The genetics of hair shaft disorders

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Many of the genes causing hair shaft defects have recently been elucidated. This continuing medical education article discusses the major types of hair shaft defects and associated syndromes and includes a review of histologic features, diagnostic modalities, and findings in the field of genetics, biochemistry, and molecular biology. Although genetic hair shaft abnormalities are uncommon in general dermatology practice, new information about genetic causes has allowed for a better understanding of the underlying pathophysiologies. (J Am Acad Dermatol 2008;59:1-22.)

Learning objective: At the conclusion of this article, the reader should be familiar with the clinical presentation and histologic characteristics of hair shaft defects and associated genetic diseases. The reader should be able to recognize disorders with hair shaft abnormalities, conduct appropriate referrals and order appropriate tests in disease evaluation, and select the best treatment or supportive care for patients with hair shaft defects.

EVALUATION OF THE HAIR

For the student of hair abnormalities, a full review of microscopic findings and basic anatomy can be found in the textbook *Disorders of Hair Growth* by Elise Olsen,[1] especially the chapter on "Hair Shaft Disorders" by David Whiting, which offers a thorough review of the subject.[1] The recognition of the anatomic characteristics of normal hair and the effects of environmental factors are important when evaluating a patient for hair abnormalities. The normal hair cycle of anagen, catagen, and telogen is important in the foundational knowledge of hair, as is the microscopic structure of the hair shaft (Fig 1).

The normal hair cycle

Hair follicles produce hairs that range in size from minute vellus hair to long, thick terminal hair, and are divided anatomically into bulb, suprabulbar, isthmus, and infundibular zones.[2] Each follicle is ectodermally derived from hair germ cells in the developing embryo, the development of which progresses via interactions with the mesenchymal dermal papillae, leading to the formation of anagen hairs with complete follicular components, including sebaceous and apocrine glands.[3]

Anagen hair. The hair shaft is composed of three layers, called the medulla, cortex, and cuticle (Fig 1). The medulla lies in the center of the shaft and contains granules with citrulline, an amino acid, which is unique to the medulla and internal root sheath (IRS). The cortex forms the bulk of the shaft, and its outermost layer, the cuticle, interlocks with the IRS cuticle. The IRS also consists of three layers, including the IRS cuticle (the innermost layer), the Huxley layer, and the Henle layer (the outermost layer). Keratinization of the IRS, which first begins in the Henle layer, provides supports to the hair shaft up to the level of the isthmus, at which point the IRS disintegrates. Keratinization abnormalities in the IRS are involved in the pathogenesis of certain hair shaft defects, such as loose anagen syndrome (LAS). Trichilemmal keratinization begins at the level of the isthmus, where keratinization does not occur with the formation of a granular layer, and begins epidermal keratinization with the formation of both stratum granulosum and corneum only at the level of the infundibulum.[2] The hair cuticle can be divided into different sections: endocuticle (the innermost), exocuticle, exocuticular A-layer, which contains high amounts of sulfur, and fiber cuticle surface membrane (the outermost).[4,5] Finally, the last two layers of the follicular unit consist of the vitreous layer (a periodic acid–Schiff-positive and diastase-resistant zone which thickens during the early catagen phase), and a fibrous root sheath.[2]

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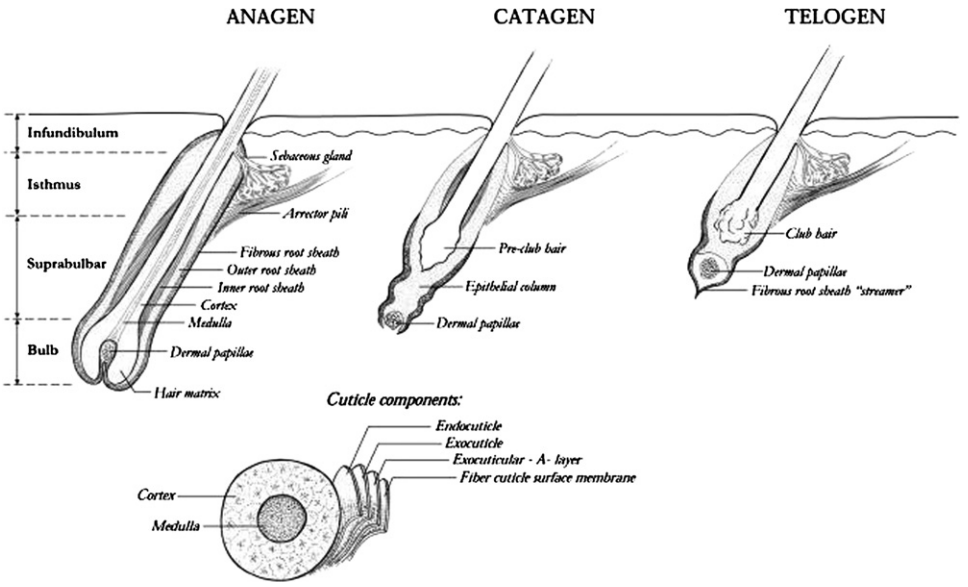

Fig 1. Schematic of anagen, catagen, and telogen hair.

The bulb of a follicular unit consists of the dermal papillae, the lowest portion of the fibrous sheath, and matrix cells whose replication forms the hair shaft. The suprabulbar region lies between the bulb and the isthmus. The isthmus lies between the attachment of the arrector pili muscle and the entry of the sebaceous duct, and the infundibulum lies above the entry to the sebaceous duct to the surface epithelium.

Anagen hairs have indented elongated roots with pigmented adjacent shafts. In the scalp, anagen follicles usually grow from 2 to 7 years, while shorter hairs and vellus hairs have more abbreviated anagen growth periods. Anagen follicles are actively replicating and therefore are especially susceptible to nutritional deficiencies and metabolic insults. They are covered by intact long inner root and outer root sheaths and are rooted deeply in the reticular dermis. Therefore, anagen hairs are difficult to detach, and do not come off with regular brushing of hair.

Catagen hair. During this phase, matrix cells retract from the dermal papillae and degenerate.[2,6] Early on, the vitreous layer thickens and a group of matrix and ORS cells begins to form the presumptive club of the follicle (Fig 1).[2] As catagen phase continues, the disintegration of the epithelial column, vitreous layer, IRS, and proximal ORS occur, along with the cessation of pigment formation. These changes lead to the migration of the dermal papillae and follicular unit towards more superficial layers of the dermis. Catagen hairs usually represent approximately 1% of all scalp hairs, and therefore are usually not easily found on a pull test or biopsy.

Telogen hair. Telogen hairs have short, white, club-shaped roots, and lack both an ORS and an IRS (Fig 1).[2,7] Pigment is lacking in the hair shaft adjacent to the root, and the vitreous and epithelium columns have regressed at this point. With the formation of the new anagen hair below the club, the developing follicle will eventually replace the telogen hair resting above, leading to shedding of an average of 50 to 100 scalp hairs a day. Telogen hairs normally consist of 6% to 10% of all terminal scalp hair. Telogen hairs are usually located more superficially in the papillary dermis, are no longer firmly anchored, and are easy to detach with a pull test or normal hair brushing.

EVALUATION OF THE HAIR SHAFT

The initial evaluation of a patient should start with a good history, physical examination, and review of symptoms. A pull test, which is performed using gentle traction on the patient's hairs, can be used to easily determine a weakness in anchoring of the hairs on the scalp.[1] For example, telogen effluvium and LAS will both release more hairs than normal. Usually 40 to 60 hairs are grasped and gentle traction is used on a pull test. Telogen hairs should roughly comprise 10% of the scalp hairs, so usually 4 to 6 or fewer hairs extracted is considered normal ($\leq 10\%$). Next, hair shafts should be evaluated by light microscopy with dry-mounting on a glass slide followed by application of a coverslip, or using glass slides previously coated with double-stick clear tape.[8] A more permanent way of looking at individual haft shafts is to use a mounting medium[9,10] (Cytoseal 60; Thermo Fisher Scientific, Waltham, MA) and observing the hairs after the medium has dried. It should be kept in mind that normal patients can have occasional hair shaft anomalies which are not clinically relevant.[1]

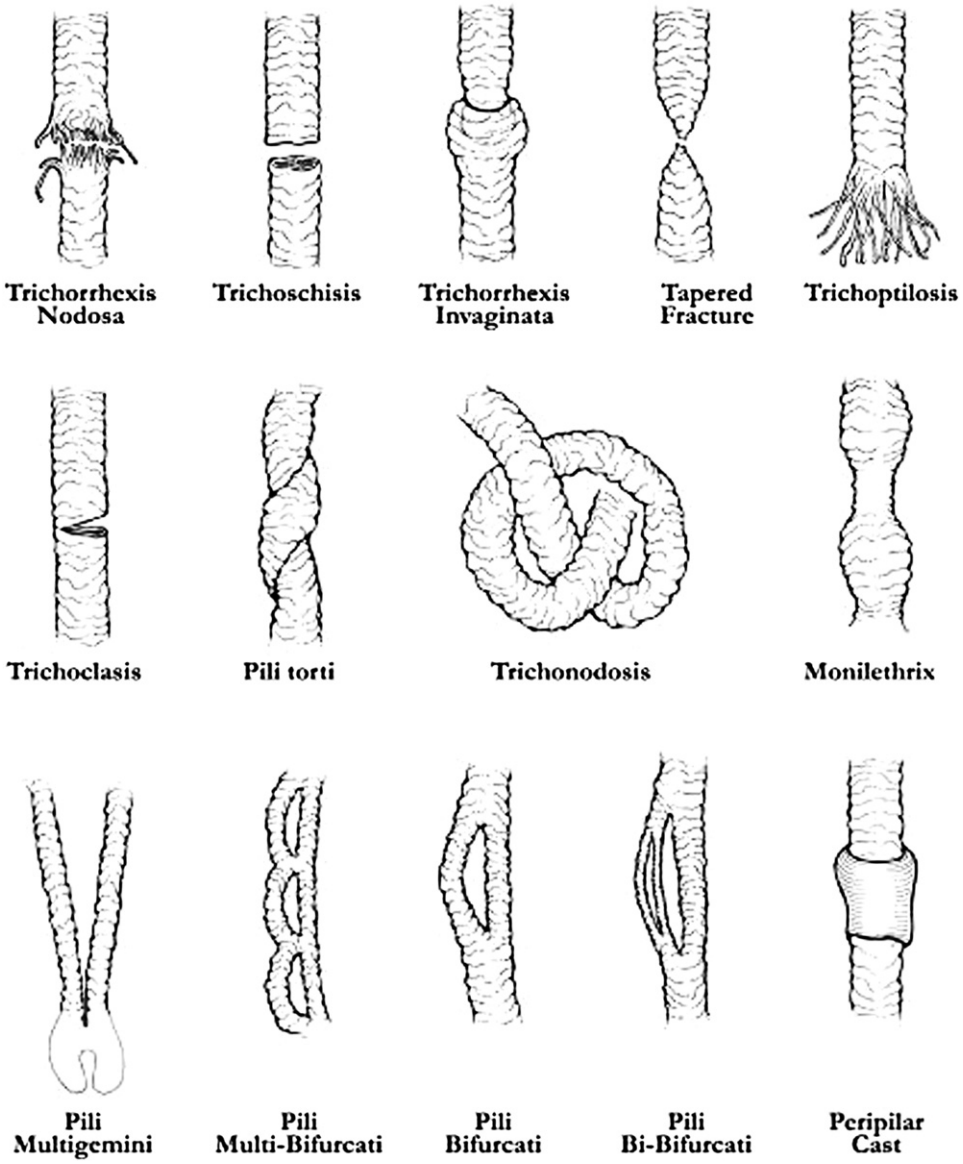

Fig 2. Schematic of hair shaft defects.

GENETIC DISEASES MOST COMMONLY ASSOCIATED WITH HAIR SHAFT DISORDERS

In order to understand the genetics of hair shaft disorders, the nomenclature for the specific hair anomalies must be understood and recognized (Fig 2). Table I lists the diseases associated with hair shaft abnormalities that are discussed in this paper; Table II separates hair shaft disorders into those with or without increased hair fragility.

Trichorrhexis nodosa

In trichorrhexis nodosa (TN), beaded swellings associated with loss of cuticle on the hair shaft are seen, along with a microscopic appearance of frayed cortical fibers pushed up against each other like two paintbrushes (Fig 3). TN is traumatic in origin and can affect hairs weakened by congenital or acquired disorders. Acquired proximal TN is most commonly seen in people with very curly hair who style their hair with chemicals and excessive mechanical trauma. Breakage of the proximal hair shaft is prominent. Acquired distal TN ("split ends") shows breakage of the distal hair shaft and is caused by mechanical trauma and weathering. Congenital TN can be seen alone and has been reported in certain genodermatoses and metabolic disorders, and is discussed further below.

Argininosuccinicaciduria. TN occurs in approximately 50% of cases of argininosuccinicaciduria,[11] an inborn error of urea synthesis caused by argininosuccinate lyase (ASL) deficiency.[12] ASL

Table I. Hair shaft and associated disorders

Trichorrhexis nodosa
Argininosuccinicaciduria
Citrullinemia
Trichoschisis
Trichothiodystrophy
Trichorrhexis invaginata
Netherton syndrome
Monilethrix
Pili torti
Bjornstad syndrome
Crandall syndrome
Menkes syndrome
Woolly hair
Naxos disease
Carvajal syndrome
Naxos-like disease
Woolly hair and skin fragility syndrome
Diffuse partial woolly hair
Woolly hair nevus
Curly hair
CHAND syndrome
Costello syndrome
Noonan syndrome
Miscellaneous
Marie Unna hypotrichosis
Uncombable hair syndrome
Loose anagen syndrome
Pili annulati
Mitochondrial disorders

Table II. Hair shaft disorders distinguished by hair fragility

Hair shaft disorders with increased fragility
Trichorrhexis nodosa
Trichoschisis
Trichorrhexis invaginata
Pili torti
Monilethrix
Hair shaft disorders without increased fragility
Pili annulati
Loose anagen hair syndrome
Uncombable hair syndrome

Fig 3. Light microscopy of trichorrhexis nodosa.

catalyzes the formation of arginine and fumarate from argininosuccinate in the urea cycle, and deficiency leads to an impairment of nitrogenous metabolism and excretion.[13,14] Accumulation of nitrogenous waste products can lead to organ toxicity, seizures, hyperammonemic coma, neurologic damage, and growth retardation.[13,15,16]

ASL is a homotetrameric enzyme[17] that has been mapped to region pter→22 on chromosome 7.[18-20] Genetic heterogeneity at this locus, along with the variable phenotype of different mutations,[21,22] results in a wide clinical spectrum of disease presentation and partly accounts for the three major clinical forms of argininosuccinicaciduria.[23-25]

The most severe phenotype occurs at birth, with the symptoms of lethargy, seizures, and respiratory distress culminating in early death if not treated early. Less severe disease presents in either the first few months of life (with mental retardation, developmental delay, and hepatomegaly) or in early childhood (with psychomotor retardation, mental retardation, and central nervous system [CNS] abnormalities). Hair is usually normal at birth, with later development of dry, dull hair and TN in infancy or early childhood (Fig 4). Low serum arginine and elevated serum and urine citrulline values are found on laboratory evaluation.

Arginine supplementation can be beneficial in patients with less severe deficiencies and can normalize systemic acidosis and improve hair texture and neurologic development; this should be initiated at diagnosis.[11,13] Arginine supplementation, however, does not reverse the deficiency in severely affected patients.[11,16,26]

Citrullinemia. Citrullinemia is caused by a deficiency of the urea cycle enzyme argininosuccinic acid synthetase (AAS). Citrulline is a normal amino acid constituent of the hair medulla and IRS that catalyzes the formation of argininosuccinate from citrulline and aspartate. Patients with infantile citrullinemia present with hyperammonemia, excess citrulline, and low plasma arginine.[27] The AAS gene is located on chromosome 9q34.[28,29]

There are two types of citrullinemia: infantile and adult-onset. Infantile citrullinemia results in the disturbance of AAS in all tissues. In the hair, this leads to findings of TN,[30,31] atrophic hair bulbs, and/or pili torti (PT).[32] A rash similar to acrodermatitis enteropathica has been reported in some patients.[27,31] Clinically, manifestations are similar to argininosuccinicaciduria. Adult-onset citrullinemia differs from infantile citrullinemia because the AAS deficiency is

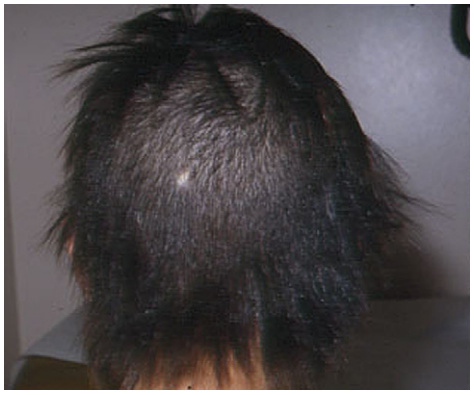

Fig 4. Patient with argininosuccinicaciduria.

liver-specific with an abnormal transporter protein citrin. This gene is located on chromosome 7q21.3.[29]

Trichoschisis

Trichothiodystrophy. Trichothiodystrophy (TTD) is a clinically diverse autosomal recessive neuroectodermal disorder with brittle hair and low sulfur content of hair[33] caused by a mutation of a regulatory gene involved in the transcription of DNA[34,35] (Fig 5). Trichoschisis is a common finding,[36] and involvement of all body hair has been reported[37,38] (Fig 6). Trichoschisis is characterized by a clean transverse fracture of the hair shaft. The low cystine (sulfur) content of hair is postulated to account for cuticular and cortical weakness.

TTD is a heterogeneous disorder with a list of more than 100 variable features.[35] Eight subgroups have been categorized by Itin et al[35] and include BIDS (*b*rittle hair, *i*ntellectual impairment, *d*ecreased fertility, and *s*hort stature), IBIDS (BIDS + *i*chthyosis), PIBIDS (BIDS + *p*hotosensitivity), SIBIDS (otosclerosis + IBIDS), ONMR (*o*nychotrichodysplasia, *c*hronic neutropenia, and *m*ental *r*etardation), and Tay, Sabinas, and Pollitt syndromes.[35,39-53]

Trichoschisis is characteristically seen on light microscopy. Under polarized light, the characteristic "tiger tail" pattern of alternating bright and dark diagonal bands is seen in most TTD patients and is rarely found in normal individuals.[54] The underlying cause of the tiger tail pattern is unknown, but it is hypothesized to be secondary to the irregular sulfur content of the hair shaft.[55] This pattern can be seen in utero,[56] but its absence does not exclude the diagnosis.[57] The sulfur and cystine content of the hair is reduced to approximately 50% in both the cuticle and the cortex,[58] with a marked absence of high sulfur content proteins[59,60] and an increase in low sulfur content proteins in the hair shaft.[33]

TTD, photosensitivity, and impaired DNA repair. Some patients with TTD exhibit photosensitivity and

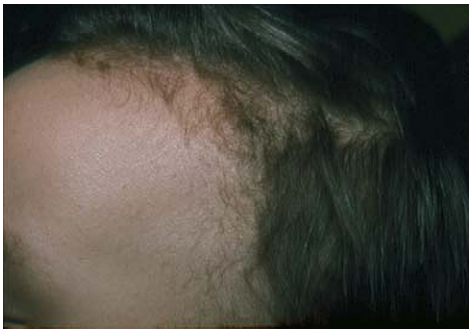

Fig 5. Patient with trichothiodystrophy. Note the short sparse hair.

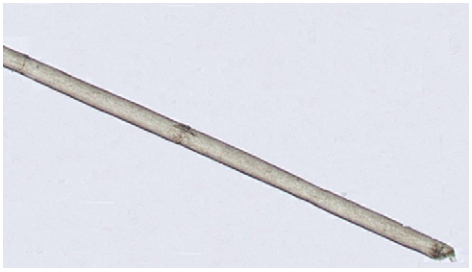

Fig 6. Light microscopy of trichoschisis. Note the clean break in the hair shaft.

impaired DNA repair mechanisms.[61-68] These DNA repair defects have been linked to abnormalities in nucleotide excision repair (NER) which eliminates ultraviolet light–induced cyclobutane pyrimidine dimers, pyrimidine pyrimodone photoproducts (6-4PP), and intrastrand crosslinks in the DNA.[69] NER comprises a complex-overlapping network of enzymatic pathways for DNA repair with approximately 30 gene products involved.[70] Studies have found that in TTD, 95% of photosensitive patients with NER defects can be assigned to the xeroderma pigmentosum (XP) complement group D (XPD).[35] In addition, defects in two other genes, the XP complement group B gene (XPB) and TTD-A gene, have been identified in a few patients.[64] XPD, first identified as excision repair cross-complementing gene (ERCC2),[71] is located on chromosome 19q13.2.[72] XPB is mapped to chromosome 2q21.[73] TTD patients with defective DNA repair are not at increased risk for developing skin cancer, in contrast to patients with XP.[68] Hypotheses for this discrepancy include differences in activation of apoptosis,[74] function of natural killer cells, expression of molecules such as intracellular adhesion molecule-1,[75] and mutation-induced changes in protein structure.[76]

XPD and XPB are two of seven known XP genes, and encode DNA helicases that are subunits in the 10 protein transcription initiation factor IIH (TFIIH) complex, a transcription factor required for RNA

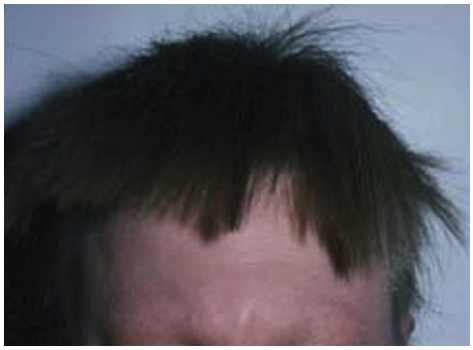

Fig 7. Patient with Netherton syndrome.

polymerase II—mediated transcription and involved in nucleotide excision repair.[35,65] Its function has only recently been elucidated.

TTD-A encodes the tenth subunit of the TFIIH complex, and is an 8-kDa protein that has been designated GTF2H5 in the human homolog.[77,78] This protein has been found to participate in ultraviolet light repair and maintainence of TFIIH levels. A mutation of the gene for TTD-A leads to decreased intracellular TFIIH levels,[35,79] which is similar to TTD patients with XPB and XPD gene defects.[77,78,80] It has been theorized that different XP gene mutations cause varying defects in DNA repair and/or gene transcription, leading to the pathognomonic presentations in each syndrome.[34,35,59,81-93]

In a small group of patients, elevated temperatures can cause in vitro instability of TFIIH.[35,79,88,94] It has been suggested that fever may cause worsening of TTD features in subgroups of patients.

Non-photosensitive TTD: Genetically heterogeneous disorder. Mutations in chromosome 7p14 at C7orf11 designated TTD nonphotosensitive 1 (TTDN1), has been identified in two types of non-photosensitive TTD: Amish brittle-hair syndrome and non-photosensitive TTD with mental retardation and/or decreased fertility.[95] The function of C7orf11 is unknown, but is expressed in the epidermis, fibroblasts, and hair follicles, and may play a role in transcriptional processes.[95] Mutation of C7orf11 does not alter TFIIH levels, suggesting that C7orf11 differs from photosensitive TTD.[95] This mutation has not been found in patients with Sabinas or Pollitt syndromes, which are two other variants of non-photosensitive TTD.

Trichorrhexis invaginata

Netherton syndrome. Netherton syndrome (NS) is an autosomal recessive disorder with variable penetrance[96-99] defined by a triad of symptoms: ichthyosis linearis circumflexa, trichorrhexis invaginata (TI), and an atopic diathesis[96,100-102] (Fig 7). TI usually appears in infancy,[57] but can develop later.[103-105] Clinically, the scalp hair is short and brittle and the eyebrows may be affected.[106]

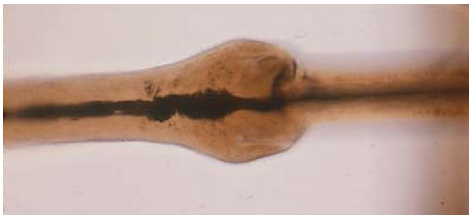

Fig 8. Light microscopy of trichorrhexis invaginata.

The extent of skin findings in NS is highly variable and ranges from ichthyosis linearis circumflexa in milder cases[107,108] to nonbullous congenital ichthyosiform erythroderma (CIE)[96,109] with severe erythroderma. Ichthyosis linearis circumflexa is a polycyclic and serpiginous scaling eruption that can change in pattern with a characteristic, double-edged scale on its borders. In NS, babies may be born with a collodion membrane, generalized scaling, or erythema.[110] Failure to thrive, recurrent infections, and dehydration can be attributable to impaired epidermal barrier function early in life.[103,109,111,112]

Atopic dermatitis, hay fever, angioedema, urticaria, allergic rhinitis, hypereosinophilia, recurrent skin infections, and elevated immunoglobulin E (IgE) levels can be found in many patients.[109,113] Short stature, growth retardation, and mental deficits can occur.[114] Other Ig levels are usually normal, although there are reports of IgG subclass deficiency.[96,109] Intermittent aminoaciduria has been described in some cases.[101,115]

Microscopically, TI ("bamboo hair") demonstrates the distal hair shaft invaginating into the proximal hair shaft (Fig 8). As the hair breaks at this area of invagination, sometimes only the proximal invaginated hair shaft can be seen ("golf-tee hair").

NS is caused by an defect in the SPINK5 gene on chromosome 5q32[116] encoding the serine protease inhibitor LEKTI (lymphoepithelial Kazal-type related inhibitor).[117,118] Absence of LEKTI is thought to lead to the premature activation of stratum corneum tryptic/chymotryptic enzymes, resulting in proteolysis of desmosomes and adhesion molecules.[119,120] Another theory is that it causes prematurely activation of phospholipase A2[119] which stimulates early lamellar body secretion.[119,121] Electron microscopy (EM) findings of premature lamellar body secretion in the stratum corneum from skin biopsies may be caused by the dysregulation of serine proteases involved in control and coordination of receptors associated with keratinocyte maturation, lamellar secretion, and normal desquamation.[120]

The correlation between the type of SPINK5 mutation and the specific phenotype has yet to be

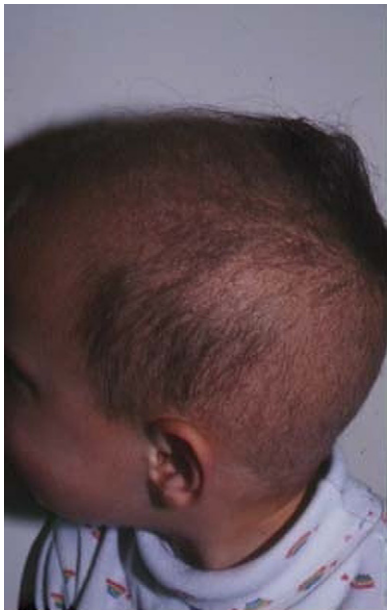

Fig 9. Patient with monilethrix.

elucidated.[104,117,120] A study of six coding polymorphisms in SPINK5 found that a Glu420→Lys mutation is linked to atopy in two extended family groups.[122]

Hair breakage may improve with age, perhaps because hair shafts become thicker. The use of oral retinoids has yielded mixed results.[96,112,123] Any topical medication should be used with extreme caution because of skin barrier dysfunction, which increases the risk for marked systemic absorption and toxicity.[119,124]

Monilethrix

Monilethrix (beaded hair) is characterized by hair shafts with elliptical nodes at regular intervals with intervening, non-medullated tapered fragile constrictions.[125] Hairs rarely grow beyond 1 to 2 cm in length because of breakage (Fig 9), resulting in a stubbly appearance. Inheritance is usually autosomal dominant with high penetrance and variable expressivity.[126,127] Other common findings are keratotic follicular papules at the nape of the neck, keratosis pilaris, and TN. Monilethrix usually presents in early childhood, but it has been reported as late as the second decade of life.[128] A diagnosis can be elucidated by examining hairs by light microscopy[129] (Figs 10 and 11). At the internodes, electron microscopy reveals increased longitudinal ridging with fluting.[130,131]

The gene for monilethrix is linked to the type II keratin gene cluster on chromosome 12q13.[132-134] Studies have isolated mutations in type II hair cortex keratins hHB6 and hHB1. The gene is divided structurally into α-helical rod domains, helix initiation motifs (HIM), and helix termination motifs (HTM).

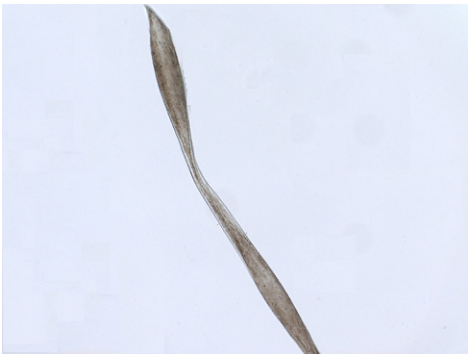

Fig 10. Light microscopy of the nodes and internodes seen in monilethrix.

Fig 11. Light microscopy highlighting the medullated nodes and nonmedullated internodes in the hair of a patient with monilethrix.

The hHB6 and hHB1 gene products are both expressed in the hair cortex.[135] The most common mutation involves lysine substitution of a high conserved glutamic acid residue in the HTM of the hHB6 gene (E413K).[135-137] No definitive link between mutational genotype and clinical phenotype has been identified.[138,139] Linkage studies have excluded type I cortex keratins and other genes involved in hair shaft formation, such as trichohyalin, involucrin, ultra-high sulfur matrix proteins, and type 1 to 3 transglutaminases,[140] but the clinical heterogeneity seen in monilethrix may still result from other related gene products[135,139,141-147] and environmental factors.[127,138,148]

Although there are no specific treatments, topical minoxidil[149] and oral etretinate have all been reported to improve hair growth.[150,151]

Pili torti

PT is characterized by hair shafts which are flattened and twist with an angle of 180°[152] (Figs 12 and 13). Fractures occur within the twists, which is the weakest point.

Classic PT. The original cases of classic PT reported by Ronchese[153] in 1932 were described

Fig 12. Light microscopy of pili torti with visible twisting of the hair shaft.

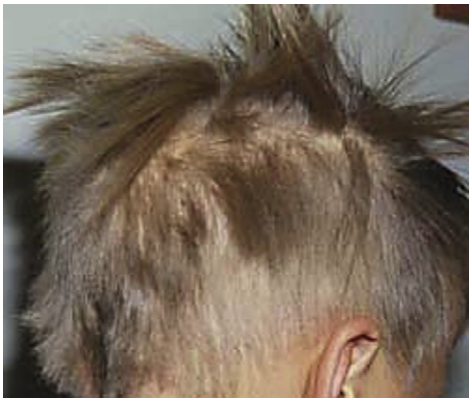

Fig 13. Patient with pili torti.

with thin fragile hair of eyebrows, eyelashes, and the entire scalp. PT presents in the first 2 years of life.[152] Inheritance patterns can be autosomal dominant,[152] autosomal recessive,[154] or sporadic.[155] A limited number of cases have been reported, and no gene defect has been elucidated.

Late-onset PT. Beare[156] described an autosomal dominant disorder with the onset of PT in childhood or after puberty in white patients with black unruly hair and non-progressive mental deficiency. The disease typically presents with breakage of eyebrows and eyelashes.

PT and hearing loss (Bjornstad and Crandall syndromes). Bjornstad syndrome is a rare disorder characterized by congenital sensorineural hearing loss and PT[157-164] which has been mapped to chromosone 2q34-36.[162,165] Crandall syndrome is similar with findings of hypogonadism.[161,164] Mental retardation is rarely associated[161,166,167] with either. Typically, patients develop PT in the first 2 years of life, and have evidence of hearing loss by 4 years of age. The severity of the hair shaft abnormality has been demonstrated to correlate with the severity of deafness.[164,167]

Genetic mapping of the region 2q34-36 revealed a mutation in BCS1L, which encodes an ATPase required for the assembly of a mitochondrial complex.[168] The BCS1L protein plays a role in the assembly of mitochondrial complex III and in the electron-transport chain of energy production.[168] Patients with Bjornstad syndrome have mutations in BCS1L that alter protein-protein interactions, whereas patients with GRACILE (*g*rowth *r*etardation, *a*minoaciduria, *c*holestasis, *i*ron overload, *l*actic acidosis and *e*arly death) syndrome, a multisystem lethal mitochondrial disorder, have altered adenosine triphosphate binding.[168] Most cases are autosomal recessive, but two reports suggest dominant transmission.[158,169] Early auditory testing is important with all children with PT.

PT and ectodermal dysplasias. As part of an ectodermal dysplasia (ED), hair can be affected. ED is a heterogenous group of hereditary diseases caused by developmental anomalies during embryogenesis of one or more epidermal appendages.[170,171] PT has been reported with different EDs.[153,154,172-184] (Table III).

PT and other associations. PT has been reported in association with other genetic hair shaft abnormalities[32,98,105,127,183-189] (Table IV).

Menkes syndrome. The primary hair finding in classic Menkes syndrome (MS; Menkes kinky hair syndrome) is PT, but other defects, such as TN, have been described.[190,191] This X-linked recessive condition is associated with skin and hair hypopigmentation, progressive neurologic degeneration with mental retardation, bone and connective tissue alterations with soft doughy skin and joint laxity, and vascular abnormalities, including aneurysms and bladder diverticula.[192-194] Patients exhibit low serum concentrations of copper and ceruloplasmin. Most patients appear normal at birth and then typically develop neurologic deteroriation, lethargy, and a loss of milestones in the second or third months of life. Hairs become sparse, short, brittle, and depigmented, and they fracture easily and resemble steel wool.[7]

Cases affecting females have been reported[195-197] because of X-chromosome translocations[196-199] or 45X/46XX mosaicism. Female heterozygotes may exhibit mild PT on close inspection.[200]

MS is caused by a defective copper export from cells with normal copper absorption into cells. The Menkes gene (MNK) has been mapped to Xq13.3[201-203] and encodes ATP7A, a P-type cation transporting ATPase localized to the plasma membrane and the trans-Golgi network (TGN).[204,205] At normal levels of intracellular copper, ATP7A is concentrated at the

Table III. Ectodermal dysplasias/defects reported with pili torti

Widely spaced teeth and enamel hypoplasia[153,172]
Acrofacial dysostosis of the palagonia type[173,174]
Tooth agenesis[175]
Arthrogryphosis[179]
Nail dystrophy[180]
Clefting[176-178]
Corneal opacities[154]
Trichodysplasiaxeroderma[181]
Hypohidrotic ectodermal dysplasia[182]
Ichthyosis[154,183,184]

Table IV. Disorders associated with pili torti

Monilethrix[127]
Pseudomonilethrix[185]
Woolly hair[221]
Mitochondrial disorders[186]
Netherton syndrome[184]
Bazex syndrome[189]
Longitudinal grooves[323]
Trichorrhexis nodosa[187]
Trichorrhexis invaginata[98,105,183]
Citrullinemia[32]
Laron syndrome[188]

TGN and functions to transfer copper into copper-dependent enzymes, such as lysyl oxidase. With increased intracellular copper absorbed through the hCTR1 transporter, ATP7A is redistributed to small cytoplasmic vesicles and to the plasma membrane, functioning to pump copper out of cells to prevent toxicity.[204-206] If copper levels fall to normal, ATP7A returns to the TGN network and resumes transfer of copper. Mutations in the MNK gene lead to accumulation of intracellular copper and prevent copper transport to copper dependent enzymes such as lysyl oxidase. With excess intracellular copper, RNA synthesis of metallothionine is triggered, which chelates the accumulated copper to prevent cellular toxicity, but further reducing the transfer of copper to enzymes.

Accumulation of copper occurs in intestinal enterocytes, which absorb copper from nutritional sources and in renal tubular cells, which absorb copper present in the glomerular filtrate. With inadequate functional transfer of copper from the intestines and kidney, copper cannot be exported into the enterohepatic and systemic circulation for liver absorption and processing respectively. The enzyme ATP7A is also expressed in cells involved in copper transport across the blood–brain barrier and cardiac myocytes, leading to low levels of copper in these organs.

Functional deficiency of copper-dependent enzymes is involved in collagen/elastin/keratin cross-linkage,[207] myelin synthesis, free radical defense, melanin formation, and electron transport chain function,[204,208,209] and results in clinical features (Table V). Keratinization abnormalities[190] of the hair shaft, with impaired formation of disulfide cross-links in the keratin,[193] are likely to be secondary to dysfunction of copper-dependent enzymes, leading to increased hair fragility.

Milder variants of classic MS arise from mutations in the Menkes genetic locus that allow some residual ATP7A function, primarily from missense mutations that result in altered mRNA splicing.[204] Occipital horn syndrome (OHS) manifests with PT and connective tissue abnormalities, such as soft doughy lax skin and diverticula, and little neurologic aberration. It is called OHS because of bony projections (exostoses) which occur on the occipital bone of the skull.

Mouse models exist for MS and its variants,[205,206,210-214] where the effects of decreased levels closely parallel findings in humans. From mouse and human models, phenotypic expression resulting from the ATP7A mutation is determined by the effect of the mutation on protein function, intracellular localization, and trafficking.[204]

Treatment of MS syndrome consists of infusions with copper-histidine. Copper-histidine increases serum copper levels and can permit survival into adolescence. However, many children do not survive beyond the first decade of life, and death is caused by a multitude of factors including neurologic deterioration and organ failure. The full function of copper histidine and how it works is not well characterized. It must be administered early in life, because it may prevent but not reverse permanent neurologic damage.[215-220] Copper-histidine therapy has limited effects on connective tissue abnormalities. Postmortem examination of a 10-year-old child treated with copper-histidine revealed straight coarse hypopigmented hair, skeletal abnormalities, vascular degeneration, and bladder diverticula, but limited CNS pathology and normal mentation. Treatment is thought to alter its phenotype to one that is closer to OHS if treatment is implemented early.[217,218]

Woolly hair

Woolly hair (WH) occurs in persons of non-African ancestry.[131] Hairs are tightly curled, with an average curl diameter of 0.5 cm,[221] and can also contain wide twists over several millimeters along its own longitudinal axis.[222] It was originally described by Hutchinson[221] as "pseudopili-torti." Hair shafts are ovoid, flattened, or irregular.[221-223] Associated hair findings may include increased hair fragility, TN,[224]

Table V. Copper-dependent enzymes in Menkes syndrome

Enzyme	Function	Consequence of enzyme deficiency
Lysyl oxidase	Cross-linking of collagen/elastin	Connective tissue abnormalities, laxity of skin/joints, vascular abnormalities, bony abnormalities, and bladder diverticula
Tyrosinase	Melanin formation	Hypopigmentation
Cytochrome c oxidase	Electron transport chain	Hypothermia, muscle weakness, ataxia, seizures, and energy deficiency
Peptidylglycine a amidating monooxygenase (PAM)	Neuropeptide processing	Unknown, possible neurodegeneration
Superoxide dismutase	Free radial scavenger	Low tolerance of oxidative stress, demyelination
Cross-linkase	Cross-linkage of keratin	Coarse, brittle hair
Dopamine B hydroxylase	Catecholamine production	Hypothalamic imbalance, hypothermia, hypotension

Adapted from Mercer[204] and Peterson.[208]

trichoschisis, and pili annulati (PA).[221] The rate of hair growth is typically normal (approximately 1 cm/month), and the composition of keratin and amino acids do not differ from normal hair.

Hereditary dominant woolly hair. Hereditary dominant woolly hair usually affects the entire scalp and is seen either at birth or within the first few months of life.[220,225] It usually occurs alone, but has been reported with PT and PA,[221] ocular problems, or keratosis pilaris.[226-231] The genetic defect is unknown.

Familial recessive woolly hair. Hair is fragile and fine with a light pale or blonde color[221] at birth, and the hair may not grow beyond the length of a few centimeters, probably secondary to a shortened anagen phase. The genetic defect is unknown.

Woolly hair with cardiac abnormalities: Naxos disease, Carvajal syndrome, and Naxos-like disease. In Naxos disease, WH is usually present at birth; palmoplantar keratoderma (PPK) usually develops during childhood. Arrhythmogenic right ventricular cardiomyopathy (ARVC)[232] begins to manifest during adolescence or early adulthood. Definitive diagnosis of ARVC requires biopsy of the myocardium showing fibrofatty replacement.[233]

Naxos disease has been mapped to chromosome 17q21 and is an autosomal recessive disorder. The candidate gene for this disorder is plakoglobin, a key component of desmosomal and tight junctions, and is found in the heart, skin, and hair.[233,234] Carriers of Naxos disease can show minor phenotypic features, such as woolly hair, mild electrocardiographic abnormalities, and mild right ventricular dilatation without progression to ARVC.[235,236] Mutational heterogeneity has been demonstrated in the Naxos gene locus, and may account for the variable phenotype in patients and carriers of the disease.[235]

Desmoplakin mutations have also been reported with WH and cardiomyopathy without keratoderma. Desmoplakin is a protein found in desmosomes in cell—cell junctions in the heart, skin, and hair. It contains three functional domains: an N-terminal domain that binds to cadherins (desmogleins and desmocollins) via plakoglobin and plakophilin interactions; a rod domain; and a C-terminal domain which binds intermediate filaments.[237]

Abnormalities in desmoplakin are involved in Carvajal syndrome, an autosomal recessive disorder with biventricular dilated cardiomyopathy, PPK, and WH.[238] Mutation analysis of an Ecuadorian family with Carvajal syndrome demonstrated a 7901delG mutation in exon24 on chromosome 6, forming a premature stop codon. A truncated desmoplakin protein missing the terminal part of the C-terminal domain results.[239] Postmortem analysis of a heart specimen from a patient with Carvajal syndrome demonstrated reductions in desmoplakin, plakoglobin, connexin 43 staining, and reduced levels of desmin, an intermediate filament protein, at the intercalated discs of cardiac myocytes.

Naxos-like disease is an autosomal recessive disorder with ARVC, WH, early-onset blistering on the knees, palms and soles, and dry skin.[240] Skin biopsies of the blister sites demonstrate histology similar to pemphigus foliaceus on hemotoxylin—eosin staining. Mutation analysis demonstrates a missense mutation in the C-terminus of the desmoplakin protein.

The pathogenesis of WH and its associated findings is not well known. Hair follicle desmosomes contain desmoplakin, plakoglobin, and plakophilin1. Fragility at desmosomal junctions is hypothesized to dysregulate hair development leading to the common phenotype of WH.[234,239,241] Plakoglobin has been shown to be important in hair follicle proliferation and differentiation.[242] However, the pathogenesis of WH, PPK, and cardiomyopathy has yet to be elucidated in desmosomal mutations. Even more confusing is the report of two Arab families with clinical findings consistent with Naxos disease without plakoglobin,

desmoplakin, plakophillin, desmocollin, and desmoglein mutations.[242,243]

Woolly hair without cardiac abnormalities. *Woolly hair and skin fragility syndrome.* WH and skin fragility syndrome consists of early-onset blistering, focal and diffuse PPK, WH, dystrophic nails, and alopecia.[241] It differs from Naxos-like disease in that there are no cardiac abnormalities. Blistering at the heels and lower extremities is reported during infancy and recurrent during childhood, and blistering can also affect the scalp and other regions of the body. It is associated with recurrent secondary infections with *Staphylococcus aureus* on the palms and soles. Electron microscopy of palmoplantar skin desmonstrates suprabasilar dysadhesion. Mutations in desmoplakin have been identified with this disorder, but there is no associated cardiac disorder. A patient with a plakophilin1 mutation was also reported to exhibit a similar phenotype, except the proband had short sparse hair without reported features of WH.[244]

Diffuse partial woolly hair. Autosomal dominant diffuse partial WH has been found in six members of a family[245] and patients presented in early adult life. The underlying genetic defect is unknown. WHs are short, fine, and kinky. Normal-appearing family members had a smaller percentage of WHs interspersed within normal scalp hair, and therefore did not have any apparent clinical complaints, while clinically apparent members had a higher fraction of WHs. Another family was described with wavy hypopigmented, thin, and short hairs interspersed with normal-appearing straight hairs.[221] A trichogram (examination of hair roots by microscopy after epilation) of the wavy/WHs revealed a predominance of dysplastic anagen and telogen hairs without the presence of normal anagen hairs.

Spontaneous improvement in one adolescent-onset case has been noted.[246] Cataracts,[228] pupillary membranes, and retinal dysplasia have been reported.[227]

Woolly hair nevus. WH nevus (WHN) is a rare sporadic disorder that affects a localized area on the scalp and typically presents generally within the first 2 years of life,[247,248] although onset in a teenager has been reported.[246] The hair is usually thinner and lighter in color when compared to the adjacent normal hairs,[131,246] and examination reveals tightly curled hair with decreased cross-sectional diameter. Half of the cases reported have been associated with an epidermal or a congenital nevus, usually located ipsilaterally on the neck or arms.[246,249,250] WHN syndrome has been reported with epidermal nevi, boney abnormalities, precocious puberty, speech and dental anomalies.[251,252] WHN can follow Blaschko lines, suggesting that it may be a mosaic disorder. The genetic mutation has not been identified, and probably represents a variant of epidermal nevus syndrome.

Curly hair

Curly hair demonstrates large loose spiral locks. It can be seen in many genetic syndromes, including tricho-dento-osseous (TDO), CHAND (*c*urly *h*air, *a*nkyloblepharon, and *n*ail *d*ysplasia), Costello, and Noonan syndromes and lipoatrophic diabetes (Table VI).

With TDO, patients are born with diffuse curly hair that frequently straightens with age. Associated anomalies include enamel hypoplasia; small, eroded, widely spaced, and taurodont teeth (enlarged pulp chambers); otosclerosis, dolichocephaly (long and narrow cranium), and frontal bossing.[226,253-256] TDO is autosomal dominant and the proposed mutant gene, *DLX3* on chromosome 17q21, is a homeobox gene important for embryonic development.

CHAND syndrome includes the symptoms above along with variable ataxia.[257] It is an autosomal recessive disorder,[258] and the gene mutation is unknown.

Costello syndrome is characterized by sparse curly hair, growth deficiency, mental retardation, coarse facies, loose skin on the hands and feet, nasal and perioral papillomata, and other variable features.[259-263] There is also an increased risk of developing solid tumors, such as rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma. Twisting of the hair shaft has been demonstrated by light microscopy.[264] HRAS mutations have been identified in 12 out of 13 patients with Costello syndrome in one study.[265] RAS proto-oncogenes encode GTP-binding proteins that function in the mitogen-activated protein kinase pathway (MAPK), and play a role in cell regulation and proliferation.

Noonan syndrome is characterized by dysmorphic facies, ear and ocular anomalies, cardiovascular anomalies, multiple nevi, short stature, keratosis pilaris atrophicans, webbed neck, and either curly or woolly hair.[231,266,267] It is an autosomal dominant disorder with near complete penetrance, and approximately one-half of all cases are caused by gain of function mutations in PTPN11, a gene encoding the SHP-2 tyrosine phosphatase.[268] The SHP-2 protein is important in intracellular signal conduction and has effects on developmental processes.

Miscellaneous

Marie Unna hypotrichosis. In Marie Unna hypotrichosis (MUH), affected persons are born with normal to coarse sparse hair and eyebrows and develop progressive coarsening within the first few

Table VI. Disorders associated with curly hair

Disorder	Hair features	Other features	Transmission/gene
Trichodento-osseous syndrome	Curly hair at birth, straightens with age; no specific defects	Small, eroded, widely spaced teeth; enamel hypoplasia; taurodont teeth; frontal bossing; square jaw; dolicheocephaly; otosclerosis[226,254-256]	AD, gene on 17q21,[255] DLX3 (Homeobox gene)
CHAND syndrome	Curly hair at birth; no specific defects	Ankyloblepharon, nail dysplasias, ataxia (variable)[257]	AD[257]
Costello syndrome	Curly hair at birth	Growth deficiency; mental retardation; coarse facies; loose skin on hands/feet; nasal/perioral papillomata; brittle dystrophic nails; dark hyperpigmentation, hyperextensible fingers[259-262,324,325]	AR[259,260] or AD[260,325] HRAS[265]
Noonan syndrome	Curly or woolly hair	Dysmorphic facies, ear and ocular anomalies, cardiovascular anomalies, short stature, webbed neck[231,267]	AD, PTPN11 gene[268]

years of life. Eyebrows, eyelashes, and axillary hair are also affected. On the scalp, hair loss typically starts in the parietal and vertex areas, with partial sparing of the posterior part of the occipital scalp. Heterogeneity of clinical presentations exist.[269] Histologically early on, mild to moderate inflammation with little fibrosis is seen in the dermis.[270] In the late stages, follicles are dramatically reduced in number.[269-271]

MUH[270,271-273] is an autosomal dominant disorder[273] involving an unknown hair growth regulatory gene on chromosomal region 8p21.[274-277] The exact gene for MUH has yet to be identified. Genetic heterogeneity likely exists based on recent studies linking MUH in a Chinese family to chromosome 1p21.1-1q21.3.[278]

A recently described entity, "progressive patterned scalp hypotrichosis," was found to have curly hair and a similar pattern of hair loss, but is distinct from MUH in several ways. A family of 22 members demonstrated progressive patterned scalp hypotrichosis with wiry/curly hair, onycholysis, and associated cleft lip and palate.[279] This family had wiry hair starting at about 2 years of age. Onset of patterned alopecia developed from 15 to 23 years of age with an increased number of telogen hairs found on hair pull test. Distal onycholysis of the fingernails and facial clefting were reported in 5 members of the family with the hair anomaly, but were not features in any of the unaffected members. The gene is unknown.

Uncombable hair syndrome

Uncombable hair syndrome (UHS; also known as spun glass hair or pili trianguli et canaliculi) was first described in the French literature in 1973 by Dupre et al.[280] The entire hair shaft is rigid with longitudinal grooving. On cross section, the shaft has a triangular shape.[281,282] Scalp hair typically has greater than 50% involvement.[283] Hair shafts are not twisted as in PT. The hair cannot be combed flat (Fig 14). Although it can be present in dark hair, it is usually not as noticeable. UHS usually manifests during childhood. Analysis of the hair shaft has found no consistent physical or chemical abnormalities,[284-286] although one study demonstrated increased exocuticle high-sulfur protein content,[286] and another study demonstrated decreased solubility of abnormal fibrous proteins in the hair shaft.[286,287]

UHS is thought to arise from premature keratinization of a triangular-shaped IRS caused by an abnormally shaped dermal papilla.[288] Another author suggested that longitudinal grooves arose from an asymmetric matrix defect.[289] The definitive diagnosis of UHS is made by scanning electron microscopy,[283,284,290] although it is easy to see on standard microscopy.

Familial cases show autosomal dominant inheritance with variable penetrance.[291-294] Associated anomalies are rare but have been described include: cataracts,[294,295] anomalies in bone development,[294,296-298] alopecia areata,[290] PT,[299] and lichen sclerosus.[300]

Hair tends to become more manageable with age, although the defect persists. A positive response to biotin has been reported in a few cases.[283,284]

Loose anagen syndrome. In LAS, anagen hairs lack IRS and external root sheaths, have ruffled cuticles, and are easily pulled from the scalp[301-303] (Fig 15). Most patients are blonde girls older than 2 years of age (mean, 6 years). Symptoms may persist into adulthood. Adult-onset LAS is frequently misdiagnosed as telogen effluvium.[304,305] More than 80% of the plucked anagen hairs are devoid of root sheaths.[304] The hair is typically not brittle and has normal tensile strength. Gentle hair care is recommended.

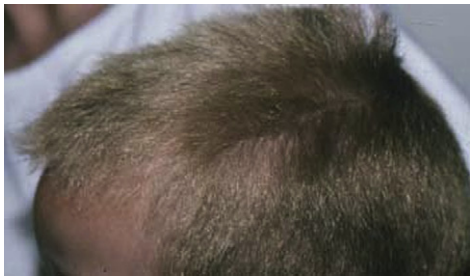

Fig 14. Patient with uncombable hair syndrome.

The genetic defect in LAS has not been well characterized, but is thought to be a keratin defect.[306] A mutation of keratin K6hf was found in three of nine families with autosomal dominant LAS. K6hf is a type II cytokeratin found exclusively in the companion layer connected to Henle layer via desmosomes. More than one keratin gene may be involved in the pathogenesis of LAS.[306]

There is evidence of autosomal dominant transmission with variable expression and incomplete penetrance,[304,306,307] but sporadic cases and rare associations[308-310] have been reported.

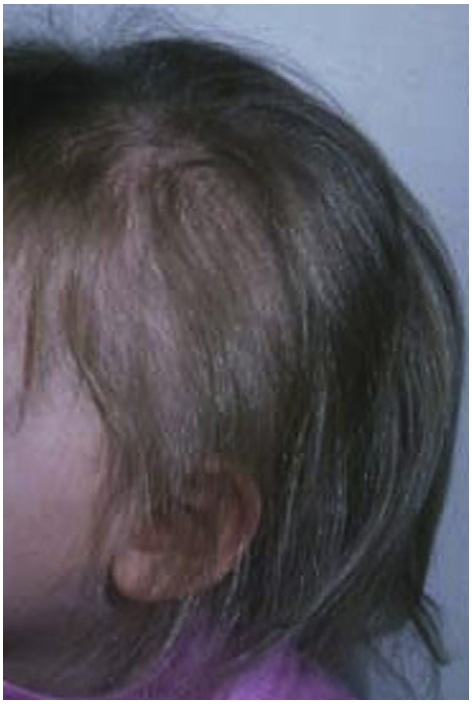

Fig 15. Young child with loose anagen hair syndrome.

Pili annulati

PA has characteristic alternating light and dark bands in the hair shafts that can be seen on clinical and microscopic exam. It is thought that this hair disorder is caused by the formation of abnormal air cavities in the hair shaft. It is usually clinically seen only detectable only in blonde or lightly pigmented hair,[10] because the banding pattern caused by the air cavities tends to be obscured by the additional pigment in dark colored hair.

PA appears at birth or during infancy. It is a rare keratinization abnormality with autosomal dominant[311,312] or sporadic inheritance.[313] Axillary hair,[314] beard hair,[315] and pubic hair[316] are occasionally affected, and the hair is not brittle. Growth of scalp hair is usually normal, although in one case growth rate was decreased.[311]

Both small and large air spaces are found between macrofibrillar units within the cortex of the hair shaft.[313] An unknown defect in the formation of the micro/macrofibril matrix complex is considered to be the cause.[315,317,318] The hairs themselves are not excessively fragile[311]; however, it has been reported in some patients that excessive weathering occurs in the bands, suggesting that intrinsic shaft weaknesses may occasionally exist.[319]

On transmission electron microscopy, a large number of abnormal cavities of varying shapes and sizes are visible within the cortex between cortical macrofibrils and within cortical cells.[313] In one study, the cystine content of hair from PA is hypothesized to be lower than normal, despite a normal amino acid analysis and sulfur content.[311] Gummer et al[317] found a cystine-positive, electron negative opaque material in the intermicrofibrillar spaces. They speculated that this material is formed because not all the available cystine is utilized in keratinization as a result of insufficient production of a cortical component, and hypothesize that the deposit sites will go on to form cavities when the material is washed out of the hair shaft.

There is no associated hair or systemic abnormalities in PA. There have been reports of alopecia areata,[320,321] WH,[221] and blue nevi of the scalp[311] occuring concurrently with PA, possibly coincidentally. No treatment for PA is usually necessary, and most patients do not experience hair fragility.

Mitochondrial disorders. TN, trichorrhexis, longitudinal grooving, trichoschisis, and PT have been reported with mitochondrial disorders. In a French series of 140 children with mitochondrial disorders, 14 had cutaneous findings, of which six had hair shaft anomalies including longitudinal grooving, trichoschisis, and/or PT.[186] In another study, 8 out of 25 children with a mitochondrial disorder had slow growing, sparse and fragile hair and microscopic evidence of TN and PT.[322] Electron microscopy demonstrates loss of the hair cuticle. The authors suggest that hair anomalies may be an early clinical sign of a mitochondrial disorder.[322]

CONCLUSION

Clinically, hair shaft defects may cause hair to be fragile or have an unusual appearance. With the use of light microscopy, defects may be classified by the hair shaft morphology combined with clinical presentation. Recently, there have been advances in the genetic causes of hair shaft disorders, but work in the fields of molecular biology, biochemistry, genetics, and dermatology is still ongoing. The ultimate goal is to understand mechanisms of these defects, and to elucidate normal and pathogenic pathways, so that successful therapies can be found.

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