triangular, reniform, oval, and less frequently (7, 15, 43) heart-shaped (40) or completely irregular (44) cross-sections (Fig. 4). The grooves might be isolated (1, 15, 21, 39, 45–48), and they were reported to improve in parallel with clinical improvement (28). Other scanning electron microscopic findings were twists (pili torti) (4, 9). In addition, the cuticle may appear weathered (40) or scaly (27), showing diminished (9) or distorted scales (49). However, normal cuticular patterns along with normal cuticular cells and keratinization have also been reported (16). In addition to light and scanning electron microscopy, longitudinal

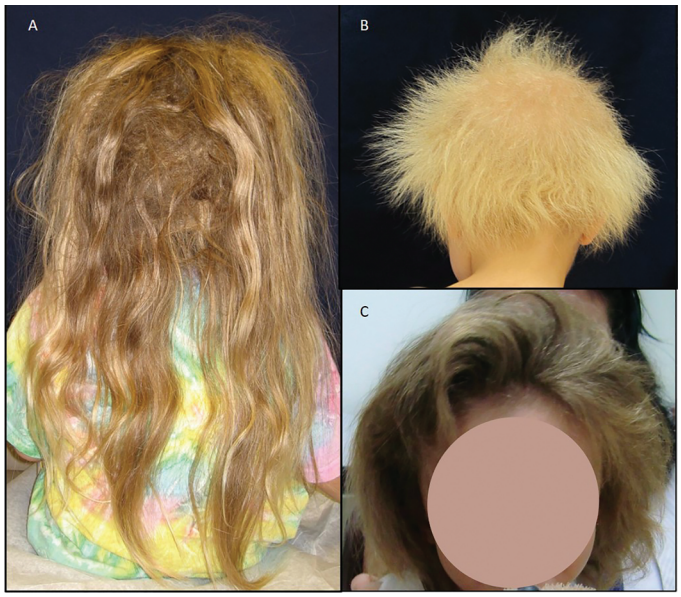

Figure 2 | Uncombable hair syndrome A) a 4-year-old girl with concurrent uncombable hair and normal hair (courtesy of Tor Shwayder), B) a 19-month-old girl with spun glass hair (courtesy of Tor Shwayder), and C) a 4-year-old girl with blond rough hair (courtesy of Alejandro Novoa).

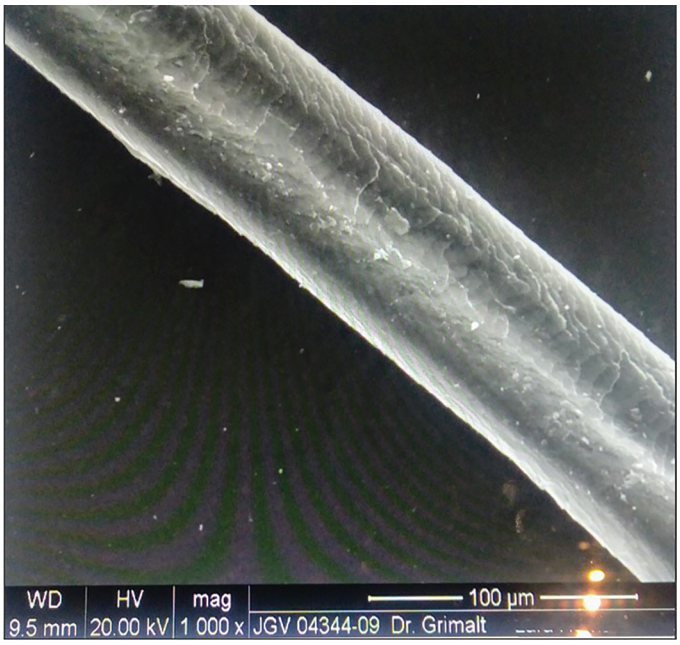

Figure 4 | Longitudinal groove under electron microscopy in uncombable hair syndrome (courtesy of Ramón Grimalt).

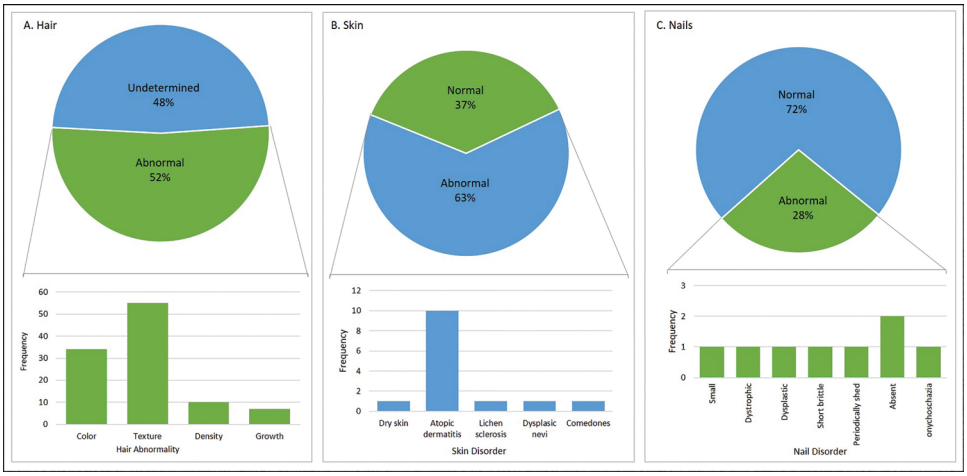

Figure 3 | Frequency of A) hair, B) cutaneous, and C) nail manifestations in uncombable hair syndrome.

grooves have also been detected bedside by trichoscopy (1, 32). However, transmission electron microscopy usually reveals normal hair cross-sections (8).

The specificity of the longitudinal grooves is uncertain. For instance, isolated longitudinal grooves were reported in loose anagen hair syndrome (50), Chédiak–Higashi syndrome with parkinsonism (51), giant axonal neuropathy (45, 52), acquired kinking in hair (53), Marie Unna congenital hypotrichosis (54, 55), Rapp–Hodgkin syndrome (56), tricho-dento-osseous syndrome (57) and ankyloblepharon-ectodermal defects–cleft lip/palate syndromes (56). Longitudinal grooves are detectable in the hair shafts of healthy individuals, and so Aguiar et al. (43) claimed that longitudinal grooves are unspecific to uncombable hair syndrome (58). It was also suggested that such grooves might instead be an artefact, given that these are invisible in cross-sections (43). The sensitivity of longitudinal grooves is also questionable. Studies showed that grooves are seen in only 50% of hairs collected from patients with uncombable hair syndrome, suggesting that scanning electron microscopy examination should not be limited to a small number of hair fibers. Grooves are also observed in monilethrix, pili torti, and progeria. Triangular and oval hair cross-sections are also nonspecific. These have also been observed in mucopolysaccharides and normal hair (43, 59). However, rectangular cross sections are observed in Rapp–Hodgkin syndrome (60).

Beyond microscopy

Uncombable hair fibers have been subject to many investigations. Interesting mathematical calculations to explain the stiffness of uncombable hair were suggested by Swift (61). The study hypothesized that the internal structures of uncombable hair fibers (i.e., cuticle and cortex) resemble normal hairs. Mathematically, triangular hairs always have a bending stiffness that is greater than elliptical (or circular); however, this is not true all the time. For instance, triangular hairs seem to potentially be 1.73 times stiffer compared to normal elliptical hairs, whereas Chinese hairs seems to be 2.85 stiffer than European hairs, although Chinese hairs are hardly considered stiffer in clinical practice. Hence, stiffness was attributed to other factors, including the outer layer of the pseudo-triangular hair, where curvatures contribute to stiffness.

Uncombable hair was also evaluated for degree of damage. Resonance running time examination showed that uncombable hair was comparable to grade 3 (brittle, weathered) and 4 (felting, tangling, matting) damaged hair (62).

Another study looked at the biochemical components of uncombable hair. Protein solubilization using Trisurea-mercaptoethanol buffer showed that uncombable hair had markedly reduced protein solubilization in comparison to normal hair. However, given that the matrix component was solubilized and X-ray diffraction and strain tests were normal, the reason behind reduced solubilization could not be established (63). Hair sulfur content was also reported normal in multiple patients (14, 16).

Histologic examination of an affected scalp was conducted by Ahmed et al. (14), who reported that hematoxylin and eosin-stained horizontal sections of scalp biopsy mostly showed a triangular inner root sheath accompanied by deformed hair shafts. In addition, inner root sheath vacuolization along with irregular eosinophilic trichohyalin granules was observed. On the other hand, the external root sheaths, hair bulbs, and follicular unit numbers were normal.

Beyond the hair

Other ectodermal structures and functions were frequently reported as normal (40), including skin (37%, $n = 7$), mucosa ($n = 2$), teeth (75%, $n = 18$), nails (72%, $n = 21$), and sweating ($n = 11$).

On the other hand, skin pathologies were also documented (63%, $n = 12$), such as dry skin ($n = 1$), atopic dermatitis ($n = 10$), lichen sclerosis ($n = 1$), dysplastic nevi ($n = 1$) and comedones ($n = 1$). In addition, tooth pathologies (25%, $n = 6$) manifesting as supernumerary teeth ($n = 1$), hypodontia ($n = 1$), conical deformation ($n = 1$), enamel defects ($n = 1$), dental decay ($n = 1$); and nail pathologies (28%, $n = 8$) manifesting as small nails ($n = 1$), dystrophic nails ($n = 1$), dysplastic nails ($n = 1$), short brittle nails ($n = 1$), periodic shedding of nails ($n = 1$), absent nails (anonychia; $n = 2$), and onychoschizia ($n = 1$) have all been reported in the literature (Fig. 3).

Beyond the ectoderm

Uncombable hair syndrome usually presents with normal general examination ($n = 6$), growth ($n = 5$), and development ($n = 8$). Neurologic assessment ($n = 17$), including psychomotor function ($n = 5$), electroencephalograph ($n = 3$), brain scans ($n = 3$), and intelligence quotient ($n = 1$); ophthalmic assessment ($n = 6$); hearing assessment ($n = 3$); cardiopulmonary assessment ($n = 6$), including electrocardiogram ($n = 3$) and chest X-ray ($n = 1$); external genitalia ($n = 1$); and skeletal and osteoarticular assessment ($n = 4$), including cervical spine radiography ($n = 1$), are usually normal. In addition, apart from borderline changes in serum amino acids ($n = 1$), other investigations, including routine and special blood chemistries ($n = 7$), routine urine microscopy ($n = 4$), urinary amino and organic acids ($n = 4$), karyograms ($n = 2$), investigations of the immune system ($n = 1$), and imaging, such as abdominal ultrasound and intravenous pyelograms ($n = 2$), have also been normal.

On the other hand, uncombable hair syndrome has been reported concurrently with a wide spectrum of phenotypes, some of which are serious. For instance, a wide spectrum of dysmorphic features ($n = 8$) have been reported involving the face (thin pointed face ($n = 1$), bossing ($n = 1$) and receding hairline ($n = 1$)); the eyes (hypotelorism ($n = 1$), narrow palpebral fissures ($n = 1$), mongoloid slant ($n = 1$), everted eyelids ($n = 1$), and inner epicanthal fold ($n = 1$)); the ears (low-set ears ($n = 1$), prominent antihelix ($n = 1$), poorly folded helix ($n = 1$) and cup-shaped ears ($n = 2$)); the nose (long nose ($n = 2$), prominent nose ($n = 2$), and narrow nasal bridge ($n = 1$)); the oral cavity (narrow lips ($n = 1$), high/ached/short palate ($n = 3$), cleft lip/palate ($n = 2$), micrognathia ($n = 1$), and bifid uvula ($n = 1$)); and the hands and feet (small hands ($n = 1$), clubfoot ($n = 1$), short fingers/toes ($n = 2$), large toe ($n = 1$), syndactyly ($n = 2$), clinodactyly ($n = 2$), extra digit ($n = 1$), and single palmar crease ($n = 2$)).

A neuropsychiatric/developmental assessment was reported as abnormal in eight cases. Reports include developmental delay ($n = 4$), mental retardation ($n = 4$), hyporeflexia ($n = 2$), hypotonia ($n = 1$), type-1 neurofibromatosis ($n = 1$), and poor motor coordination ($n = 1$). Likewise, ophthalmic abnormalities ($n = 7$) were reported, including cataract ($n = 3$), pigmentary retinopathy ($n = 3$), visual impairment ($n = 2$), astigmatism ($n = 1$), squint ($n = 1$) and congenital absence of tears ($n = 1$). Otic abnormalities ($n = 4$) were hearing impairment/deafness ($n = 2$), recurrent otitis media ($n = 2$), and periauricular pitting ($n = 1$). Cardiopulmonary disorders

(n = 3) were pneumonia (n = 2), asthma (n = 1), and bronchitis (n = 1); see Figure 5.

It is unclear whether this wide spectrum of systemic involvement is incidental or if it reflects a true association.

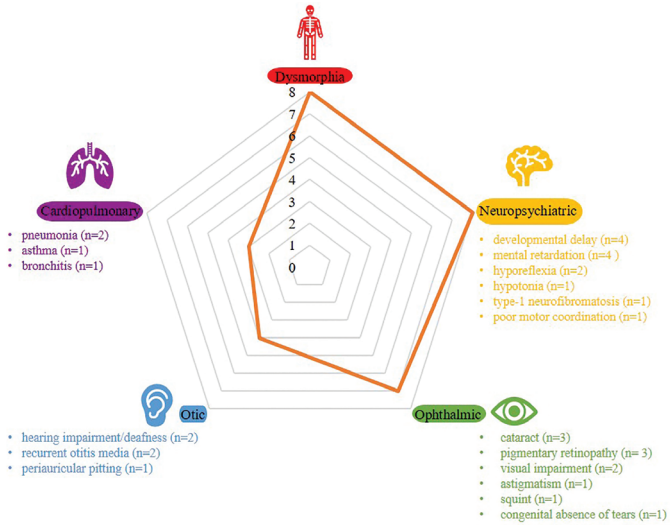

Figure 5 | Frequency of systemic disorders in uncombable hair syndrome.

Molecular aspects

Our literature review using Google Scholar and ClinVar revealed five mutated genes reported in cases with uncombable hair syndrome (Table 1). However, two of them, microdeletion of 17q11.2 and PVRL1, are not closely related to the syndrome and are hence omitted from further analysis.

The remaining three genes, PADI3, TGM3, and TCHH, interact together. PADI3 converts arginine to citrulline, and hence it mediates deamination of TCHH and reduces its overall charge. This in turn facilitates TCHH association with keratin intermediate filaments. Both TCHH and keratin intermediate filaments are then crosslinked by TGM3 (37).

Peptidyl arginine deiminase 3 (PADI3)

PADI3 (OMIM * 606755) is a 35,136-nucleotide gene that is located on the short arm of chromosome 1 (1p36.13). The gene consists of 18 exons and codes for a 664–amino acid. It is a cytoplasmic protein that is highly expressed in the urinary bladder, esophagus, and skin (64, 65).

PADI3 belongs to the peptidyl arginine deiminase family. In the presence of calcium ions, it converts positively charged arginine residues into neutral citrullines. This is particularly important in the modulation of filaggrin and trichohyalin during hair follicle formation (64).

According to OMIM, uncombable hair syndrome 1 (#191480) is an autosomal recessive disease caused by pathogenic variants in PADI3 (66). A literature review revealed six pathogenic variants in PADI3 that were reported in association with uncombable hair syndrome, five of which presented as either homozygote or compound heterozygote, suggesting an autosomal recessive pattern of inheritance, whereas the zygosity status of the sixth pathogenic variant could not be identified. Four pathogenic variants were missense and the remaining two were nonsense. Basmanav et al. (1) reported that three single nucleotide polymorphisms in uncombable hair syndrome (p.L112H, p.A294V, and p.P605T) are conserved across the five PADI human enzymes as well as across PADI3 genes in other species, suggesting an important role of these nucleotides. In addition, p.A294V and p.P458T modify the β-sheet and α-helix in the immunoglobulin-like domain NH-2, the calcium binding sites, and the catalytic sites. Functional studies revealed that the three single nucleotide polymorphisms and two nonsense pathogenic variants exhibited reduced, if any, activity.

Transglutaminase 3 (TGM3)

TGM3 (OMIM *600238) is a 45,079-nucleotide gene that is located on the short arm of chromosome 20 (20p13). It consists of 13 exons coding for a 693–amino acid protein. This gene is highly expressed in the esophagus and skin. It consists of 16 helices, 40 beta sheets, and eight turns (67, 68).

TGM3 is found in the extracellular region, but it is also detectable within the cytoplasm. It catalyzes the calcium-dependent crosslinking formed between glutamine and lysine, which hardens the inner root sheath in hair follicles (67, 68). TGM3 dysfunction impairs the crosslinking between trichohyalin and hair keratins, which in turn compromises the attachment of hair cuticle to cortex. The improvement of phenotype observed with aging among patients (and TGM3 knockout mice) is attributed to partial compensation of the lost protein (PADI3 or TGM3) with another isoform of PADIs or TGMs such as transglutaminase 1 and transglutaminase 5 (37, 69, 70).

According to OMIM, uncombable hair syndrome 2 (#617251) is an autosomal recessive disease caused by pathogenic variants in TGM3 (66). A literature review revealed one reported pathogenic variant in association with uncombable hair syndrome presenting as a homozygote, confirming the autosomal recessive pattern of inheritance. In the reported single nucleotide polymorphism, thymine replaces cytosine in locus 1351, which induces a termination codon with a subsequent loss of 242 amino acids. Functional studies showed that the resulting short protein exhibits reduced enzymatic activity (1).

Trichohyalin (TCHH)

TCHH (OMIM *190370) is a 9,128-nucleotide gene located on the long arm of chromosome 1 (1q21.3). It consists of three exons coding for a 1,943–amino acid protein. It is expressed in many tissues, including the placenta, spleen, testes, and skin. TCHH consists of two domains; the first is 26 amino acids in length, and the second is 36 amino acids in length. Both domains are located within the S100-like region (71, 72).

TCHH is detectable in the cytoskeleton, cytosol, and cornified envelope. It provides mechanical strength to the hair follicle inner root sheath by forming crosslinked complexes with keratin intermediate filaments (73).

According to OMIM, uncombable hair syndrome 3 (#617252) is an autosomal recessive disease caused by pathogenic variants in TCHH (66). A literature review retrieved eight pathogenic variants within TCHH, two of which are single nucleotide polymorphisms resulting in termination codons with a subsequent loss of 266 amino acids in the first and 1,612 amino acids in the second; four deletions and another two insertions, resulting in frameshift pathogenic variants. Functional studies showed that the protein resulting from the termination codon with the loss of 1,612 amino acids is a very short protein that fails to properly interact with keratin intermediate filaments, and subsequently it loses its function in strengthening the inner root sheath of the hair follicle (73).

Conclusions

Uncombable hair syndrome usually presents with isolated hair manifestations; however, special attention should be paid to the potential concurrence of neuropsychiatric, ophthalmic, otic, and cardiopulmonary manifestations. Molecular genetic analysis is recommended to establish genotype–phenotype correlation, which should further help in patient management.

Acknowledgments

I sincerely acknowledge Tor Shwayder, the director of Pediatric dermatology at Henry Ford Hospital (Detroit, MI), and Alejandro Novoa, a pediatrician at Vendrell Comarcal Polyclinic (El Vendrell, Spain), for sharing clinical and microscopic photos.

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Supplementary Table 1 | **Reported cases with uncombable hair syndrome**

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Bertlich et al., 2020 (31)	2y/M	FH-	ND	dry, rough, short, straight, dark-blond, "straw-like," and tousled @1y	TC and LG	ND	Plagiocephalus; streptococcal sepsis with reactive arthritis @6m	nails, teeth, hair and sweat glands	ND
Agrawal et al., 2020 (35)	7y/M	NC; FH-	ND	glistening silvery sheen, slowly growing @2.5y, loose anagen syndrome	light brown pigment, shaft undulations, variable shaft diameter, LG	ND	ND	development, eyebrows, eyelashes, body hair, teeth, nails, palms, soles, eyes, heart, neural system, skeleton	normal routine blood, urine routine and microscopic exam and electrocardiogram
Krenitsky et al., 2020 (20)	1y/M	ND	ND	blond	TC and LG by frozen section	ND	ND	ND	ND
Krenitsky et al., 2020 (20)	4y/M	ND	ND	blond	KC or TC by frozen section	ND	ND	ND	ND
Krenitsky et al., 2020 (20)	2y/F	ND	ND	blond	KC or TC by frozen section	ND	ND	ND	ND
Reis et al., 2020 (12)	2y/F	ND	atrichia	light-colored, dry and frizzy	TC or KC	ND	ND	general exam	ND
Reis et al., 2020 (12)	3y/F	FH+ (maternal aunt)	straw-colored to silvery-blond	straw-colored to silvery-blond	TC or KC	ND	ND	general exam	ND
Vickers et al., 2020 (5)	23mo/F	FH-	wispy	roughly textured @6mo, patchy alopecia	normal	ND	ND	eyelashes, eyebrows, nails	ND
Marijnissen et al., 2019 (76) (A)	3y/F	ND	ND	ND	ND	ND	ND	ND	ND
Martinez et al., 2019 (32)	9y/M	ND	ND	blond	LG by trichoscopy	ND	atopic dermatitis, abnormal teeth	neural, osteoauricular and immune systems	ND
Piccolo et al., 2018 (77)	ND	ND	ND	ND	TC, LG	ND	ND	ND	ND
Villarreal-Rodríguez et al., 2018 (36)	9y/F	ND	ND	light brown, glistening, dry, unruly @3y	TC, KC	ND	ND	ND	ND
Cobb et al., 2017 (10)	17mo/F; born @36w by vaginal delivery	ND	straight dark brown	(P)silvery-blond, dry, stiff, unruly @4mo	ND	TC, LG	perinatal jaundice, hypotonia, hyporeflexia, global developmental delay, dysphagia	eyebrows, eyelashes, body hair, fingernails, toenails, vision screening, hearing screening, electroencephalogram, brain magnetic resonance image	normal array comparative genomic hybridization, new-born metabolic screen, Prader–Willi syndrome test, urine organic acids, plasma amino acids, transferrin isoelectric focusing for congenital disorders of glycosylate, ammonia, lactate, copper, ceruloplasmin, creatine kinase

Supplementary Table 1 | **Continued.**

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Hsu et al., 2017 (75)	4y/M	PC, FH+ (cousins; anonychia); PADI3 (c.C1372A) (p.P458T) (HM, uncombable hair syndrome); RSPO4 (IVS1+ 1G>A) (HZ, anonychia)	ND	hypotrichosis, slowly-growing, wavy	ND	ND	©anonychia, ©squint	ND	ND
Basmanav et al., 2016 (1)	ND	PADI3 (c.C881T) (p.A294V) (HM)	ND	ND	TC, LG		ND	ND	ND
Basmanav et al., 2016 (1)	ND	PADI3 (c.T335A) (p.L112H) (HM)	ND	ND	TC, LG		ND	ND	ND
Basmanav et al., 2016 (1)	2 cases	PADI3 (c.C881T) (p.A294V), (c.T335A) (p.L112H)	ND	ND	TC, LG		ND	ND	ND
Basmanav et al., 2016 (1)	2 cases	PADI3 (c.C881T) (p.A294V), (c.C1813A) (p.P605T)	ND	ND	TC, LG		ND	ND	ND
Basmanav et al., 2016 (1)	ND	PADI3 (c.C881T) (p.A294V), (c.A1732T) (p.K578*)	ND	ND	TC, LG		ND	ND	ND
Basmanav et al., 2016 (1)	ND	TCHH (c.C991T) (p.Q331*) (HM)	ND	ND	TC, LG		ND	ND	ND
Yoshida et al (4)	7y/M	PC, *PVRL1* (c.C400T) (p.R134*) (HM)	ND	sparse, brittle, fine, dry	ND	TC, LG, pili torti	hypodontia, cleft lip/palate, syndactyly, mild mental retardation	ND	ND
Shao et al., 2014 (78)	F	FH+ (sibling)	ND	ND	TC, LG		ND	ND	ND
Shao et al., 2014 (78)	F	FH+ (sibling)	ND	ND	TC, LG		ND	ND	ND
Shao et al., 2014 (78)	F	ND	ND	ND	TC, LG		ND	ND	ND
Shao et al., 2014 (78)	F	ND	ND	ND	TC, LG		ND	ND	ND

Supplementary Table 1 | **Continued.**

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Shao et al., 2014 (78)	F	ND	ND	ND	TC, LG		ND	ND	ND
Shao et al., 2014 (78)	F	ND	ND	ND	TC, LG		ND	ND	ND
Kilic et al., 2013 (21) Basmanav et al., 2016 (1)	24y/M	PC, TGM3 (c.C1351T) (p. Q451*) (HM)	ND	slowly-growing, blond, unruly	LG detected on trichoscopy as well	LG	bilateral juvenile cataract, dysplastic nevi	eyebrows, eyelashes, body hair, mucosae, teeth, nails, sweating	ND
Nissen et al., 2013 (79) Basmanav et al., 2016 (1)	ND	PADI3 (c.C881T) (p.A294V)	ND	ND	ND	ND	ND	ND	ND
Novoa et al., 2012 (46) Basmanav et al., 2016 (1)	4y/F	PADI3 (c.C881T) (p.A294V), (c.T335A) (p.L112H)	ND	brown, rough, sparse	ND	LG	ND	general exam including eyebrows, eyelashes, teeth, nails, skin	ND
Valdivielso-Ramos et al., 2012 (22)	5y/F	FH-	ND	silver-blond, dry, wavy electrified @1y	TG, LG	ND	ND	ND	ND
Weibel et al., 2010 (13)	M	FH+	yellowish, dry, frizzy	yellowish, dry, frizzy	ND	TC, LG	ND	ND	ND
Calderon et al., 2009 (38)	16y/F	FH-	ND	lusterless, frizzy, improve by age	ND	TC, LG	ND	teeth, nails, skin	ND
Filho et al., 2008 (39)	26y/M	NC; FH+ (11 relatives in 3 generations); autosomal dominant	ND	coarse, dry, slowly-growing, hypotrichosis	indentations, polymorphic contours (TC, KC, square, irregular)	LG	ND	teeth, nails, sweating	ND
Filho et al., 2008 (39)	56y/M	NC; FH+ (11 relatives in 3 generations); autosomal dominant	ND	(P)hypotrichosis⋯⋯› alopecia	indentations, polymorphic contours (TC, KC, square, irregular)	LG	ND	teeth, nails, sweating	ND
Filho et al., 2008 (39)	49y/M	NC; FH+ (11 relatives in 3 genera-tions); autosomal dominant	ND	brown, tousled	indentations, polymorphic contours (TC, KC, square, irregular)	LG	ND	teeth, nails, sweating	ND
Rudnicka et al., 2008 (80)	ND	ND	ND	ND	ND	ND	ND	ND	ND
Boccaletti et al., 2007 (23) Giordano et al., 2009 (24)	2y/M	FH+ (sister, mother, maternal grandmother, mother's uncle, maternal great grandmother)	ND	dry, unruly, blond @18mo	normal	LG, elliptical or TG	atopic dermatitis, onychoschizia	ND	normal blood counts, zinc, copper, antigliadin, anti-endomysium, antithyroid peroxidase, thyroid stimulating hormone

Supplementary Table 1 | Continued.

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Jarell et al., 2007 (25)	4y/M	ND	ND	Kinky, unmanageable @infancy; thin, blond	TC, LG	ND	ND	body hair, skin, eyes, teeth, nails, skeleton	ND
Rieubland et al., 2007 (26)	2.5y/F	NC; FH+ (uncle, maternal side)	ND	blond, frizzy, coarse, peculiar texture	ND	TC, LG	preauricular pit, small 4th and 5th toe nails, sacral dimple	growth, psychomotor development, skin, teeth, nails, sweating	ND
Schena et al., 2007 (3)	2y/F	FH-; microdeletion of 17q.11.2	ND	straight like a hedgehog's aculei, a glistening appearance @1y	ND	LG, TC, KC	type 1 neurofibromatosis: 8 café -au-lait macules >5 mm, freckles, low-set ears, arched palate, single palmar crease, dorsal kyphosis, delayed psychomotor and language development, cerebellar hamartomas	eyebrows, eyelashes, cardiac and ophthalmic exam	normal blood tests, abdominal ultrasound, cervical spine radiography, and electroencephalograph
De Funes et al., 2006 (81)	27y/M	NC, FH-	ND	ND	ND	TC, LG	↓intelligence quotient, pigmentary retinopathy, ↓visual acuity, ↓night vision	facial and body hair, nails, skin, mucosa, teeth	ND
Pereira et al., 2006 (11)	2y/F	ND	straight, black	curly, blond @6m, hair loss	ND	elliptical or KC, longitudinal ridge	ND	ND	ND
Ahmed et al., 2005 (14)	4y/F	FH-	dry, glossy, light-colored, frizzy, normal density, nonfragile	ND	ND	TC, KC, LG, disruption of the tonofilament-desmosomal complex in inner root sheath and hair shaft, disruption of cell-to-cell junction	ND	general exam, eyes, teeth	• hair mount brightfield microscopy: lightly pigmented hairs, LG, twists. • hair mount polarization microscopy: LG • hematoxylin and eosin stain of scalp biopsy: triangular inner root sheath, vacuolization of inner root sheath, irregular eosinophilic trichohyalin granules
Luca et al., 2005 (34)	7y/M	FH-	ND	silvery-blond, coarse, dull @2y	ND	TC, LG	ND	ND	ND
Smith et al., 2005 (82)	10 cases	ND	ND	ND	TC, LG	ND	one case with mental retardation, calcification of basal ganglia	ND	ND
Bell et al., 2002 (6)	4y/F	FH-	straight, dark brown	shiner, light-colored, dry, coarse	ND	TC, LG	ND	skin, teeth, nails	ND
Beringer et al., 2000 (27)	2.5y/F	FH-	t semicircular stripes with normal hairs of the back of head	(P) light blond, brittle	ND	TC, KC, LG, scaly cuticle	atopic dermatitis, spastic bronchitis, conical deformation of all 4 canines	eyebrows, eyelashes, nails, sweating	ND

Supplementary Table 1 | Continued.

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Powell et al., 1998 (28)	11y/F	NC; FH-	ND	unruly, short, blond, spangled appearance, never required cutting	ND	TC, LG 6y; flat @11y (clinically improving)	intrauterine growth retardation, thin, pointed face and nose, non-growing dystrophic nails, asthma, pneumonia, eczema, lichen sclerosis, dental decay	eyebrows, eyelashes, sweating, development, cognition, hearing	normal thyroid stimulating hormone
Kozlowski et al., 1997 (17)	15y/M	NC; FH+ (brother); born @38w by c-section	soft, thin, poorly-growing	uncombable hair, normal growth	ND	LG, deformities of the tunic	delayed psychomotor development and growth, bossing, narrow palpebral fissures, hypotelorism, mongoloid slant, prominent nasal root, narrow nasal bridge, narrow lips, micrognathia, prominent antihelix, poorly folded helix, underdeveloped lobule and antitragus, high palate, short hyper lordotic neck with decreased mobility, pectus carinatum, dysplastic widely-spaced nipples, small hands, short fingers and clinodactyly of the 5th finger, single palmar crease, extra digit, inguinal hernia, dysplastic scrotum, cryptorchism, small bowed penis, equino-valgus, syndactyly of 2nd and 3rd toes, large broad big toe, conductive deafness, kyphosis, recurrent middle ear and pulmonary infections	heart, eyes	ND
Boyer et al., 1996 (83)	7y/F	ND	ND	loose anagen hair syndrome, difficult to manage, diffuse alopecia	ND	resemble findings of uncombable hair syndrome	ND	ND	ND
Selvaag et al., 1995 (47)	3y/M	ND	ND	rough, glass	ND	LG	atopic skin	ND	ND

Supplementary Table 1 | Continued.

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Mallon et al., 1994 (40)	9 cases	FH-	ND	ND	dark band extending along the hair shaft	heart-shaped or TC, LG, minimal cuticular weathering	ND	ectoderm	ND
Itin et al., 1993 (19)	9y/F	ND	atrichia till 6mo	silvery-blond, dry unruly @7mo	ND	TC, LG	short brittle toenails, enamel defects, dry skin	eyebrows, eyelashes	ND
Saito et al., 1993(41) (A) Koike et al., 1994 (42)	1y/F	FH-	ND	unusual appearance	normal	TC, LG	ND	general exam	ND
Silengo et al., 1993 (58)	6y/M	NC; FH-; born ž@36w	ND	sparse, dry, uncombable	nonspecific	TC, LG	hiatus hernia, language delay, supernumerary teeth, short 5th fingers and toes, clinodactyly, hyperactive, short attention span; retinal pigmentary dystrophy	growth, nails, sweating, hearing	normal blood and urine amino acids, copper, ceruloplasmin, karyogram
Yoon et al., 1993 (84)	ND	ND	ND	unmanageable	ND	TC, LG	ND	ND	ND
De Jong et al., 1990 (29)	7y/F	NC; FH + (paternal side hearing loss); maternal rubella during 3rd month of pregnancy	ND	fragile, slowly-growing, shiny, blond, wiry, difficult to handle	TC, LG	TC, LG	(P) axial crystalline cataract, ↓ visual acuity, hyporeflexia, hearing loss	nose, throat	• normal karyogram • trichogram: telogen effluvium, detached hair sheaths • hair amino acid: high lysine and alanine and ↓ serine and cysteine
McCullun et al., 1990 (85) (A)	3 cases	ND	ND	ND	ND	ND	ND	ND	ND
Rest et al., 1990 (59)	ND	FH-	ND	ND	ND	TC, KC, LG	ND	ND	ND
Rest et al., 1990 (59)	ND	FH-	ND	ND	ND	TC, KC, LG	ND	ND	ND
Rest et al., 1990 (59)	ND	FH-	ND	ND	ND	TC, KC, LG	ND	ND	ND
Rest et al., 1990 (59)	ND	FH-	ND	ND	ND	TC, KC, LG	ND	ND	ND
Bork et al., 1987 (18) (A)	Family	autosomal dominant	hypotrichosis	uncombable hair	ND	ND	juvenile cataract, retinal pigmentary dystrophy, oligodontia, brachymetacarpia	ND	ND
Ludwig et al., 1987 (86) (A) Dupre et al., 1978 (87) (A)	2 cases	ND	ND	uncombable hair @1y	ND	TC, LG	ND	physically, mentally	ND

Supplementary Table 1 | Continued.

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Matis et al., 1987 (15)	3y/F	NC-; FH-	scant growth	pale blond, unmanageable	normal	oval and TC, LG	ND	ectoderm	• increased serum taurine and aspartic acid, ↓ cysteine • normal serum chemistries
Matis et al., 1987 (15)	2.5y/F	FH-	light brown ringlets	fine, pale blond, radiating from scalp	normal	LG	ND	growth, development, intelligence, scalp, eyelashes, teeth, nails	ND
Matis et al., 1987 (15)	7y/M	FH-	ND	silvery-blond, soft, wavy standing straight up from scalp	180-degree twists	LG	ND	comedones	ND
Matis et al., 1987 (15)	2.5y/M	FH-	woolly	bright gold, spangled highlights, standing out from scalp	ND	LG	atopic dermatitis	ND	ND
Ravella et al., 1987 (7)	3y/M	NC; FH-	normal hair	two patches of unruly, sparse, straw-like, light brown and straight hair @3m	thin	LG, ovoid and KC	ND	development	ND
Zegpi et al., 1987 (48) (A)	M	ND	ND	ND	LG	LG	ND	general exam	ND
Chanwichitrana et al., 1986 (8)	5y/F	NC; FH-	normal hair, normal density and growth rate	whirly, disorderly @ early infancy involving eyebrows and eyelashes	slight hair twisting	TC, LG	ND	growth, development, nails, teeth, sweating	ND
Forslind et al., 1985 (88) (A)	2 cases	ND	ND	spun-glass hair	ND	normal cross sections; typical findings in transmission electron microscopy	ND	ND	ND
Luna et al., 1985 (9)	3y/F	FH+ (father and paternal side); born by c-section	dark brown	silvery-toned, curly, dry, difficult to comb	ND	LG, twisted and flattened hairs, ↓ number of cuticular scales	ND	development	ND
Luna et al., 1985 (9)	M	FH+ (paternal side, daughter)	ND	uncombable, androgenic alopecia @18y	ND	TC, LG, ↓ cuticular scales	ND	growth, cognition	ND
Luna et al., 1985 (9)	26y/M	FH+ (maternal side)	good density	hair loss; uncombable @11yrs, improve with age	ND	TC, LG	ND	ND	ND

Supplementary Table 1 | Continued.

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Shelly et al., 1985 (16)	18mo/M	ND	©straw-colored, stand out from scalp	slowly-growing, come out in clumps with gentle traction, fragile, scaly scalp	normal	TC, LG, normal cuticular pattern, keratinization and number of cuticle cells	anonychia, otitis media, bronchitis	eyelashes, eyebrows, fingernails, toenails, teeth	• normal urine test for organic acids, acid metabolites (FeCl), ketoacids (dinitrophenylhydrazine), sulfur amino acids (cyanide-nitroprusside), reducing sugars (Clinitest), glucose (Clinistix), mucopolysaccharides (cetyltrimethylammonium bromide), amino acids, mono-, di- and oligosaccharides (thin-layer chromatography) • normal serum copper
Shelly et al., 1985 (16)	5y/M	FH+(sister))	chronic scalp dermatitis, sparse eyelashes	• unruly, sparse, brittle, dark blond, straw-like • 3 cm erythematous crusted and pustular patch	ND	TC, LG	craniofacial abnormalities (receding hairline over forehead, long prominent nose, small cup-shaped ears, everted eyelids), poor motor coordination, mild mental retardation; ©infection (*Staphylococcus*), ©absence of tears, clumsiness @18mo; ⇣ attention span, short palate, bifid uvula, astigmatism, dysplastic nails, electroencephalogram: mild diffuse disorder	teeth, hands, feet, external genitalia	• almost normal blood counts and chemistry, urinalysis, electrocardiogram, intravenous pyelogram, brain scan • normal hair sulfur • biopsy (ectodermal dysplasia): ⇣ development of hair follicles and sebaceous glands
Shelly et al., 1985 (16)	2y/F	FH+ (brother)	raw scalp	chronic scalp dermatitis with crusts and pustules, scarring alopecia, unruly, sparse, brittle, and straw like, patchy hair	ND	TC, LG	facial dysmorphia (long nose, cup-shaped ears), cleft palate, clubfoot, eczematous dermatitis of nipples, infections (*Staphylococcus*), anomalous incisor crowns, moderate hypochromia	nails, sweating, motor coordination, ectodermal dysplasia with possible incomplete ectodermal dysplasia syndrome	• normal urinalysis, blood chemistry, electrocardiogram, chest x-ray, intravenous pyelogram, brain scan, electroencephalogram • scalp biopsy (ectodermal dysplasia): ⇣ hair follicle and sebaceous glands development • normal hair sulfur content
Kresbach et al., 1985 (89) (A)	ND	ND	ND	ND	ND	TC, LG, peripilar casts	periodic shedding of nails, abnormal teeth, nipples dysplasia, Morbus Scheuermann, atopic disorders, specific IgE sensitization, potential tricho-odonto-onychial subtype of ectodermal dysplasia	ND	ND

Supplementary Table 1 | **Continued.**

Article	Background		Hair		Microscopy		Other abnormalities	Normal	Investigations
	Demographic	Genetic	At birth	Current	Light	Electron			
Aguiar et al, 1983 (43)	5y/F	FH-	ND	ND	ND	TC, LG	ND	ND	ND
Garty et al., 1982 (33)	2y/M	PC; FH+ (father, paternal grandfather and great-grandfather)	ND	frizzy, dry, coarse, thick, nonfragile, reddish blond, normal growth, shiny @6mo, thick eyebrows with similar color, resolved with age	uneven scanty distribution of pigment, small pits, slight twisting	TC, LG	coarse facial features, inner epicanthal folds hoarseness	psychomotor development, skin, eyelashes, nails, teeth, hair volume	normal blood chemistry: amino acids, lipids, iron, copper, zinc, thyroxine; urinalysis, mucopolysaccharides, urinary amino acids
Braun-Falco et al., 1982 (90)	6 cases	familial, autosomal dominant with incomplete penetrance	ND	typical clinical picture	ND	KC, LG	+/- alopecia areata +/- atopic eczema	ND	ND
Baden et al., 1981 (64)	3 cases	ND	ND	ND	ND	ND	ND	ND	• normal hair X-ray diffraction and stress strain tests, amino acid analysis • ⚓ protein solubilized with a Trisurea-mercaptoethanol buffer • polyacrylamide gel electrophoresis: mainly the matrix component that was solubilized
Goerz et al., 1981 (30)	5y/F	FH+ (aunts, maternal side)	ND	blond, frizzy	oval, TC, KC	LG	atopic dermatitis	cognition, internal organs	normal hair fiber thickness, strength, tensile elongation
Schoenfeld et al., 1981 (49)	6y/M	FH+ (sibling)	ND	crimping	ND	TC, LG, distorted and disoriented cuticular scales	ND	mental, physical	ND
Schoenfeld et al., 1981 (49)	3y/M	FH+ (sibling)	ND	crimping	ND	TC, LG, distorted and disoriented cuticular scales	ND	mental, physical	ND
Ferrando et al., 1980 (44) (A)	10 cases	ND	ND	ND	ND	irregular, TC, KC, LG	ND	ND	ND

(A) = abstract; (P) = progressive; @ = at the age of; ⇧ = increased; ⚓ = reduced; © = congenital; FH = Family history; HM = homozygote; HT = heterozygote; KC = kidney-shaped, reniform or bean-shaped cross sections; LG = longitudinal groove; mo = months; NC = non consanguineous; ND = not determined; PC = positive consanguinity, TC = triangular cross sections; w = weeks; y = year(s).