

# Hair Shaft Abnormalities – Clues to Diagnosis and Treatment

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## Key Words

Hair shaft disorders · Hair dysplasias · Ectodermal dysplasia · Genetic predisposition · Physical examination

## Abstract

Hair dysplasias are congenital or acquired alterations which often involve the hair shaft. Hair shaft abnormalities are characterized by changes in color, density, length and structure. Hair shaft alterations often result from structural changes within the hair fibers and cuticles which may lead to brittle and uncombable hair. The hair of patients with hair shaft diseases feels dry and looks lusterless. Hair shaft diseases may occur as localized or generalized disorders. Genetic predisposition or exogenous factors produce and maintain hair shaft abnormalities. Hair shaft diseases are separated into those with and those without increased hair fragility. In general, optic microscopy and polarized light microscopy of hair shafts provide important clues to the diagnosis of isolated hair shaft abnormalities or complex syndromes. To establish an exact diagnosis of dysplastic hair shafts, a structured history and physical examination of the whole patient are needed which emphasizes other skin appendages such as the nails, sweat and sebaceous glands. Profound knowledge on hair biology and embryology is necessary to understand the different symptom complexes. Therapy of hair shaft disorders should focus on the

cause. In addition, minimizing traumatic influences to hair shafts, such as drying hair with an electric dryer or permanent waves and dyes, is important. A short hairstyle is more suitable for patients with hair shaft disorders.

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## Introduction

Although hair has no vital function, it may serve as an indicator for human health. Clinical and morphological hair abnormalities can be clues to specific complex disorders. The human hair form and the diameter are determined by the anatomy of the hair follicle [1]. Changes in the hair shaft can occur physiologically such as in pregnancy but in general mirror a disease process. Nissimov and Elchalal [2] described for the first time that hair diameter increases during a normal physiological process. Anomalies of the hair shaft are separated into those with and those without increased hair fragility. Hair shaft abnormalities can be inherited or acquired, can reflect a local problem or a systemic disease (table 1). It is important to know whether the hairs do never grow, or whether a defect in the hair cycle exists such as in the anagen, limiting the duration of hair growth. The fact that alopecia in a given case is caused by hair which is falling out to light traction while still growing may be a clue for loose anagen hair syndrome.

**Table 1.** Features of hair shaft diseases

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Classification
Acquired or congenital
Exogenous or genetic
Diffuse or localized
Clinical aspect
Dry hair and lusterless
Uncombable hair
Fair hair
Breaks easily
Diagnosis
History
Physical examination
Light and scanning electron microscopy
Biochemical analysis

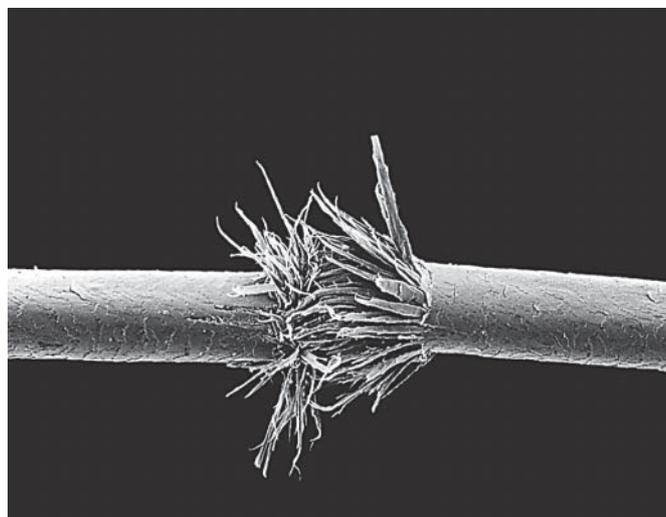
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Most of the genotrichoses show a Mendelian trait of inheritance. However, some are non-Mendelian phenotypes representing lethal mutations surviving only by mosaicism. These traits may follow paradominant inheritance as emphasized by Happle and König [3]. There are polygenic and monogenic hair disorders. 'Online Mendelian inheritance in man' gives 66 entries for hypotrichosis and 153 entries for alopecia which illustrates the heterogeneity of the problem.

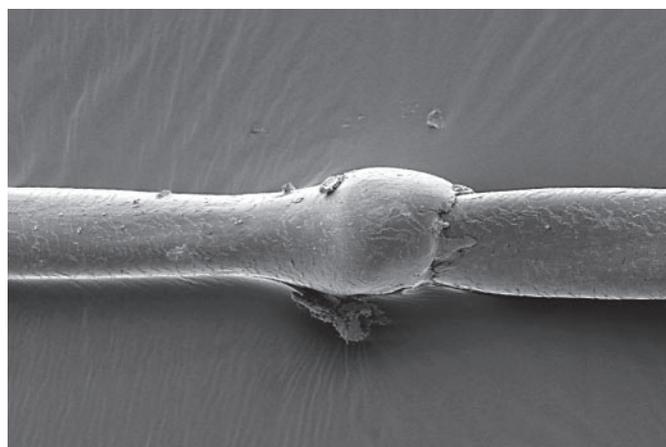
In the daily work, a clinical classification of alopecia which also includes hair shaft abnormalities as proposed by Happle seems reasonable: (1) total or subtotal absence of scalp hair in early childhood, (2) more or less diffuse hypotrichosis that may or may not deteriorate during life or even diminish, (3) absence of hair in distinctly demarcated patches or streaks [4]. Complex systemic diseases may lead to typical hair shaft alterations such as trichorrhexis nodosa, trichorrhexis invaginata and trichoschisis (fig. 1, 2). Hair shaft disorders include 'uncombable hair' with a triangular and canalicular diameter (fig. 3, 4).

### Embryology and Biochemistry of Hair

Hair is an ectodermal structure, and its formation is regulated by master genes important in embryology. The mammalian hair follicle develops from the epidermis [5]. The major biochemical components of human hair are the intermediate filaments or keratins and the keratin-associated proteins [6]. Keratins belong to the superfamily of proteins that form 8- to 10-nm filaments in the cytoplasm of many epithelial cells. The terminology for human hair basic keratins is abbreviated internationally as



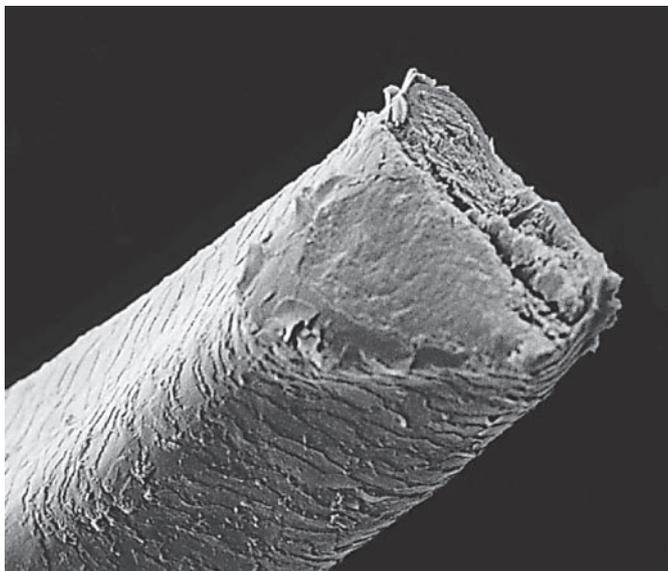
**Fig. 1.** Trichorrhexis nodosa.



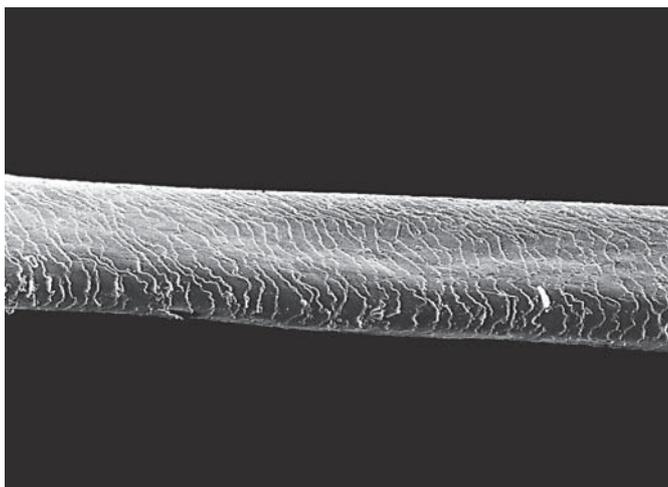
**Fig. 2.** Trichorrhexis invaginata.

'hHb' [7]. Keratin-associated proteins are divided into two groups, high-cyst(e)ine and high glycine-tyrosine-rich polypeptides, according to the amino acid composition. Cyst(e)ine-rich keratins contain high-sulfur (15–30%) proteins and ultra-high-sulfur proteins composed of >30% cyst(e)ine residues [8]. A trichohyalin gene is only characterized in rabbits so far, and further work is necessary to unravel the human homologue [9].

Syndromes with ectodermal malformations often show altered hair shafts. Almost 200 different entities out of the spectrum of ectodermal dysplasias are known today. In many cases of ectodermal and/or mesodermal disorders, the developmental anomalies of other organs predominate those of the hair.



**Fig. 3.** Pili trianguli.



**Fig. 4.** Pili canaliculi.



**Fig. 5.** Dysplastic hair in KID syndrome.

## Hair Shaft Alterations and the Dymorphologist

Hair changes may be a significant finding or even the initial presentation of a syndrome giving the clue to the diagnosis, e.g. trichothiodystrophy (TTD). Clinically hair in these syndromes may be sparse, slow growing, fragile and brittle, uncombable, dry and lusterless. The hair color may give further information on the existence of genetic disorders with hair shaft anomalies. Clinical diagnosis in dysmorphology is often like a puzzle, and numerous stones help to complete the whole picture. Hair morphology as a tool for the diagnosis of genetic diseases has been recognized by dymorphologists [10]. In KID syndrome (keratosis, ichthyosis and deafness), more than 90% of patients have alopecia often associated with hair shaft alterations [11] (fig. 5). To investigate hair shaft disorders, about 50 hairs should be visualized under light microscopy. There are exceptions such as Netherton's syndrome where repeated samples of hairs may be necessary to confirm the diagnosis. The hair sampling should be performed where clinical hair abnormalities are most prominent. There are hair shaft disorders which have more impressive changes in the occipital area because of maximal trauma such as in TTD and monilethrix. It is important to compare normal and affected hairs. In patients with hair shaft diseases, hair should be cut just above the scalp to make sure that weathering of hair which is found on the distal parts does not interfere. In case no hair shaft alteration is found, alopecia could result from a defect in the hair cycling process, and therefore in such cases hair should be plucked by a pair of forceps with rubber or plastic tubing over the tips as in loose anagen hair syndrome or in dystrophic anagen hair. Examination under light and scanning electron microscopes is an important step in the diagnosis of hair shaft disorders. A diagnostic clue for breaking hair is a brush on the distal end of the shaft. An important question is also whether cuticles are normal, sparse or even lacking.

## Hair Shaft Alterations in Ectodermal Dysplasias

Ectodermal dysplasias are a large group of heritable conditions characterized by congenital defects of one or more ectodermal structures [12]. Selvaag et al. [13] investigated hair samples of patients with various ectodermal dysplasias such as hypohidrotic ectodermal dysplasia, pachyonychia congenita, trichodento-osseous syndrome

and trichorhinophalangeal syndrome by scanning electron microscopy. The hairs of those patients showed twisting, longitudinal grooves, trichorrhexis nodosa and variations in hair caliber.

X-linked hypohidrotic ectodermal dysplasia is characterized by hypotrichosis with fine, slow-growing scalp and body hair, sparse eyebrows, hypohidrosis, nail anomalies and hypodontia [14]. The hair is sparse, dry, lusterless and light colored. Rogers [15] observed that the bar code appearance which mirrors a microscopic artifact is often seen in patients with hypohidrotic ectodermal dysplasia. There are parallel dark bands of different lengths running across the full width of the hair shaft. Kere et al. [16] found mutations in ectodysplasin, a TNF ligand, to be the cause of the X-linked hypohidrotic ectodermal dysplasia. The ectodysplasin pathway, a new TNF pathway, has an important function in embryonic development and especially in the formation of ectodermal structures including hair. Mutations in the human homologue of the mouse *downless* (dl) gene cause autosomal recessive or dominant hypohidrotic ectodermal dysplasia [17].

Ectrodactyly, ectodermal dysplasia and cleft palate (EEC) syndrome has initially been described in 1804. Since then the clinical spectrum has been further delineated. EEC syndrome is an autosomal dominant trait involving ectodermal and mesodermal tissue. Marked scalp dermatitis may occur early in the disease [18, 19]. Scarring folliculitis in a 16-year-old boy was observed by Trüeb et al. [20]. They documented reduced hair elasticity indicating either an abnormal composition or a disordered arrangement of microfibrils within the apparently normal keratin matrix. Hair is affected in all cases. Hair is light colored, coarse and dry. Axillary and pubic hair may be sparse. An increase in hair pigmentation with age has been observed. A germline missense mutation in the p63 gene underlying EEC syndrome has been reported [21]. Heterozygous germline mutations in the p53 homologue p63 are critical for maintaining the progenitor cell populations that are necessary to sustain epithelial development, limb and craniofacial morphogenesis [22, 23]. AEC syndrome is inherited in an autosomal dominant fashion and stands for ankyloblepharon, ectodermal defects and clefting of the lip and palate [24]. It is allelic with the EEC syndrome and can be distinguished by the presence of lobster type malformations of the hands and feet.

Pili trianguli et canalliculi may appear as isolated uncombable hair syndrome, but associations with other ectodermal malformations may occur. Uncombable hair syndrome is characterized by scalp hairs arranged in bun-

dles in all directions, resistant to brush and comb. Hair diameter in this condition shows a triangular to reniform to heart shape aspect on cross-sections, and a groove, canal or flattening along the entire length of the hair in at least 50% of hairs examined by scanning electron microscopy [25]. Several entities may lead to uncombable spunglass hair. As a rule, the syndrome becomes obvious during the first years of life. The hair is normal in quantity, but dry and silvery blond. Increased fragility is not common.

Trichorhinophalangeal syndrome is inherited as an autosomal dominant trait and clinically characterized by growth retardation, craniofacial abnormalities, severe brachydactyly, pear-shaped nose, elongated philtrum, thin upper lip and sparse and slow-growing hair with hair shaft alterations. In addition, mental retardation and cartilaginous exostoses may occur depending on the type of the syndrome.

Cartilage-hair hypoplasia, also called McKusick type metaphyseal chondrodysplasia, is an autosomal recessive skeletal dysplasia with disproportionate short stature, alopecia and metaphyseal abnormalities in skeletal radiographs. Hair is fine, sparse, light colored with sparse eyebrows and eyelashes. Other common features are a defective immunity and an increased risk for malignancies. The major mutation causing cartilage-hair hypoplasia is a nucleotide substitution in the ribonuclease mitochondrial RNA gene which encodes the untranslated RNA that is a component of mitochondrial RNA-processing endoribonuclease [26].

Netherton's syndrome is a rare (<1:100,000) autosomal recessive disease characterized by hair shaft defects, ichthyosis and atopy. 18% of 51 cases with neonatal and infantile erythrodermas were finally diagnosed as Netherton's syndrome [27]. The main hair abnormality in Netherton's syndrome was initially named bamboo hair and later called trichorrhexis invaginata. Less specific hair abnormalities are torsions, trichorrhexis nodosa and helical hairs. However in the neonatal period, hair shaft anomalies can still be lacking which makes an early diagnosis rather difficult [28]. Sometimes the diagnosis of the hair shaft anomalies is easier to perform in the eyebrows than on scalp hair [29]. The typical trichorrhexis invaginata is easily recognized under light microscopy, although scanning electron microscopy gives a nicer picture. Chavanas et al. [30] mapped the disease to chromosome 5q32 by linkage analysis and homozygosity demonstrated in 20 families with Netherton's syndrome. The same group finally found mutations in *SPINK5*, encoding a serine protease inhibitor as the cause for Netherton's syndrome [31].

Trichothiodystrophy (TTD) is a heterogeneous group of autosomal recessive disorders with distinctive features of short, brittle hair and abnormally low-sulfur content [9]. The hair of patients with TTD is dry and sparse, and the hair shafts break easily with trauma. Environmental factors and mechanical stress play an important role. Interestingly, intermittent hair loss during infections was observed by Kleijer et al. [32] and Foulc et al. [33]. In addition, hair loss may occur with periodic cyclicity. Fractures of the hair shaft develop, and the viscoelastic parameters of hair are compromised compared to controls. Within the spectrum of the TTD syndromes are numerous interrelated neuroectodermal disorders. The TTD syndromes show defective synthesis of high-sulfur matrix proteins. Abnormalities in nucleotide excision repair of ultraviolet-damaged DNA exist in about half of the patients. Three complementation groups have been characterized among photosensitive patients with TTD. Most patients have mutations on the two alleles of the *XPD* gene. Rarely, mutated *XPB* gene or *TTD-A* gene may result in TTD. In UV-sensitive TTD patients, the TFIIH transcription factor containing XPB and XPD helicase activities necessary for both transcription initiation and DNA repair is damaged. Beyond deficiency in the nucleotide excision repair pathway, basal transcription is altered leading to decreased transcription of specific genes. Depressed RNA synthesis is probably responsible for some clinical features, such as growth retardation, neurological abnormalities and brittle hair and nails. In patients with TTD hair abnormalities are the only obligatory and diagnostic findings that identify the sulfur-deficient neuroectodermal dysplasias. Scalp hairs, eyebrows and eyelashes are brittle, unruly, of variable lengths, easily broken and generally feel dry. It is important to investigate the proximal parts of hair shafts, as the distal portions often show marked weathering that may produce findings similar to TTD [34]. Macroscopic alterations are observed especially in the occipital hair, where microscopic abnormalities are best visible. For adequate diagnosis, hairs should be collected from different areas of the scalp and subjected to further light- and electron-microscopic examination [35, 36]. Light microscopy reveals clean transverse fractures through the hair shafts (trichoschisis), and there is an irregular hair surface and diameter. In addition, a decreased cuticular layer with twisting and a nodal appearance may mimic trichorrhexis nodosa. The distal hair shaft often terminates in 'brush breaks'. The flattened hair shafts tend to fold over like a ribbon or shoe lace during microscopic mounting. This abrupt 180-degree twist of the hair shaft mimics pili torti. Polarizing microscopy with crossed polarizers shows the typical appearance of

alternating light and dark bands, giving a 'zigzag' or 'tiger tail' pattern. Brusasco and Restano [37] reported the interesting finding that the typical tiger tail pattern of the hair shaft in TTD may not be evident at birth. This classical pattern was clearly evident only at 3 months of age in their case. However, hair examination from a 21-week gestation, aborted fetus showed the alternating light and dark banding pattern under the polarized light microscope [38]. Within the last few years, it has been shown that the tiger tail pattern on polarized hair microscopic examination may also be found in healthy infants, and therefore amino acid analysis quantitating sulfur – specifically cyst(e)ine levels – remains the definitive test for TTD [39, 40]. In this regard, Garcia-Hernandez et al. [41] have documented alternating dark and white zones within the hair shaft of a young patient who scratched his scalp intensely. Cessation of scratching and application of minoxidil 2% and cysteine therapy resulted in marked improvement within a year. The condition appears sufficiently different by polarizing light microscopy, and this sulfur-deficient hair alteration is referred to as 'pseudo tiger-tailing'. Sperling and Di Giovanna [42] noticed that fibers within the hair shafts of patients with TTD undulate up and down (or back and forth), a feature that is easily observed because of melanin granules embedded in each fiber. The undulations corresponded exactly to the banding seen with polarization. Therefore, the tiger tail phenomenon seen in TTD and other hair shaft disorders was interpreted to be caused by a regular undulation of hair fibers within the shafts. Normal hair shafts do not show the phenomenon because the hair fibers are straight and parallel to the long axis of the hair.

Naxos disease is a recessively inherited arrhythmogenic right ventricular cardiomyopathy caused by a mutation in the gene encoding plakoglobin (cell adhesion protein) in which the cardiac phenotype is associated with diffuse palmoplantar keratoderma and woolly hair [43]. Woolly hair associated with striate keratoderma and cardiomyopathy is called Carvajal disease and caused by a recessive deletion mutation in desmoplakin which links desmosomal adhesion molecules to intermediate filaments of the cytoskeleton [44].

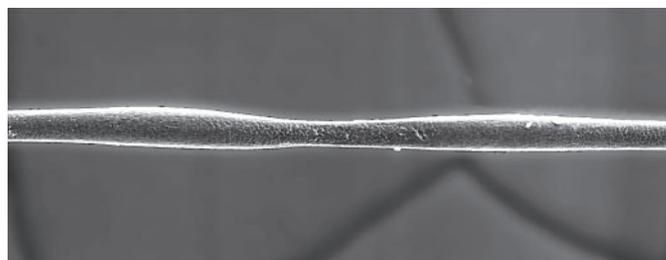
### **Metabolic Disorders and Neurological Syndromes with Hair Shaft Alterations**

Metabolic disorders with alopecia are numerous including multiple carboxylase deficiency, homocystinuria, Hartnup disease, phenylketonuria, citrullinemia, argini-

nosuccinase deficiency, acrodermatitis enteropathica and Menkes disease. Recently, abnormally fine, sparse and slow-growing hair which lacked luster and was coarse in texture was reported in congenital disorders of glycosylation (CDG type 1) [45]. Light-microscopic investigations showed trichorrhexis nodosa and torsion of the shaft along the longitudinal axis. CDG syndromes are a group of genetic, multisystemic disorders with autosomal recessive inheritance characterized by defective biosynthesis of the glycan moiety of glycoproteins.

Classical Menkes disease or Menkes kinky hair syndrome is an X-linked recessive multisystemic disorder. Four types of Menkes disease can be distinguished. The severe classical form and the mildest, called occipital horn syndrome, comprise more than 90%. The two additional types are classified as a moderate and a mild form. The latter two rather reflect clinical transitions between Menkes disease and occipital horn syndrome than fully independent entities. As a rule, only males are affected although a few females have been reported to express the disease due to a variety of genetic defects within the X-chromosome. In more than 90%, the natural course of the disease leads to death in early infancy in affected males. In general, female carriers of the gene defect are phenotypically normal, but in 50% they do have hair shaft anomalies. The syndrome leads to progressive neurodegeneration, connective tissue abnormalities and abnormal hair. The color of the hair is most often reported as white, silver or gray, a result of marked reduction of melanin and an associated abundance of tyrosinase. Clinically the hair appears short, sparse, coarse, lusterless and twisted. Hair shaft abnormalities include pili torti and monilethrix, sometimes trichorrhexis and trichoptilosis. These structural changes are due to a defect in the copper-enzyme-dependent cross-linkage of disulfide bonds in the hair's keratin. Diagnosis is made by documenting low serum copper (below 25% of normal range) and low ceruloplasmin levels. Menkes disease is due to a defect in the copper homeostasis and transport system. ATP7A encodes for the copper-binding enzyme ATPase which is essential for intracellular copper transport and metabolism [46].

Giant axonal neuropathy is an autosomal recessive condition characterized by progressive degeneration of the central and peripheral nervous system. Children have curly hair and characteristic pilar alterations with pseudo-pili torti aspect occurring early in life before neuropathy is clinically present. Therefore hair abnormalities have an important diagnostic impact [47]. Recently, a defective protein, gigaxonin, has been identified, and different pathogenic mutations in the gigaxonin gene have



**Fig. 6.** Monilethrix.

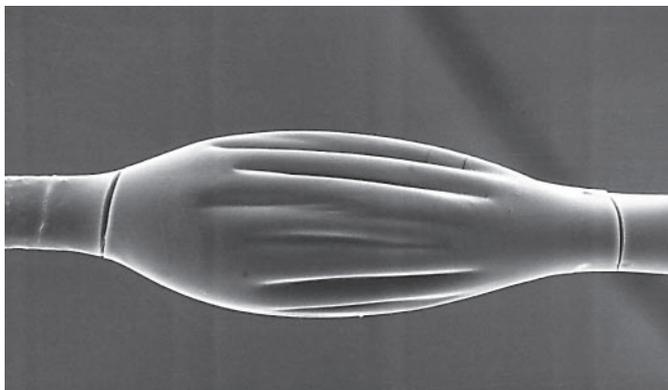
been reported as the underlying genetic defect. Gigaxonin seems to play a crucial role in the cross-talk between the intermediate filaments and the membrane network [48].

More than 30 cases of the Bjornstad syndrome (sensorineural deafness and pili torti) have been reported since its description in 1965. The clinical spectrum is rather heterogeneous, and hypogonadism and mental retardation may be associated in this syndrome. Both autosomal dominant and recessive inheritance patterns may occur. The responsible gene was mapped to the gene locus 2q34–q36 [49, 50]. As a rule, hair loss appears within the first 2 years of life and hearing loss develops in the first 3–4 years of life.

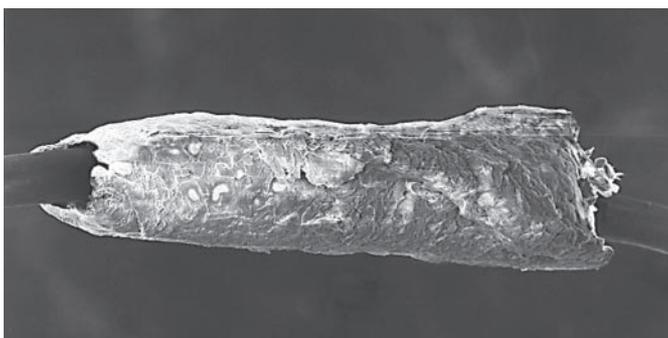
### **Isolated Genetic Hair Shaft Alterations**

Monilethrix is a rare inherited defect of the hair shaft resulting in hair fragility and dystrophic alopecia. Follicular keratosis especially in the occipital area is a prominent feature. In contrast to recent reports, mapping monilethrix to the type II epithelial and trichocyte keratin gene cluster on 12q13, we strongly excluded these candidate genes in a family with autosomal dominant monilethrix (fig. 6) [51].

Pili anulati (PA) are a rare hair shaft disorder characterized by discrete banding of hairs. There have been multiple reports of familial PA, segregating in an autosomal dominant fashion. A locus for PA at the telomeric region of chromosome 12q has been shown [52]. PA are defined by characteristic alternating light and dark banding in the hair shaft, due to air-filled spaces between the macrofibrillar units of the hair cortex, and are regarded as a congenital hair shaft disorder without increased hair fragility. However Günther et al. [53] observed that with onset of hair thinning due to androgenetic alopecia, progressive reduction of hair shaft diameter may cause increased fragility in PA.



**Fig. 7.** Hair shaft encircled with lacquer.



**Fig. 8.** Hair cast.

Multiple twisted and rolled body hairs that may develop into multiple large knots may appear as a minor variant of hair matting or felting. Scanning electron microscopy shows multiple hairs that originate from different hair follicles and roll and stick together centrally [54]. A genetic trait has been discussed.

*Pili bifurcati* is a rare hair shaft dysplasia with bifurcation of the hair shaft. The two characteristics that define the dysplasia are the fact that each bifurcation produces two separate parallel branches fusing again to form a single shaft, and that each branch of the successive bifurcations is covered with its own cuticle. In contrast, papillar tips that divide into several tips will produce multiple hair shafts that do not fuse again [55].

*Pili multigemini* is a developmental defect of hair follicles resulting from hairs with multiple matrices and papillae originating through one single pilosebaceous canal [56]. Linear distribution according to the lines of Blaschko may occur. Ring hair may be observed as isolated hair changes but also occurs with palmoplantar keratoderma [57].

## Acquired Hair Shaft Alterations

Acquired hair shaft alterations by cosmetic procedures are common. Various cosmetic products affect hair color and texture and can lead to structural alterations in the hair shaft. Clinical damage to the hair shaft occurs with the application of hair dye. Hair returns to its precoloring state and this requires 8 weeks [58]. Hair changes can occur by lacquer and gel application. Light microscopy may demonstrate that the hairs are encircled by a material with a glassy appearance that seems to splinter at several points (fig. 7). Scanning electron microscopy shows that the hairs are encased by a glue-like material, and under the lacquer normal cuticles are visible. Cosmetically induced hair shaft disorders are numerous and include matting of scalp hair, bubble hair and trichorrhexis nodosa. Hair sprays often contain polyvinylpyrrolidone and vinyl acetate. Hair styling gels and sculpturing gels have an extremely high-hold effect especially if they contain methacrylate copolymers [59].

Hair casts are characterized by white keratinous material adherent to hair shafts, and they can look very similar to nits from an infestation with *Pediculus capitis* (fig. 8). In contrast to nits, the small cylinders of 1–2 mm in length adhering to the hair shafts can easily be moved up and down along the hair shaft. Microscopic examination provides the correct diagnosis. An investigation on the incidence of hair casts was made in the Chengdu district of China. Of 3,548 individuals surveyed, 30.24% suffered from hair casts [60]. Long-term and frequent traction on hair with excessive force appears to be the major cause of hair casts, although inflammatory skin diseases on the scalp may also induce such lesions.

Bubble hair is an acquired hair shaft change induced by focal heating of damp. This physical trauma is sufficient to cause bubbles forming inside the hair fibers which results in weak, dry and brittle hair which breaks easily [61].

As shown in this review hair shaft diseases are rather heterogeneous, and a structured diagnostic approach is necessary to make the exact diagnosis.

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