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Genetic hair and nail disorders

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Abstract Hair and nails are skin appendages that share with other ectodermal tissues a common developmental pathway. Inherited disorders affecting these two structures therefore very often involve other epithelial components and present with multiple anomalies, generating both physical and psychological distress among patients and their families. The present review briefly describes major recent advances in our understanding of hair and nail genodermatoses.

Absence of hair or nails is obviously compatible with normal lifespan, yet patients often experience the loss of either one of these two skin appendages as a very detrimental condition, affecting many aspects of their personal and social life. In addition, today little relief can be offered to affected individuals. During the last decade, through the study of rare genetic disorders, much has been learned about the physiology of hair and nail development, generating much hope for better and more rationale treatment approaches in the future. A complete discussion of all hereditary nail and hair disorders is beyond the scope of this article. The following review succinctly describes recent and major avenues of research in hair and nail inherited disorders, based on a number of selected examples. Tables 1-3 present a more exhaustive list of disorders for which mutations in specific genes or linkage to specific chromosomal loci have been described. Relevant references can be searched for at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM. General guidelines for genetic testing for the various diseases in this article can be found at http://www.genetests.org/. Because many of the disorders mentioned in this review are exceedingly rare, genetic testing is often exclusively offered by the research laboratories investigating those diseases.

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Hair follicle development

Hair follicles start to develop during the 10th week of gestation, when a mesoderm-derived signal induces overlying ectodermal cells to form the primordial hair follicle bud. Subsequently, specialized mesenchymal cells form the dermal papilla located at the bottom of the growing hair follicles and responsible for generating mesenchymal growth and differentiation factors.[1] Competition between various morphogenetic stimulatory (eg, sonic hedgehog) and inhibitory proteins (eg, bone morphogenetic proteins) eventually determines the final distribution and density of hair follicles.[2,3] At birth, about 5 million of hair follicles cover the body surface and no additional follicles are formed thereafter. The mature hair follicle, however, continues to grow in a cyclical fashion, progressing through 3 distinct phases known as anagen (growth phase), catagen (regression phase), and telogen (resting phase). Hair cycling recapitulates follicular morphogenesis in many aspects

Table 1 Genodermatoses with prominent hair anomalies

Disorder	Inheritance	MIM	Locus	Gene
Isolated hair disorders				
AUC	AR	203655	8p21	*HR*
APL	AR	209500	8p21	*HR*
Congenital generalized hyportrichosis	XLR	307150	Xq24-q27.1	Unknown
Hyportrichosis simplex	AD	146520	6p21	*CDSN*
	AD	605389	18p11.32	Unknown
Localized autosomal recessive hypotrichosis	AR	607903	18q12	*DSG4*
Loose anagen syndrome	AD	600628	12q13	*K6hf*
Marie Unna hypotrichosis	AD	146550	8p21	Unknown
Syndromic hair disorders				
Androgen insensitivity syndrome	XLR	313700	Xq11-q12	*AR*
Argininosuccinicaciduria	AR	207900	7cen-q11.2	*ASL*
Bamforth-Lazarus syndrome	AR	241850	9q22	*FKHL15*
Bazex syndrome	XLD	301845	Xq24-q27	Unknown
Berardinelli-Seip syndrome	AR	269700	9q34	*AGPAT2*
			11q13	*BSCL2*
Biotinidase deficiency	AR	253260	3p25	*BTD*
Björnstad syndrome	AR	262000	2q34-q36	Unknown
Chondrodysplasia punctata	XLD	302960	Xp11.23	*EBP*
Cornelia de Lange syndrome	AD	122470	3q26.3	*NIPBL*
Carvajal syndrome	AR	605676	6p24	*DSP*
Giant axonal neuropathy	AR	256850	16q24.1	*GAN*
Griscelli syndrome	AR	607624	15q21	*MYO5A*, *RAB27A*
Hypohidrotic ectodermal dysplasia	XLR	305100	Xq12-q13	*EDA*
	AD	224900	2q11-q13	*EDAR*
Hypotrichosis with juvenile macular dystrophy	AR	601553	16q22.1	*CDH3*
Hypotrichosis-lymphedema-telangiectasia syndrome	AR	607823	20q13.33	*SOX18*
Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis	AR	607626	3q27-q28	CLDN1
Keratosis follicularis spinulosa decalvans cum ophiasis	XLR	308800	Xp22.2-22.13	Unknown
Keratitis-ichthyosis-deafness syndrome	AD	148210	13q11-q12	*GJB2*, *GJB6*
Leprechaunism	AR	246200	19p13.2	*INSR*
Menkes disease	XLR	309400	X12q-q13	*ATP7A*
Naxos disease	AR	601214	17q21	*JUP*
NTS	AR	256500	5q32	*SPINK5*
Oculocutaneous albinism, type I	AR	203100	11q14-q21	*TYR*
Oculocutaneous albinism, type II	AR	203200	15q11.2	*P*
Oculodentodigital dysplasia	AD	164200	6q21-q23.2	*GJA1*
Orofaciodigital syndrome	XLD	311200	Xp22.3	*CXORF5*
Progeria syndrome	AD	176670	1q21.2	*LMNA*
Vitamin D–resistant rickets	AR	277440	12q12-q14	*VDR*
Waardenburg syndrome I	AD	193500	2q35	*PAX3*
Waardenburg syndrome IIA	AD	193510	3p14.1	*MITF*
Werner syndrome	AR	277700	8p12-p11.2	*RECQL2*

because it involves the proliferation and differentiation of epithelial stem cells in response to dermal papilla-derived signals.[4,5] A number of additional anatomical, hormonal, nutritional, and genetic factors further modulate hair shaft size, shape, and color.[1] This developmental scheme forms the basis for the classification of inherited hair disorders into disorders of hair morphogenesis, hair cycling, and hair shaft structure. The dual role played by a number of molecules during hair morphogenesis and hair cycling accounts for the great deal of overlap existing between the different groups of hair genodermatoses.

Disorders of hair morphogenesis

In this group of disorders, abnormal hair is evident at birth and persists throughout life.

Hypotrichosis with juvenile macular dystrophy

This rare autosomal recessive disorder is characterized by short and sparse hair at birth, which predicts the later occurrence of progressive macular degeneration (Fig. 1), eventually leading to blindness during the first to fourth

Table 2 Genodermatoses with prominent nail anomalies

Disorder	Inheritance	MIM	Locus	Gene
Isolated nail disorders				
Isolated congenital nail dysplasia	AD	605779	17p13	Unknown
Syndromic nail disorders				
Brachydactyly, type B1	AD	113000	9q22	*ROR2*
Darier disease	AD	124200	12q23-q24.1	*ATP2A2*
Huriez syndrome	AD	181600	4q23	Unknown
Nail patella syndrome	AD	256020	9q34.1	*LMX1B*
Otopalatodigital syndrome, type I	XLD	311300	Xq28	*FLNA*
Pallister-Hall syndrome	AD	146510	7p13	*GLI3*
Pycnodysostosis	AR	265800	1q21	*CTSK*
Rubinstein-Taybi syndrome	AD	180849	16p13.3	*CREBBP*
Scleroosteosis	AR	269500	17q12-q21	*SOST*
Witkop syndrome	AD	189500	4p16.1	*MSX1*
Yellow nail syndrome	AD	153300	16q24.3	*FOXC2*

decade of life.[6] Histologically, a high ratio of vellus to terminal hair as well as a high number of regressing hair follicles have been reported. Hair microscopy reveals a number of morphological anomalies such as pili torti and pseudomonilethrix.[7] Normal hair shaft structure, however, has also been observed.[6] The disease maps to 16q21, which harbors a cluster of classical cadherins, the major components of adherens junctions. Deleterious mutations have

Table 3 Genodermatoses with combined hair and nail anomalies

Disorder	Inheritance	MIM	Locus	Gene
Cartilage hair hypoplasia	AR	250250	9p21-p12	*RMRP*
CHILD syndrome	XLD	308050	Xq28	*NSDHL*
Coffin-Lowry syndrome	XLD	306600	Xp22.2p.22.1	*RPS6KA3*
Costello syndrome	AD	218040	22q13.1	Unknown
Dyskeratosis congenita	XLR	305000	Xq28	*DKC1*
	AD	127550	3q21-q28	*TERC*
Ectodermal dysplasia – hidrotic type	AD	129500	13q11-q12	*GJB6*
Ectodermal dysplasia – Margarita Island type	AR	225060	11q23-24	*PVRL1*
Ectodermal dysplasia/skin fragility	AR	604536	1q32	*PKP1*
Ellis-van Creveld syndrome	AR	225500	4p16	*EVC, EVC2*
Epidermolysis bullosa (simplex, junctional, and dystrophic)	AR, AD	131760, 226700, 226650, 131750	12q13, 17q12, 6q22, 1q25, 3p31.3, 18q11.2, 10q24.3	*K5, K14, LAMA3, LAMB3, LAMC2, COL17A1, COL7A1*
Hay-Wells syndrome; Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome	AD; AD	106260; 129900	3q27	*p63*
Hereditary bullous dystrophy, macular type	XLR	302000	Xq27.3-ter	Unknown
Incontinentia pigmenti	XLD	308300	Xq28	*NEMO*
Lymphedema-distichiasis syndrome	AD	153400	16q24.3	*FOXC2*
Monilethrix	AD	158000	12q13	*hHb1, hHb6*
Naegeli-Franceschetti-Jadassohn syndrome	AD	161000	17q11.2-q21	Unknown
PC-1/PC-2	AD	167200	12q13	*K6a,K6b, K16, K17*
		167210	17q12-q21	
Rothmund-Thomson syndrome	AR	268400	8q24.3	*REQL4*
Sotos syndrome	Sporadic	117550	5q35	*NSD1*
T-cell immunodeficiency, congenital alopecia, and nail dystrophy	AR	601705	17q11-q12	*WHN*
Trichodentoosseous syndrome	AD	190320	17q21.3-q22	*DLX3*
Trichorhinophalangeal syndromes	AD	190350	8q22-8q24	*TRPS1 (EXT1)*
		150230		
		190351		
Trichothiodystrophy	AR	601675	19q13.2-q13.3	*TFIIH/XPD*

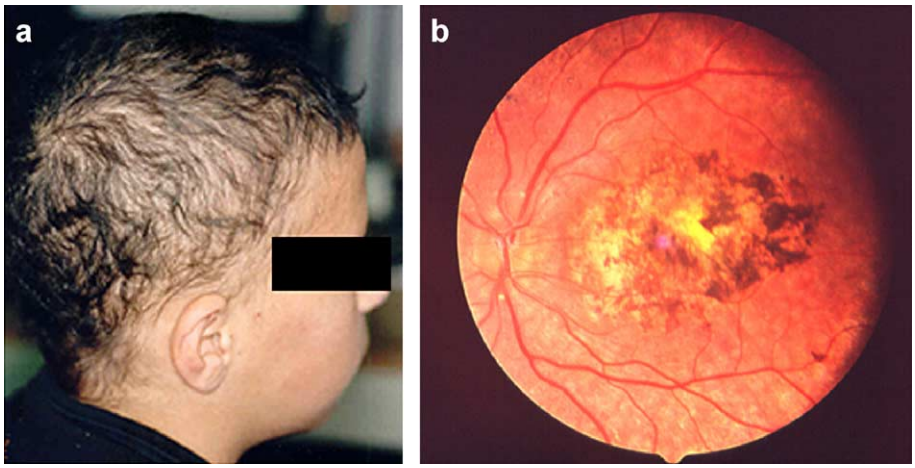

Fig. 1 a, Hypotrichosis of scalp. b, Severe macular pigmentary degenerative changes in a patient with hypotrichosis with juvenile macular dystrophy.

been identified in families of various ethnic origins in CDH3, which encodes P-cadherin, a transmembranal classical cadherin expressed in hair follicles and retinal pigment epithelium.[7-9] The exact pathomechanism underlying the clinical manifestations of hypotrichosis with juvenile macular dystrophy (MIM601553) is still elusive. Interestingly, β-catenin, which is bound to the intracytoplasmic part of P-cadherin, has been shown to play a major role during hair morphogenesis through down-regulation of E-cadherin expression.[3] As a result, under physiological conditions, P-cadherin remains the major classical cadherin being expressed at sites of mesenchymal-epithelial contacts during the early stages of hair differentiation. This may explain the consequences of P-cadherin deficiency on hair morphogenesis in hypotrichosis with juvenile macular dystrophy.

Localized autosomal recessive hypotrichosis

Localized autosomal recessive hypotrichosis (MIM 607903) was recently described in 2 Pakistani families. Affected individuals display sparse hair over the scalp, chest, arms, and legs.[10] In addition, small papules are visible over some parts of the scalp. Examination of skin biopsies reveals atrophic and coiled hair shafts as well as a marked swelling of the precortical region, reflecting a defect in differentiation with concomitant epithelial hyperproliferation. The disease was mapped to 18q12 and shown to result from deleterious mutations in a novel gene encoding desmoglein 4,[10] a major desmosomal cadherin in the hair follicle.[11] Interestingly, a number of additional desmosomal proteins have been shown to be involved in the pathogenesis of inherited hair disorders including corneodesmosin, plakophilin 1, and desmoplakin and plakoglobin, which are abnormally expressed in hypotrichosis simplex (MIM146520), skin fragility/ectodermal dysplasia (MIM604536), and woolly hair with palmoplantar keratoderma and cardiomyopathy syndrome (MIM610214/MIM605676), respectively.[12-15] Altogether, these observations underscore the importance of cell-cell junctions during hair morphogenesis.

Disorders of hair cycling

In this group of disorders, hair is normally distributed at birth and becomes sparse or absent later.

Atrichia with papular lesions

Affected children are usually born with normal hair, which is shed during the first months of life. During the first to second decade of life, patients develop a diffuse papular rash, which has been noted to be particularly prominent over the cheeks and scalp but can involve almost any part of the body.[16] Various associations with mental retardation, gastrointestinal polyposis, and delay in bone age have rarely been reported.[17-19] Another inherited form of congenital atrichia, termed alopecia universalis congenita (AUC; MIM203655), is clinically identical to atrichia with papular lesions (APL; MIM209500) except for the absence of skin papules.[20] Alopecia universalis congenita was initially mapped to 8p21.2, which harbors the *hairless* (*HR*) gene.[21,22] Mutation analysis of APL/AUC families of various ethnic origins revealed the existence of a large number of pathogenic mutations scattered over the entire length of the *HR* gene (reviewed in ref. 23). Most of these mutations result in premature termination of protein translation. Full delineation of the consequences of missense mutations in the *HR* gene awaits a better understanding of the function of the hairless protein. Hairless is highly expressed in the skin and the brain.[24] It is thought to function as a transcription factor and contains a zinc-finger domain, which was found to be affected by a mutation segregating with AUC in several families.[25,26] The hairless protein is located within the nucleus in association with the nuclear matrix.[27] Nuclear matrix-associated hairless may

regulate the activity of other transcription factors such as the thyroid hormone receptor, with which hairless has been shown to physically and functionally interact.[28] Interestingly, a homozygous *HR* missense mutation, causing AUC, was found to affect an amino acid residue previously shown to play a role in rat hairless binding to the thyroid hormone receptor.[23] Absence of functional hairless protein results in disintegration of hair follicles and their transformation into rudimentary cysts. This phenomenon may be caused by the loss of contact between the dermal papilla and the overlying follicular epithelium shortly after the entry of the hair follicle into the first catagen phase.[29] Thus, hairless seems to regulate the transition from anagen to catagen during hair cycling. Given that the common androgenetic alopecia is thought to result from abnormal kinetics of hair cycling, hairless was anticipated to play a role in androgenetic alopecia pathogenesis. Two studies failed, however, to provide convincing evidence in support of a major etiologic role of hairless in androgenetic alopecia.[30,31]

Vitamin D–resistant rickets

Vitamin D–resistant rickets (VDRR; MIM277440) is inherited in an autosomal recessive fashion. It was shown to result from end organ unresponsiveness to 1,25-dihydroxycholecalciferol. Affected patients display normal serum 25-hydroxyvitamin D, high serum 1,25-(OH)2-cholecalciferol and profound hypocalcemia, which manifests with seizures and tetany.[32] Affected individuals present early in childhood with chronic rickets, resulting in progressive bone abnormalities and loss of teeth. Vitamin D–resistant rickets with hair loss (type IIa) must be differentiated from VDRR without hair loss (type IIb). Patients with VDRR type IIa are born with normal hair, which is shed during the first year of life and never significantly regrows thereafter. In contrast, bony changes can improve with age.[33] Milia-like lesions similar to those observed in APL have also been described in VDRR. The disorder was first shown in 1988 to result from mutations in the gene encoding the vitamin D3 receptor (*VDR*), which is located on 12q12-q14.[34] Most of the disease-causing mutations are located within the N-terminal DNA-binding domain, which harbors 2 zinc-finger domains responsible for DNA binding and interactions with other proteins. Mutations at this site generally cause VDRR type IIa. In contrast, several mutations in the vitamin D–binding domain, situated at the C-terminus, were shown not to cause alopecia. Thus, vitamin D binding to the *VDR* is not necessary for normal hair development, which may explain why other forms of inherited rickets, with defective vitamin D binding, are not associated with alopecia.[33] These studies emphasized the importance of *VDR* binding to DNA and its interactions with other transcription factors during hair cycling. Because VDRR bears significant clinical and histological similarities to APL (Fig. 2), it has been suggested that *VDR* and hairless may be involved in the same pathophysiological pathway.[35] Interestingly, mutations in the murine *HR* and *VDR* genes have been shown to result in phenotypes resembling their human counterparts, APL and VDRR.[35] In addition, retinoid X receptor-α ablation and overexpression of the ornithine decarboxylase gene have been shown in mice to lead to both alopecia and dermal cyst formation.[36,37] The exact nature of the functional interactions between hairless, members of the steroid family of nuclear receptors, and ornithine decarboxylase is still unclear.

Disorders of the hair shaft structure

In hair shaft structural disorders, hair follicles develop and are able to cycle but display a defective structure, which often results in aberrant hair distribution, color, length, or texture.

Monilethrix

This autosomal dominant disorder is characterized by the appearance of beaded hair shafts due to the presence of alternating segments of normal and abnormally low diameters. Hairs tend to break at the constricted sites, resulting in varying degrees of alopecia with short and sparse hair over the scalp. Abnormal hairs may be visible at birth or, more often, during the first months of life. Marked interfamilial and intrafamilial variations in disease severity have been observed. In addition, patients may display prominent follicular hyperkeratosis as well as various nail

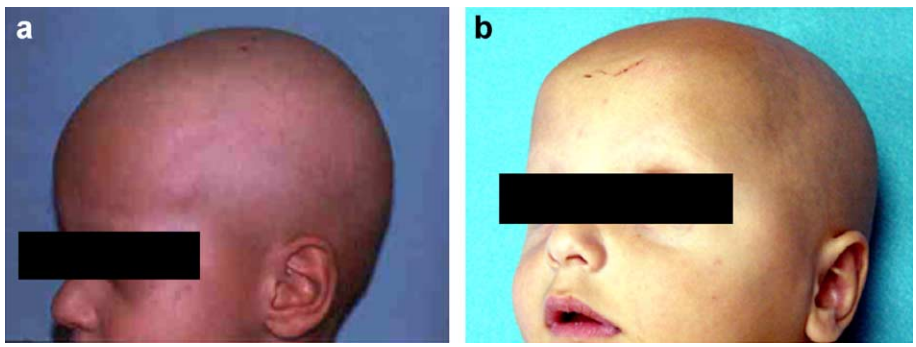

Fig. 2 Total atrichia in 2 patients with (a) APL and (b) VDRR.

abnormalities.[38] The disease was mapped to 12q11-q13 in 1996.[39] A year later, studying a large affected British family, Winter et al[40] identified a pathogenic mutation in the hair cortex-specific keratin gene, *hHb6*. Since then, a number of substitutions have been identified in the central α-helical rod coding region of the *hHb6* and *hHb1* hair keratin genes.[41] Monilethrix (MIM158000) hairs have also been observed in Menkes' syndrome, an X-linked disorder characterized by neurological and hair manifestations due to deleterious mutations in the *ATPA7A* gene, encoding a copper-binding protein.[42] Abnormal posttranslational processing of keratin molecules due to intracellular copper deficiency may explain the common occurrence of beaded hair in monilethrix and Menkes' syndrome.

Netherton syndrome

The autosomal recessive Netherton syndrome (NTS, MIM256500) is characterized by a triad of symptoms, which include congenital ichthyosis, atopic features, and hair structural abnormalities. The syndrome often manifests soon after birth with generalized erythroderma and scaling. Due to breakdown of the epidermal barrier, newborns are at risk for numerous and often life-threatening complications such as hypernatremic dehydration and other electrolyte imbalances, impaired thermoregulation, and systemic infections. Some patients remain erythrodermic for their entire lifetime, whereas, in others, the ichthyosis evolves into ichthyosis linearis circumflexa, characterized by migratory, serpiginous plaques bordered by a peculiar double-edged scale (reviewed in Ref. 43). These cutaneous features are invariably accompanied by atopic manifestations such as allergic rhinitis, asthma, allergic reactions to food and common antigens, and elevated IgE levels. Increased susceptibility to skin, respiratory tract or systemic infections, malnutrition, and failure to thrive are also characteristic. Hair abnormalities, in contrast with skin changes, are seldom apparent before the first year of age. At that time, hair microscopy can reveal the characteristic bamboo hairs or trichorrhexis invaginata, which underlie a progressive alopecia involving the eyebrows first and scalp areas later on.[44] This hair abnormality is thought to result from abnormal keratinization leading to intussusception of the fully keratinized distal hair shaft into the proximal partially keratinized hair shaft. Other abnormalities including pili torti (twisted hair) and trichorrhexis nodosa (hair of varying diameter) have also been observed in children with NTS. The disorder was shown to result from pathogenic mutations in *SPINK5*, located on 5q32,[45-47] resulting in decreased expression of a large serine protease inhibitor termed LEKTI.[48] How hair abnormalities are related to decreased levels of a serine protease inhibitor is still a matter of debate. Of interest is a number of publications describing the expression of functional proteases within the hair follicle and epidermis.[49] These proteases have been hypothesized to play a role in the dissolution of cell-cell junctions during epithelial differentiation. Cell-cell junction reorganization may be pivotal during both epidermal barrier ontogenesis[50] and hair shaft formation.[7,10] Because LEKTI may function by inhibiting these epidermal proteases, decreased LEKTI activity may logically lead to excessive proteolytic activity within the follicle and epidermis, possibly explaining abnormal hair shaft and barrier development in NTS. Supporting that possibility are recent observations demonstrating increased hydrolytic activity in the stratum corneum of patients with NTS.[51]

Nail development

Nail development starts around the ninth week of gestation and is completed during the fifth month of pregnancy. Little is currently known about the molecular signals regulating nail morphogenesis. A number of homeobox and transcription factors such as the Msx proteins and *LMX1B*, a LIM-homeodomain transcription factor, have been implicated in the control of this process, although the details of the way they affect nail development remain poorly explored.[52,53] The mature nail plate grows continuously through life as a result of matrix epithelial cell differentiation and consists of a number of hard and soft keratin molecules embedded in an amorphous matrix. Most inherited nail disorders manifest either with nail hypoplasia or nail hypertrophy.

Nail hypoplasia

Isolated congenital nail dysplasia

Isolated nail dysplasia is rare and most probably represents a very heterogeneous group of disorders. Some patients with isolated congenital nail dysplasia have been shown to carry mutations in genes known to be associated with complex genodermatoses such as COL7A1, associated with dystrophic epidermolysis bullosa, and GJB6, defective in hidrotic ectodermal dysplasia, implying that these cases do not represent more than formes frustes of those disorders.[54,55] True isolated congenital nail dysplasia was shown to segregate in an autosomal dominant fashion in a large multigenerational German family in which affected members display thinning and impaired formation of fingernail and toenail plates. Recently, Krebsova et al[56] successfully mapped isolated congenital nail dysplasia in this family to a 6-cM interval on 17p13.

Nail patella syndrome

Nail patella syndrome (NPS; MIM256020) is dominantly inherited and is characterized by a number of nail anomalies ranging from slight longitudinal ridging, nail splitting, and nail fragility to generalized nail hypoplasia or aplasia (anonychia). A triangular or V-shaped lunula is particularly

typical. The second major feature in this disorder involves the patella, which can be either absent or hypoplastic. Other bony deformations such as iliac horns, elongated radius with hypoplasia of radial head, elbow deformities, and rib hypoplasia have been described. Ocular signs including corneal malformations, congenital cataract, iris pigmentation (Lester's sign) are variable manifestations of the syndrome. Finally, a large proportion of patients with NPS develop progressive glomerulopathy manifesting with massive proteinuria and sometimes resulting in end-stage renal failure.[57] Mutations in LIM homeobox transcription factor 1 (*LMX1B*) gene, located on 9q34.1, were found to underlie NPS in most affected kindreds.[58] The protein encoded by this gene is a transcription factor. It was shown to play a central role in limb development, which may explain why *LMX1B* dysfunction leads to bone and nail abnormal morphogenesis. Interestingly, mutant *LMX1B* is thought to lead to the NPS phenotype due to aberrant patterning along the proximal-distal and anterior-posterior axes. In this regard, it is of note that a gradual increase in severity of nail dystrophy has been observed in NPS from thumbs to little fingers.[57] Finally, *LMX1B* was shown to regulate the expression of collagen IV, a major component of the glomerular basement membrane, which may explicate the renal pathology in NPS.[59]

Nail hypertrophy

Pachyonychia congenita type 1 and type 2

Hallmarks of pachyonychia congenita (PC) are greatly thickened and malformed nail plates (see also *Inherited defects in keratins* by A Irvine). Pachyonychia congenita type 1 (PC-1; MIM167200; Jadassohn-Levandowsky syndrome) is characterized by nail thickening and yellowish discoloration due to subungual hyperkeratosis, focal palmoplantar keratoderma, follicular hyperkeratosis, and oral leukokeratosis. Pachyonychia congenita type 2 (PC-2; MIM167210; Jackson-Lawler syndrome) is accompanied by less severe nail dystrophy and milder keratoderma and is readily distinguished by the presence of multiple steatocystomas and a history of neonatal teeth (Fig. 3). Both disorders are inherited in an autosomal dominant fashion. Additional variants with corneal leukokeratosis (PC type 3) and laryngeal lesions with mental retardation (PC type 4) have also been described. Pachyonychia congenita type 1 results from mutations in *K6a* or *K16* keratin genes whereas PC-2 is caused by mutations in *K6b* and *K17* keratin genes (reviewed in Ref. 60). The pattern of expression of these 2 pairs of keratin explain the specific clinical manifestations of the 2 PC subtypes: keratins 6a and 16 are expressed in the nail bed and nail fold as well as in palmoplantar skin and oral mucosae; keratins 6b and 17 are found in the nail bed, hair follicle, and eccrine glands as well as in selected areas of palmoplantar skin. Marked phenotypic variability has been observed in this group of disorders. For example, mutations in *K16* have been shown to underlie keratoderma in the absence of nail changes typical of PC-1,[61] and mutations in *K17* have been shown to cause steatocystoma multiplex with no other manifestation of PC-2.[62] To complicate the picture even further, combined features of PC-1 and PC-2 have recently been shown to result from a deleterious mutation in *K6a*.[63]

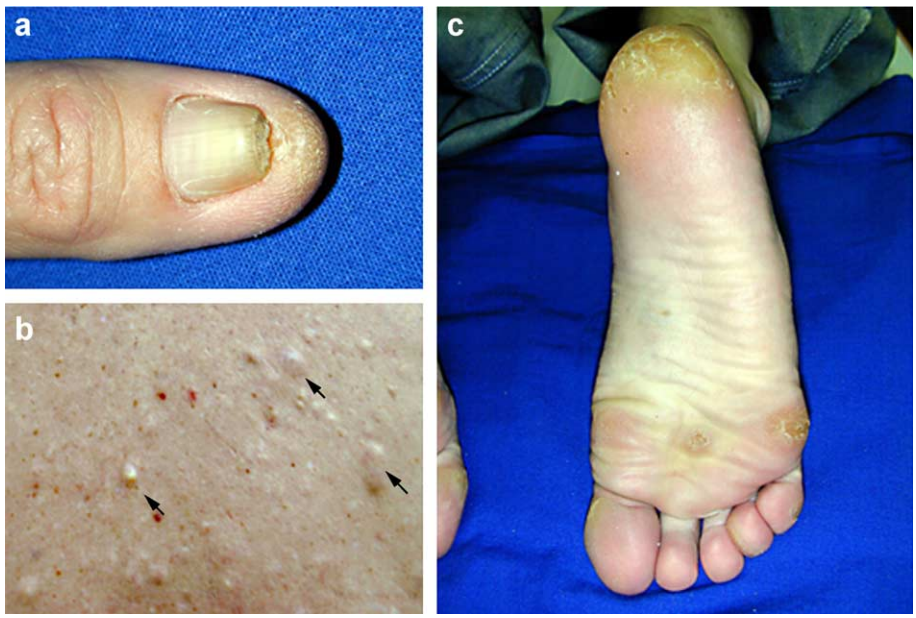

Fig. 3 a, Nail thickening and yellowish discoloration. b, Steatocystoma multiplex (arrows). C, Focal palmoplantar keratoderma in a patient with PC-2.

Conclusions

The molecular basis of a steadily growing number of genetic hair and nail disorders has been elucidated during the last decade. This rapidly expanding body of information has already brought major changes in the life of families afflicted by these disorders by providing them with a definitive diagnosis and, when indicated, with the possibility of premarital counseling and prenatal diagnosis. Our ultimate goal remains the application of this novel knowledge to foster the development of innovative therapies to alleviate and possibly cure our patients' disease. The burgeoning science of topical gene therapy, which is of particular relevance to the treatment of skin appendage disorders, has already generated fascinating observations[64], which suggest that this goal may not be out of reach.

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