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REVIEW

Unraveling the Molecular Mechanisms of Hair and Nail Genodermatoses

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Inherited hair and nail diseases have long been considered a group of rare and obscure disorders with a largely unknown genetic basis. In the postgenomic era, a large portion of the genes that are responsible for these genetic disorders has been identified, yielding new insights into the complex molecular pathways that regulate the development and biological function of epidermal appendages. This article reviews the recent progress accomplished in this field and discusses the novel clinical and experimental observations in several hair and nail genodermatoses.

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During the past decade we have witnessed an unprecedented explosion in molecular biology and genetic research that has helped refine our understanding of the pathogenesis of many human diseases. The wide application of molecular techniques in the field of dermatology has elucidated many biological functions of the skin such as the structural role of cytokeratins and adhesion molecules, the composition of the dermoepidermal junction, and the molecular mechanisms of pigmentation. One of the most exciting areas of cutaneous research has focused on the biology of skin appendages and particularly of the hair follicle because of its involvement in a variety of skin disorders and its increasingly recognized role in epidermal homeostasis, wound healing, and tumorigenesis.

Genetic research has shed new light on the basic molecular mechanisms that underlie the morphogenesis, differentiation, and cycling of the hair follicle and has identified a number of novel genes or molecules that are involved in these complex biological processes. Genetic hair diseases are caused by mutations in specific genes that encode structural molecules, enzymes, adhesion molecules, transcription factors, or morphogenetic factors of the hair follicle.[1] The molecular pathways that regulate the development of the nail are less understood, but considerable information is beginning to come forward from the study of single gene disorders with nail involvement such as pachyonychia congenita and nail patella syndrome. In this article we discuss the inherited hair and nail diseases with a known genetic defect and review their clinical and molecular aspects (**Table**).

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ECTODERMAL DYSPLASIAS

Ectodermal dysplasias are a heterogeneous group of more than 50 rare inherited disorders distinguished by the impaired development of ectodermal appendages. Their genetic basis is largely unknown, but recent evidence implicates a genetic defect in the signaling pathways that regulate ectodermal organogenesis.[2] The most common types of ectodermal dysplasia are the anhidrotic/hypohidrotic type and the hidrotic type.

Anhidrotic/hypohidrotic ectodermal dysplasia (EDA), also termed *Christ-Siemens-Touraine syndrome*, is characterized by the triad of hypotrichosis, abnormal teeth, and complete or partial absence of sweat glands.[3] Affected individuals develop heat intolerance due to reduced or absent sweating and often present with episodes of hyperthermia or unexplained fever in infancy or childhood. The hypoplastic lacrimal glands of the respiratory system cause persistent, foul-

Inherited Hair and Nail Diseases With a Known Genetic Defect*

Disease	MIM No.	Locus	Gene/Gene Product
Ankyloblepharon, ectodermal defects, cleft lip palate syndrome	106260	3q27	*p63* Gene
Argininosuccinic aciduria	207900	7cen-q11.2	Argininosuccinic acid lyase
Atrichia with papules (congenital alopecia universalis)	203655	8p21.2	*Hairless* gene
Cartilage-hair hypoplasia	250250	9p21-p12	*RMRP* gene
Giant axonal neuropathy 1 (GAN1)	256850	16q24.1	Gigaxonin
Griscelli syndrome	214450	15q21	*Myosin-Va* gene
Ectodermal dysplasia—anhidrotic/hypohidrotic type (autosomal forms)	224900	2q11-q13	downless (*dl*) gene/EDAR receptor
Ectodermal dysplasia—anhidrotic/hypohidrotic type (X-linked forms)	305100	Xq12-q13	*EDA* gene/ectodysplasin (epithelial morphogen)
Ectodermal dysplasia—hidrotic type (Clouston syndrome)	129500	13q11-q12	*GJB6* gene/connexin-30
Ectodermal dysplasia—Margarita Island type	225060	11q23-24	Cell-cell adhesion molecule/herpesvirus receptor PVRL1
Ectodermal dysplasia with skin fragility	604536	1q32	Plakophilin-1 (PKP1)
Ectodermal dysplasia—hypohidrotic type with immune deficiency	300291	Xq28	*IKK-γ* gene
Menkes kinky hair	309400	X12q-q13	*ATP7A* gene/MNK-copper binding protein
Monilethrix	158000	12q13	hHb6 and hHb1 hair keratins
Netherton syndrome	256500	5q32	*SPINK5* gene/LEKTI protein (serine protease inhibitor)
Nail-patella syndrome	161200	9q34.1	LMX1B homeodomain protein
Pachyonychia congenita type 1 (Jadassohn-Lewandowsky type, PC-1)	167200	17q12-q21 12q13	Keratins 16 or K16a isoform
Pachyonychia congenita type 2 (Jackson-Lawler type, PC-2)	167210	17q12-q21 12q13	Keratins 17 or K6b isoform
Trichodentoosseous syndrome	190320	17q21.3-q22	Homeo box–gene *DLX3*
Trichorhinophalangeal syndrome (types I, III)	190350 190351	8q24.12	*TRPS1* gene/transcription factor
Trichothiodystrophy	601675	19q13.2-q13.3	*TFIIH*/XPD and XPD helicases (involved in DNA repair and transcription initiation)
T-cell immunodeficiency, congenital alopecia, nail dystrophy (human nude phenotype)	601705		Winged-helix-nude (*whn*) gene/transcription factor
Dyskeratosis congenita—X-linked (Zinsser-Cole-Engman syndrome)	305000	Xq28	Dyskerin (DKC1)—involved in cell cycle and nucleolar function

*MIM indicates Mendelian Inheritance in Man. Based on McKusick VA, ed, Online Mendelian Inheritance in Man.[1]

smelling nasal discharge and predispose to chronic respiratory infections.[4] Stomatitis, diarrhea, and recurrent otitis can also occur due to defective mucous gland function of the mouth, gastrointestinal system, and ear canal, respectively. The hair is usually hypopigmented, sparse, and short, and the teeth can be either entirely absent or partially present with a characteristic conical or peg-shaped appearance. Furthermore, the skin is smooth, soft, and dry and frequently appears finely wrinkled and hyperpigmented around the eyes. In the most complete forms, patients have a distinctive pathognomonic facies with sparse hair, saddle nose, frontal bossing, sunken cheeks, and protrusive lips. The disease is mainly inherited through an X-linked recessive trait, even though autosomal dominant and recessive forms also exist and are phenotypically indistinguishable from the X-linked entity.[5] Female carriers do not develop the full syndrome, but they can present with dental defects, sparse hair, and a patchy or mosaic pattern of hypohidrosis following the Blaschko lines.[6]

The causative gene (*EDA* gene) for the X-linked form of hypohidrotic ectodermal dysplasia has been identified on chromosome Xq12-q13 and encodes a novel transmembrane protein, ectodysplasin, which seems to play a critical role in epithelial-mesenchymal interactions during hair follicle morphogenesis.[7] The gene is evolutionary highly conserved, showing a protein homology of 94.6% with the mouse *Tabby* strain of equivalent phenotype.[8] It is expressed in a variety of tissues including the developing and mature appendages. Although the original complementary DNA (cDNA) encoded a 150-kd type II transmembrane protein, recent evidence has shown that the *EDA* gene undergoes extensive alternate splicing, producing several isoforms: the original shortest *EDA-O* form, the longest *EDA-A* form, and 5 others (*EDA-B*, *EDA-C*, *EDA-D*, *EDA-E*, and *EDA-F*).[9] All transcripts have a type II orientation (ie, their N-terminus is located intracellularly) and also share a similar structure with a short predicted intracellular domain, a single transmembrane domain, and extracellular domains of variable lengths. The longest isoform, the *EDA-A*, includes an extracellular collagenous domain of 19 Gly-X-Y repeats and a motif conserved in the tumor necrosis factor (TNF)–related ligand family.[10] Recently, the gene for the autosomal dominant and recessive forms of *EDA* was isolated and termed *downless* (*DL*) after the mouse homologue (*dl*).[11] This gene encodes for a transmembrane protein of the TNF receptor superfamily and most likely functions as a receptor for the ectodysplasin isoform *EDA-A1* (*EDAR*). A related but distinct TNF receptor for the *EDA-A2* isoform has been recently identified and designated X-linked ectodysplasin-A2 receptor (*XEDAR*).[12] These findings suggest that the *EDA/DL* genes activate

an important signaling pathway during the early morphogenetic stages of ectodermal appendage formation.

Hidrotic ectodermal dysplasia (HED), also termed *Clouston syndrome*, is an autosomal dominant disorder characterized by nail dystrophy, hair defects, and keratoderma of the palms and soles. Several reports have described an extensive kindred of French extraction that migrated to the northern United States, Canada, and Scotland.[13] In contrast to the hypohidrotic type, patients with HED have a normal sweat and sebaceous gland function. The prominent feature of this syndrome is the dystrophy of the nails, which can be the only obvious manifestation of the disease in about one third of affected patients. The nails are thickened, striated, and often discolored. They grow slowly and are frequently affected by persistent paronychial infections that can partially or completely destroy the nail matrix. In addition, the skin appears thickened under the free nail edges, over the finger joints, and occasionally on the knees and joints. Palmoplantar keratoderma occurs frequently and can sometimes extend to the dorsal aspects of the hands and feet. Although normal appearing in infancy, the hair becomes sparse, fine, and brittle. Multipoint linkage analysis has mapped the disease to the pericentromeric region of chromosome 13q (13q11-12).[14] In a recent study, Lamartine et al[15] demonstrated missense mutations in the *GJB6* gene encoding connexin-30 (*CX-30*). The connexins are structural components of the intercellular gap junctions and have been linked to several other inherited skin disorders, ie, Vohwinkel syndrome (mutant *GJB2*) and erythrokeratodermia variabilis (mutant *GJB3*).[16,17] Aside from HED, mutations of the *GJB6* gene have been also found in dominant forms of nonsyndromic deafness, implying a diverse effect of mutant *CX-30* in the epidermis and the auditory cells in these two different pathologies.[18]

Hypohidrotic ectodermal dysplasia with skin fragility is a novel form of ectodermal dysplasia characterized by skin fragility, nail dystrophy, and sparse hair. During the first years of life the affected patients develop palmoplantar keratoderma along with a reduced sweating capacity. Electron microscopy studies of the skin demonstrate loss of keratinocyte-keratinocyte adhesion and a reduction in the size and number of desmosomes, particularly at the lower suprabasal layer.[19] This autosomal recessive disorder has been recently attributed to homozygote mutations of the desmosomal plaque plakophilin-1 (*PKP1*) gene located on chromosome 1q32.[20] Plakophilin is an entirely intracellular protein that binds the keratinocyte cytoskeleton to the intracellular component of the desmosomal cadherins, particularly desmocollin 1. It is preferentially expressed in the spinous layer of the epidermis and the outer root sheath of the hair follicle.[21] As a member of a multigene family homologous to the armadillo signal transduction proteins of *Drosophila*, plakophilin may have an additional function as a signaling molecule aside from its structural role in desmosomal stabilization.

MONILETHRIX

Monilethrix is probably the only congenital hair disease that has been so far attributed to a defect in hair keratins (hard α-keratins). It is mainly an autosomal dominant disease, although autosomal recessive cases have been reported in several pedigrees.[22] Monilethrix may occur alone or in association with physical retardation, keratosis pilaris, cataracts, syndactyly, and nail or teeth abnormalities. The disease usually develops during the first months of life and is characterized by the occurrence of very short, sparse, and brittle hair on the scalp emerging from follicular hyperkeratotic papules. In milder forms, the clinical findings are limited to the occiput and the nape of the neck, but in more severe cases the entire scalp, eyelashes, eyebrows, and the general body hair can be affected. The microscopic morphologic features of the hair show elliptical nodes with a regular periodicity (0.7-1 mm), which accounts for the "beaded" appearance of the affected hair under light microscopy. The internode segments of the hair shaft are constricted and break easily. Ultrastructural analysis of the affected hair shafts has demonstrated defects in the microfibrillar structure of the hair shaft, implicating a structural abnormality of hair keratins in the pathogenesis of the disease.[23] The disease was mapped by linkage analysis on chromosome 12q13, the location of the type II keratin gene cluster.[24] At present, causative mutations have only been found in two type II cortex keratin genes, *hHb6* and *hHb1*.[25] The mutations occur primarily at mutation hot spots of the helix termination motif of these two hair keratins and represent point mutations that lead to single amino acid substitutions (ie, *hHb6*/Glu413Lys substitution). A point mutation (ie, *hHb6*/Glu402Lys mutation) in the helix initiation motif of keratin *hHb6* was recently identified in a large 3-generation Swedish family and was linked to a more severe phenotypic expression of the disease.[26] Interestingly, type I keratin mutations have not been identified in monilethrix families, which is a considerable difference from other diseases involving epithelial keratins in which the rate of pathogenic mutations is equal in both types of keratin (I and II).[27]

Trichorrhexis invaginata (TI) is a distinct hair shaft abnormality that occurs sporadically or as part of Netherton syndrome (NS), an autosomal recessive disorder combining ichthyosis, atopic diathesis, and hair shaft abnormalities.[28,29] The primary defect in TI involves an abnormal keratinization of the hair shaft in the keratogenous zone, allowing the intussusception of the fully keratinized distal shaft into the incompletely keratinized soft proximal hair shaft. This leads to the typical "ball and socket" appearance and, if the shaft is fractured, a golf tee–shaped distal end is produced. In NS, the affected hairs are short and sparse with irregular distribution on the scalp. The ichthyosis appears in different forms (eg, ichthyosis vulgaris or X-linked type), although the most common presentation is polycyclic ichthyosis linearis circumflexa. Ultrastructural features of the hair in NS show a premature secretion of lamellar body contents in addition to an abnormal transformation of the lamellar body–derived lamellae into mature lamellar membrane srtuctures.[30] These features may explain the disrupted permeability barrier in NS and account for the hypernatremia and dehydration in affected infants. By linkage analysis and homozygosity mapping in 20 families with NS, Chavanas et al[31] mapped the disease locus to chromosome 5q32. Subsequently, the *SPINK5* gene was mapped to the same critical region of 5q, thus making it a candidate gene for NS.[32] The *SPINK5* gene is expressed in a variety of human tissues such as the thymus, vaginal

epithelium, Bartholin glands, oral mucosa, tonsils, and parathyroid glands. It encodes a novel human serine proteinase inhibitor, termed *LEKTI*, that possibly contributes to the anti-inflammatory and antimicrobial protection of mucous epithelia.[33] A mutation search in the *SPINK5* gene revealed 11 different mutations in 13 families with NS, most of which caused premature termination codons of translation and predicted messenger RNA (mRNA) instability. These results indicate the critical role of *SPINK5/LEKTI* in epidermal barrier function and immunity and also emphasize the importance of proteolysis in epithelia formation and hair morphogenesis. In addition, the observed tissue specificity of *LEKTI* suggests a specific role in the thymus. Aberrant maturation of T cells in patients with NS may deregulate the T_H2 immune responses to allergens and lead to the atopic diathesis and elevated IgE levels seen in these patients. The structural resemblance of *LEKTI* with other differentiation factors, ie, agrin or thrombin, supports the possibility of a comparable function of *LEKTI* in the regulation of various differentiation processes, for example, T-lymphocyte maturation.[34]

TRICHOTHIODYSTROPHY

Trichothiodystrophy (TTD) is a rare disorder of autosomal recessive inheritance in which patients have sulfur-deficient brittle, short, and sparse hair that frequently break transversely (trichoschisis).[35] The salient feature of this disorder is the alternating light and dark bands along the hair shaft that give a typical "tiger tail" appearance of the shaft under polarized light microscopy. An amino acid analysis of affected hair shafts has demonstrated a decrease in cysteine and serine levels and an irregular distribution of calcium, the latter being normally present in the dark bands and absent in the light bands.[36] Trichothiodystrophy is seen in a number of interrelated neuroectodermal syndromes showing defective synthesis of high-sulfur matrix proteins and manifesting with brittle hair, intellectual impairment, decreased fertility, and short stature (BIDS); ichthyosis (IBIDS); and photosensitivity (PIBIDS).[37] Other disorders associated with TTD are follicular keratosis, erythroderma, hypohidrosis, ocular dysplasia, dental caries, and cryptorchidism. Almost half of the cases have photosensitivity to UV-B and UV-A radiation, exhibiting a DNA excision repair defect similar to the XPD and, in very few patients, to the XPB complementation group of xeroderma pigmentosum (XP).[38]

Besides these 2 complementation groups, an exceptional TTD complementation group has been identified and designated TTD-A.[39] In patients without photosensitivity, the DNA repair capacity can vary significantly from normal to severely defective.[40] The repair deficient form of TTD results from mutations in the genes *XPD* (*ERCC2*) or, less often, *XPB* (*ERCC3*) that encode helicases of the transcription/repair factor *TFIIH*.[41] This is a multisubunit protein complex involved in RNA polymerase II transcription initiation and nucleotide excision repair, which removes a variety of photochemical lesions, including the UV-induced photoproducts. Because of its dual function as a helicase and a transcription factor, the *TFIIH/XPD-XPB* complex could exert its influence on many diverse proteins, accounting for the varied nature of TTD syndromes. In fact, it has been hypothesized that the developmental abnormalities of TTD, such as the neurologic manifestations and the brittle hair and nails, are more related to the defective basal transcription and the depressed mRNA synthesis of certain genes in differentiated cells rather than the DNA repair deficiency.[42]

In the third complementation group of TTD (TTD-A), no *TFIIH* mutations have been found, but the significant reduction of *TFIIH* concentration demonstrated by immunoblot and immunofluorescence analyses suggests the presence of a mutation in a gene determining the stability of the complex.[43] In contrast to XP, the defect in DNA repair mechanisms in patients with TTD does not seem to increase their susceptibility to skin cancer or freckling.[44] This is one of the most intriguing questions in DNA repair research because both diseases have an apparently similar DNA repair defect. Some investigators have suggested that the DNA repair deficiencies in TTD are more moderate, possibly because of the attenuation of sunlight by the thickened ichthyotic skin.[45] In view of the lack of correlation between the severity of clinical phenotype and DNA repair deficiency, others have attributed these differences to the subtle transcriptional defects of TTD that prevent the expression of critical genes for the induction of melanogenesis and skin cancer.[45] These observations are somewhat contradicted by the demonstration of a susceptibility of the TTD mutant mouse to UV-B–induced carcinogenesis.[46]

MENKES KINKY HAIR SYNDROME

Menkes kinky hair syndrome is an X-linked recessive disorder characterized by progressive neurologic dysfunction, musculoskeletal abnormalities, and low or absent copper and ceruloplasmin plasma levels.[47] The hair is light colored, sparse, and lusterless with a "steel wool" quality. Pili torti is the most prominent hair shaft abnormality, demonstrating a flattened appearance under light microscopy with multiple twists of 180° around the long axis of the shaft. Pili torti can be also detected in female heterozygotes, who also exhibit abnormal copper metabolism in skin fibroblasts but normal serum copper levels. The gene for Menkes syndrome has been designated *ATP7A* and is located on Xq12-q13.[48] It encodes for a copper-transporting P-type adenosine triphosphatase (MNK protein) that regulates intracellular copper homeostasis and controls the function of copper-requiring enzymes. Findings from Northern blot experiments have shown that the MNK RNA is expressed in a variety of cell types and tissues with the exception of the liver where the expression is reduced or absent. This is consistent with the relative lack of liver involvement in Menkes disease. The MNK protein localizes predominantly at the trans-Golgi network. In basal copper conditions, the protein cycles between the trans-Golgi network and the plasma membrane, but under excessive copper conditions, the MNK rapidly relocalizes to the plasma membrane where it removes copper from the cytoplasm by possibly transporting it in its cycling vesicles.[49]

TRICHORRHEXIS NODOSA–ARGININOSUCCINIC ACIDURIA

The most common hair shaft anomaly leading to hair fracture is trichorrhexis nodosa, a distinctive disorder char-

acterized by the presence of grayish white nodules under microscopy and increased hair fragility. This is due to the disruption of cuticular cells and the longitudinal splitting of the cortical fibers, which under light microscopy give the "nodular" appearance of two interlocked brushes pushed end to end at the fracture point. Trichorrhexis nodosa is frequently seen as a response to physical injury, but it has also been related to several congenital hair disorders, eg, Menkes kinky hair syndrome, NS, and pili annulati. Although generally considered rare, the occurrence of congenital trichorrhexis nodosa should prompt an investigation of an underlying metabolic disorder such as argininosuccinic aciduria. In this autosomal recessive condition, the lack of the enzyme argininosuccinase (argininosuccinic acid lyase) leads to an accumulation of the precursor argininosuccinic acid. Approximately 50% of affected patients, especially those with the late-onset form, have trichorrhexis nodosa and present with dull, matted hair that fractures easily and leaves short stubby broken ends and areas of partial alopecia.[50] These hair defects are associated with psychomotor retardation, cerebellar ataxia, and a marked increase of argininosuccinic acid levels in the blood, urine, and cerebrospinal fluid. The locus of the gene for argininosuccinuria has been identified on 7cen-q11.2.[51]

CONGENITAL ATRICHIA WITH PAPULES

One of the most extensively investigated inherited alopecia in terms of its molecular basis has been the congenital atrichia with papular lesions (also termed *congenital alopecia universalis* by some authors, although it is unrelated to alopecia areata). In individuals affected with this form of alopecia, hairs are typically absent from the scalp, and patients are nearly completely devoid of eyebrows, eyelashes, and axillary and pubic hair after shedding their natural hair shortly after birth. Follicular cysts and milia-like lesions appear on the skin in later life.[52] Affected individuals do not show any physical or mental retardation, and their teeth, nails, and sweating are normal. In most afflicted families the disease follows an autosomal recessive mode of inheritance.

After a genome-wide search by homozygosity mapping, the responsible gene was isolated on chromosome 8p12 and was identified as the human homologue of the mouse *hairless* gene that derives from a murine model with striking similarities with the human phenotype.[53] Both the human and the mouse *hairless* gene possess a zinc finger domain, which suggests that it may act as a transcriptional regulator with specific nucleic acid recognition properties. Several mutations have been identified in the human *hairless* gene in atrichia families from around the world.[54,55] The precise function of hairless protein remains elusive. In the mutant hairless mice, the loss of *hairless* gene function causes an abnormal and premature catagen followed by follicular disintegration and subsequent formation of keratinous cysts.[56] The hair matrix cells undergo massive apoptosis and disconnect from the overlying epithelial sheath. As a consequence, the hair bulb and the dermal papillae remain stranded in the dermis, and critical signals between the papillae and the epithelial stem cells at the bulge are not transmitted, causing the cessation of further hair growth. In humans, the *hairless* gene seems to function at the cellular transition from the natal to the first postnatal hair cycle.[57] If the gene is mutated, the initial hair cycle will be induced, but all subsequent hair cycles will fail to occur, resulting in alopecia. This evidence suggests the importance of the *hairless* gene in regulating the molecular signals of the hair-cycling process and in maintaining follicular integrity.[58]

HUMAN NUDE PHENOTYPE

Recently the human counterpart of the nude mouse phenotype was identified. The nude mouse is characterized by a congenital absence of hair and a severe immunodeficiency, resulting from mutations in the winged-helix-nude (*whn*) gene, a member of the forkhead/winged-helix transcription family. The simultaneous occurrence of severe functional T-cell immunodeficiency, congenital alopecia, and nail dystrophy in two affected sisters led to the recognition of the human phenotype of the nude mouse (Mendelian Inheritance in Man [MIM] 601705).[59] Similar to the nude mouse model, the genetic defect involves the *whn* gene, which probably directs cell fate decisions and is regulated developmentally.[60] In mammals it is expressed specifically in the epithelial cells of the skin and the thymus where it helps maintain a balance between growth and differentiation. In the human hair follicle the expression of *whn* is localized to the differentiating cells of the hair follicle precortex and the innermost cell layer of the outer root sheath. The exact mechanism by which a defective *whn* gene causes hair loss is unclear, although it may relate to impaired keratinization.[61]

PACHYONYCHIA CONGENITA

Pachyonychia congenita (PC) consists of a group of inherited ectodermal disorders characterized by hypertrophic nail dystrophy. The two most common forms of PC are PC-1 (or Jadassohn-Lewandowsky type) and PC-2 (or Jackson-Lawler type), which are both inherited through an autosomal dominant trait. In the PC-1 form, the nails are normal in birth, but within several months they become thickened and discolored, with increased transverse curvature and subungual hyperkeratosis ("pincer nail" effect).[62] Typical associated features include focal symmetric palmoplantar keratoderma with or without hyperhidrosis, angular cheilitis, follicular hyperkeratosis, hoarseness, and oral leukokeratosis. Compared with the phenotype of PC-1, the PC-2 form has less severe nail thickening, minimal oral involvement, and milder keratoderma.[63] It is readily distinguished by the presence of multiple steatocystomas (manifesting usually during puberty), pili torti, and, in some cases, erupted teeth at birth. We now know that the genetic cause of PC are mutations in 4 differentiation-specific keratin genes that are expressed by the affected epithelia. PC-1 is due to mutations of the keratin 16 (*K16*) gene located on chromosome 12 or its expression pattern, the *K6a* isoform of *K6* located on chromosome 17.[64] Similarly, PC-2 is due to mutations in keratin 17 (*K17*) gene or the *K6b* isoform, which are located on chromosomes 17 and 12, respectively.[65] Most of the reported mutations affect the highly conserved peptide sequences at either end of the helical rod

domain of the keratin molecule, sites that are critical for the intermediate filament assembly. Phenotypic differences, however, have been found in pedigrees carrying mutations in the *K16* or *K17* genes. For example, *K16* mutations can present as focal keratoderma in the absence of nail changes or other features of PC-1.[66] Similarly, *K17* gene mutations have been identified in families with steatocystomas without any nail or other ectodermal abnormalities.[67] The reasons for these differences are unknown, but variations in severity may correspond to polymorphism in ancillary components of the cytoskeleton or to the existence of mutations in internal parts of the rod domain rather than in the helix boundary motifs.[68] The latter hypothesis is supported by the detection of mutations in the central portion of the *K16* rod domain in a case of PC with delayed onset of symptoms (age, >6 years).[69] In addition to the location of the mutation within the keratin gene, the diversity of clinical features suggests that other genetic or environmental unknown factors could be crucial in the ultimate clinical expression of the disease.

NAIL-PATELLA SYNDROME

In the nail-patella syndrome (hereditary osteoonychodysplasia), nail changes are associated with skeletal and kidney abnormalities. In a typical case, the nails are grossly defective, being smaller and never reaching the free nail edge. Triangular lunulae, when present, are considered pathognomonic of the disorder.[70] Thumbnails are almost always affected, and the rest of nails, if affected, have a decreasing degree of severity from the index to the little finger. In addition to the nail changes, the patellae are smaller than normal or rudimentary, causing instability of the knees. Chronic glomerulonephritis with proteinuria and collagen fibril deposition is seen in one third of the patients.[71] Important diagnostic signs are the posterior iliac horns that are visible on radiographic examination and Lester iris (an irregularly hyperpigmented pupillary border). The genetics of the disease have been recently elucidated with the identification of the causative gene on the long arm of chromosome 9 (9q34.1).[72] It encodes a transcription factor (*LMX1B*) that belongs to the LIM-homeodomain family, members of which are known to be important in the dorsoventral patterning of the vertebrate limb.[73] Targeted disruption of the gene in *LMX1B* mutant mice led to skeletal defects, including hypoplastic nails, absent patellae, and a unique form of renal dysplasia.[74,75] The function of this gene directly regulates the coordinated expression of α3 (type IV) and α4 (type IV) collagen, which is required for the morphogenesis of the glomerular basement membrane.[76] Mutations of this gene disrupt the integrity of the glomerular basement membrane and contribute to the nephrosis and renal pathology seen in nail-patella syndrome.

CONCLUSIONS

The ongoing discovery of the genes that are implicated in the pathogenesis of inherited hair and nail disorders has literally transformed our knowledge of the structure and the biology of epidermal appendages. It has also demonstrated the intricate and perplexing interplay among many different genes that regulate appendageal growth and differentiation. Future developments that can be expected in this exciting field include the identification and characterization of causative genes in additional diseases with a known genetic locus such as Marie Unna hypotrichosis, hypotrichosis simplex, and keratosis follicularis spinulosa decalvans.[77-79] In Marie Unna hypotrichosis (MIM 1465500), for example, a disorder characterized by hair shaft anomalies and a progressive male pattern hair loss in adulthood, the responsible gene has been mapped on chromosome 8p21, in the vicinity of the *hairless* gene, and its identification may give valuable insight into the genetic mechanisms underlying other types of baldness.[77] In addition, existing mouse models with hair or nail abnormalities that share phenotypic similarities with counterpart human diseases will complement candidate gene approaches in human patients.[57] Future molecular studies will also elucidate the genetic component of several diseases, such as alopecia areata and androgenetic alopecia, which do not exhibit the classic mendelian inheritance but possibly follow a polygenic or complex genetic trait. The high prevalence of the trait, the Gaussian curve of distribution, and the increased occurrence of the disease in first-degree relatives of affected individuals provide strong evidence in favor of a polygenic inheritance in these two common disorders.[80,81]

As we extend our knowledge over the delicate and complex molecular mechanisms that control hair and nail growth, we will undoubtedly introduce novel pharmaceutical or gene-based therapeutic strategies that will treat effectively various diseases of the hair and nails. Gene therapy for such disorders may not soon appear in the clinic, but the active research in this field certainly justifies the optimism for their effective management in the future.

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