Chapter 1

Current Genetics in Hair Diseases

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Additional information is available at the end of the chapter

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1. Introduction

(HF) is a skin appendage which exists on the entire skin surface, except for palmoplantar and mucosal regions. During embryogenesis, HF development is operated through reciprocal interactions between skin epithelial cells and underlying dermal cells [1]. The first signal to induce HF formation is considered to originate from the dermal cells. The epithelial cells which receive the dermal signal lead to form a placode (Figure 1). Then a signal from the placode results in forming a dermal condensate just beneath the placode (Figure 1). Additional interaction between these structures induces the downgrowth of the placode and forms a hair germ, which is the source of epithelial components of the HF (Figure 2). The dermal condensate is gradually surrounded by the HF epithelium and becomes a dermal papilla. It has been shown that many signaling molecules, such as Wnt, ectodysplasin (Eda),

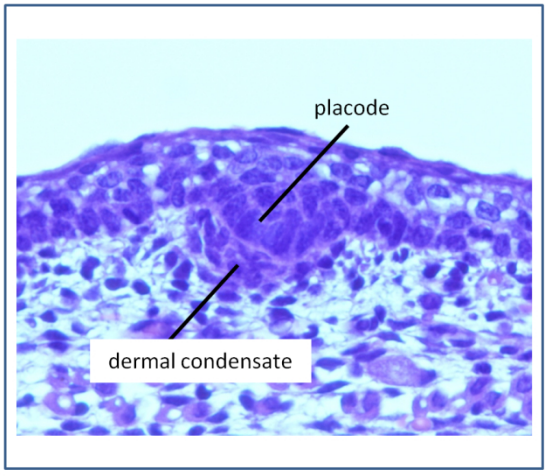

Figure 1. Hair follicle placode (mouse embryo; E15.5)

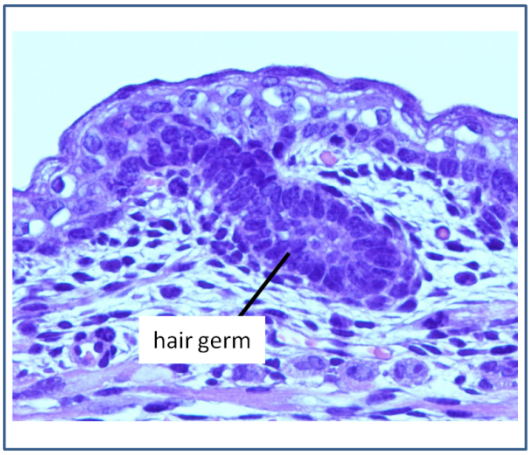

Figure 2. Hair germ (mouse embryo; E16.5)

bone morphogenic protein (Bmp), and sonic hedgehog (Shh), play crucial roles in the HF development [1]. After the HF is generated, it undergoes dynamic cell kinetics, known as the hair cycle, throughout postnatal life, which is composed of three phases: catagen (regressing) phase, telogen (resting) phase and anagen (growing) phase [2]. In human scalp HFs, duration of the catagen, telogen, and anagen phases are 1-2 weeks, 2-3 months, and 2-6 years, respectively. The hair cycle, which is an amazing ability of self-renewal, is maintained by the stem cell niche in bulge portion of the HF, as well as the dermal papilla [3, 4].

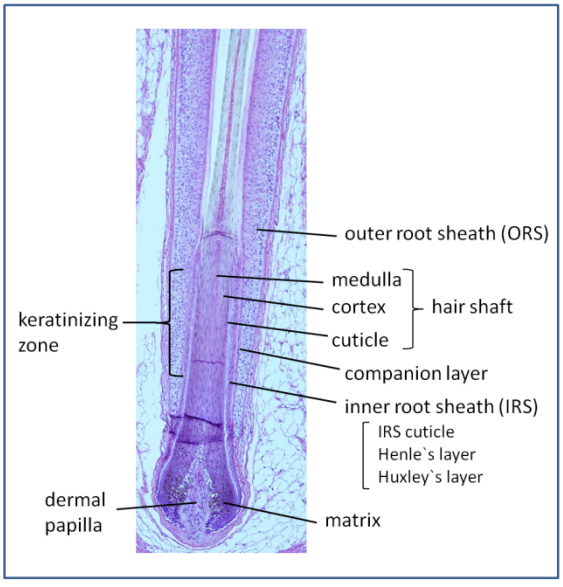

Figure 3. Human anagen hair follicle.

The anagen HF has a highly complex structure with several distinct cell layers (Figure 3). During the anagen phase, cells from the bulge portion migrate downward to matrix region, while making the outer root sheath (ORS). The matrix cells actively proliferate and differentiate into the hair shaft, the inner root sheath (IRS), and the companion layer of the HF (Figure 3) [4]. The hair shaft shares a common structural organization, in which a multicellular cortex is surrounded by a cuticular layer, occasionally with a medulla layer centrally located within the cortex. The hair shaft is strongly keratinized at the level of keratinizing zone, and forms a rigid structure (Figure 3). Growth of the hair shaft is molded and supported by the IRS, the companion layer, and the ORS. The IRS is composed of three distinct layers: the IRS cuticle, Huxley's layer, and Henle's layer (Figure 3).

2. Hair follicle

Recent advances in molecular genetics have led to the identification of numerous genes that are expressed in the HF. Furthermore, mutations in some of these genes have been shown to underlie hereditary hair diseases in humans [2]. Causative genes for the diseases encode various proteins with different functions, such as structural proteins, transcription factors, and signaling molecules. This chapter aims to update recent findings regarding the molecular basis of genetic hair diseases.

3. Keratin disorders

Keratins are one of the major structural components of the HF, and are largely divided into type I (acidic) and type II (neutral to basic) keratins. The type I and type II keratins undergo heterodimerization, which leads to form keratin intermediate filaments (KIFs) in the cytoplasm [5]. Based on the amino acid composition, keratins are further classified into two groups: epithelial (soft) keratins and hair (hard) keratins. As compared to the epithelial keratins, the hair keratins show higher sulfur content in their N- and C-terminus, which plays an important role in interacting with hair keratin-associated proteins via disulfide bindings [6, 7]. All the keratin proteins are composed of an N-terminal rod domain, a central rod domain, and a C-terminal tail domain. Importantly, the N-terminal and the C-terminal regions of the rod domain are highly conserved in amino acid sequences, which are called helix initiation motif (HIM) and helix termination motif (HTM), respectively (Figure 4). It is believed that the HIM and the HTM play essential roles in heterodimerization between the keratins. In humans, gene clusters for the type I and type II keratin genes are mapped on chromosomes 17q21 [8] and 12q13 [9], respectively. To date, a total of 54 functional keratin genes (28 type I and 26 type II) have been identified and characterized in humans. It has been shown that during differentiation of the HF, various keratin genes are abundantly and differentially expressed, and contribute to HF keratinization, leading to the formation of a rigid structure [10]. In general, epithelial keratins are mainly expressed in the ORS, the companion layer, the IRS, while hair keratins are predominantly expressed in the hair shaft. In addition, it has recently been reported that some epithelial keratins are expressed in the hair shaft medulla as well [11]. It is noteworthy that mutations in several keratin genes have been reported to underlie hereditary hair disorders in humans (Table 1).

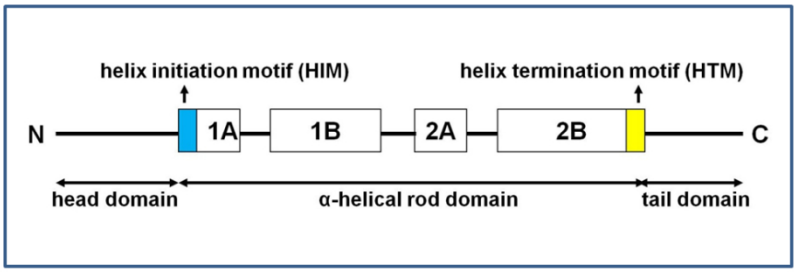

Figure 4. Structure of keratin proteins.

disease	inheritance pattern	OMIM#	main symptoms	gene	protein, function
Monilethrix	AD	158000	moniliform hair, perifollicular papules	*KRT81* *KRT83* *KRT86*	K81 (basic hair keratin) K83 (basic hair keratin) K86 (basic hair keratin)
Pure hair and nail ectodermal dysplasia	AR	602032	hypotrichosis, spoon nails	*KRT85*	K85 (basic hair keratin)
Autosomal dominant woolly hair (ADWH)/ hypotrichosis	AD	194300/613981	WH/ hypotrichosis	*KRT74* *KRT71*	K74 (basic epithelial keratin) K71 (basic epithelial keratin)

Table 1. Hereditary hair disorders caused by mutations in keratin genes. AD, autosomal dominant; AR, autosomal recessive.

Monilethrix is characterized clinically by fragile scalp hair shafts and diffuse perifollicular papules with erythema. As the hair of affected individuals with monilethrix is easily broken, they frequently show sparse hair (hypotrichosis). In most cases, monilethrix shows an autosomal dominant inheritance pattern (MIM 158000), while autosomal recessive forms (MIM 252200) also exist. Under microscopy, the hair shaft of affected individuals with monilethrix dysplays a characteristic anomaly, known as beaded or moniliform hair, which shows periodic changes in hair diameter. As a result, the hair leads to the formation of nodes and internodes (Figure 5) [12]. Autosomal dominant form of the disease is caused by heterozygous mutations in *KRT81*, *KRT83*, and *KRT86* genes, which encode type II hair keratins K81, K83, and K86, respectively [13, 14]. All the mutations identified to date result in a deleterious amino acid substitution within either the HIM or the HTM of the rod domain. These hair keratins are predominantly expressed in the keratinizing zone of the hair shaft cortex (Figure 6) [15]. Although precise mechanisms to cause moniliform hair remain elusive, mutations in these hair keratin genes are predicted to result in disruption of the KIF formation, leading to an abnormal hair shaft keratinization.

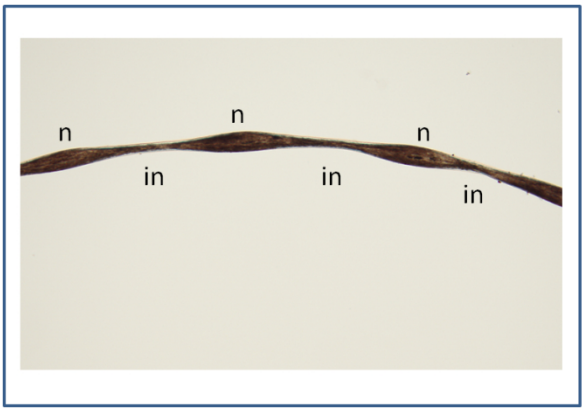

Figure 5. Moniliform hair. N, node; in, internode.

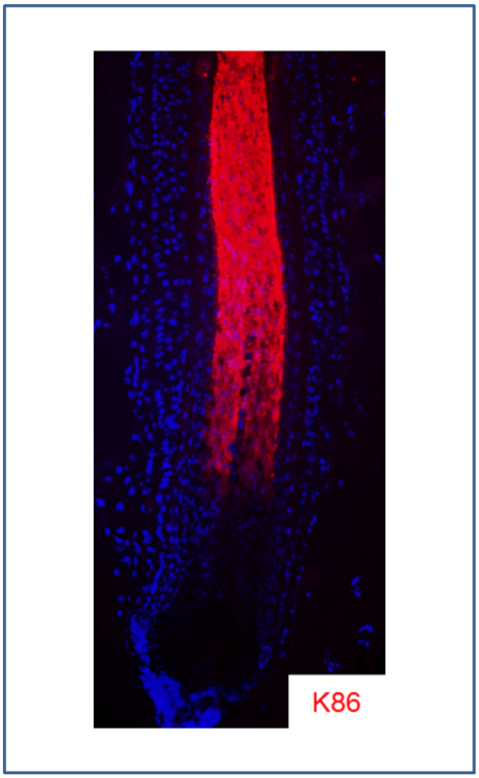

Figure 6. Expression of hair keratin K86 in the human hair shaft cortex.

Pure hair and nail ectodermal dysplasia (PHNED; MIM 602032) is characterized by absent or sparse hair, as well as nail dystrophy [16]. Hairs of affected individuals with PHNED are short

and thin, and perifollicular papules can also be observed. In addition, their nails typically show koilonychia (spoon nails). The disease can show either an autosomal dominant or recessive inheritance trait. The autosomal recessive form has been mapped to chromosome 17p12-q21.2 [17] and 12p11.1-q21.1 [18] which contain the type I and type II keratin gene clusters, respectively. Subsequently, homozygous mutations in *KRT85* gene have been identified in families with autosomal recessive PHNED [18, 19]. The *KRT85* gene encodes the type II hair keratin K85, which is abundantly expressed in the matrix region of both the HF and the nail units [15, 20]. Molecular basis for autosomal dominant PHNED is yet unknown.

In addition to hair keratins, it has recently been reported that mutations in HF-specific epithelial keratin genes are associated with hereditary woolly hair (WH)/hypotrichosis. WH is defined as an abnormal variant of tightly curled hair and is considered to be a kind of hair growth deficiency [21]. There are both syndromic and non-syndromic forms of WH. The non-syndromic forms of WH can show either an autosomal-dominant (ADWH; MIM 194300) or -recessive (ARWH; MIM 278150) inheritance pattern. It is well-known that WH is frequently associated with hypotrichosis. Recently, heterozygous mutations in *KRT74* and *KRT71* genes have been identified in families with ADWH/hypotrichosis (Figure 7) [22-24]. Importantly, the *KRT74* and the *KRT71* genes encode the IRS-specific type II epithelial keratins K74 and K71, respectively (Figure 8) [25]. It can be postulated that disruption of the KIF formation in the IRS results in a failure to guide the hair growth, and leads to WH phenotype. Interestingly, *KRT71* mutations have also been identified in mice, rats, cats, and dogs, all of which show wavy coat phenotypes [26-30]. These data strongly suggest crucial roles of the IRS-specific epithelial keratins in the HF development and hair growth across mammalian species.

Figure 7. Clinical features of autosomal dominant woolly hair/hypotrichosis caused by a mutation in the *KRT71* gene.

Figure 8. Expression of the IRS-specific karatin K71 in the human hair follicle.

4. Hereditary hair disorders resulting from disruption of cell-cell adhesion molecules

Similar to epidermis, the HF epithelium possess a number of cell-cell adhesion structures, such as desmosomes, corneodesmosomes, adherens junctions, gap junctions, and tight junctions, which play important roles in maintaining the structure and the function of the HF. It has been shown that disruption of any of these structures can result in hereditary hair disorders in humans (Table 2).

Desmosome is a critical structure for cell-cell adhesion in most epithelial tissues, including the HF. The major structural component of the desmosome is the desmosomal cadherin family, which is comprised of the desmogleins (DSGs) and desmocollins (DSCs). In humans, 4 *DSG* genes (*DSG1-DSG4*) and 3 *DSC* genes (*DSC1-DSC3*) are located on chromosome 18q12. These desmosomal cadherin family members are glycoproteins with single-pass transmembrane domain, and are involved in Ca^{2+}-dependent cell-cell adhesion, connecting with each other using their extracellular domains [31]. Within the cytoplasm, they interact with several other proteins, known as desmosomal plaque proteins, which include plakoglobin, plakophilin, and desmoplakin. The desmosomal plaque proteins contribute to anchor the KIF near the cell membrane. As such, the cell integrity and the cell-cell adhesion are maintained [31]. Recessively-inherited mutations in the *DSG4* gene have been shown to cause a non-syndromic form of hereditary hair disorder known as localized autosomal recessive hypotrichosis 1 (LAH1; MIM 607903) [32]. Affected individuals with LAH1 show sparse hairs on the scalp, chest, arms, and legs. The eyebrows and beard are less dense than normal, and the axillary hair, pubic hair, and eyelashes look normal in most cases. It is noteworthy that hair shafts of affected individuals with *DSG4* mutations are fragile and often show moniliform hair [33-35]. Therefore, the *DSG4* can also be regarded as a causative

disease	inheritance pattern	OMIM#	main symptoms	gene	protein, function
Localized autosomal recessive hypotrichosis 1 (LAH1)/monilethrix	AR	607903/ 252200	hypotrichosis, moniliform hair, perifollicular papules	*DSG4*	desmoglein 4
Hypotrichosis and recurrent skin vesicles	AR	613102	Hypotrichosis, skin vesicles or keratosis pilaris	*DSC3*	desmocollin 3
Naxos disease	AR	601214	WH, PPK, right ventricular cardiomyopathy	*JUP*	junctional plakoglobin
Carvajal syndrome	AR	605676	WH, PPK, left ventricular cardiomyopathy	*DSP*	desmoplakin
Ectodermal dysplasia/skin fragility syndrome	AR	604536	Hypotrichosis, fragile skin, nail dystrophy	*PKP1*	plakophilin 1
Hypotrichosis simplex of the scalp	AD	146520	Scalp-limited hypotrichosis	*CDSN*	corneodesmosin
Netherton syndrome	AR	256500	ichthyosiform erythroderma, atopic manifestation, bamboo hair	*SPINK5*	LEKTI (serine protease inhibitor)
Ichthyosis with hypotrichosis	AR	610765	ichthyosis, hypotrichosis	*ST14*	matriptase (serine protease)
Hypotrichosis with juvenile macular dystrophy	AR	601553	Hypotrichosis, weak eyesight	*CDH3*	P-cadherin
Ectodermal dysplasia, ectrodactyly, macular dystrophy (EEM) syndrome	AR	225280	Hypotrichosis, weak eyesight, ectrodactyly	*CDH3*	P-cadherin
Hidrotic ectodermal dysplasia (Clouston syndrome)	AD	129500	hypotrichosis, PPK, nail dystrophy	*GJB6*	connexin 30
Keratitis ichthyosis deafness (KID) syndrome	AD	148210	vascularizing keratitis, sensorial deafness, erythrokeratoderma, hypotrichosis	*GJB2* *GJB6*	connexin 26 connexin 30
Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis	AR	607626	Hypotrichosis, ichthyosis, jaundice, hapatomegaly,	*CLDN1*	claudin 1

AD, autosomal dominant; AR, autosomal recessive; WH, woolly hair; PPK, palmoplantar keratoderma.

Table 2. Hereditary hair disorders caused by disruption of cell-cell adhesion structures and the related molecules.

gene for autosomal recessive monilethrix. DSG4 is the only desmoglein member that is expressed in the hair shaft (Figure 9) [36], and its expression in the hair shaft cortex finely overlaps with K81, K83, and K86, of which mutations cause autosomal dominant monilethrix. More recently, a homozygous nonsense mutation in the *DSC3* gene has been identified in a family with an autosomal recessive form of hypotrichosis [37]. The disease is characterized by sparse scalp hairs and small vesicle formation on the scalp and extremities (hypotrichosis and recurrent skin vesicles; MIM 613102) [37], while there is an argument that the vesicles may be keratosis pilaris [38]. In addition, mutations in genes encoding desmosomal plaque proteins can also show hair phenotypes (Table 2). For example, mutations in junctional plakoglobin (*JUP*) and desmoplakin (*DSP*) genes are known to underlie Naxos disease (MIM 601214) and Carvajal syndrome (MIM 605676), respectively [39, 40]. Both diseases show an autosomal recessive inheritance pattern and are characterized by woolly hair, palmoplantar keratoderma, and severe cardiomyopathy. Furthermore, loss of function mutations in plakophilin 1 (*PKP1*) gene cause a rare autosomal recessive disease named ectodermal dysplasia/skin fragility syndrome (MIM 604536) [41].

Corneodesmosome is a modified desmosome in the stratum corneum (SC) of the epidermis, and plays a crucial in the desquamation process. One of the major components of the corneodesmosome is corneodesmosin (CDSN). CDSN is secreted by cytoplasmic vesicles into the extracellular core of desmosomes, and is progressively proteolysed by several serine

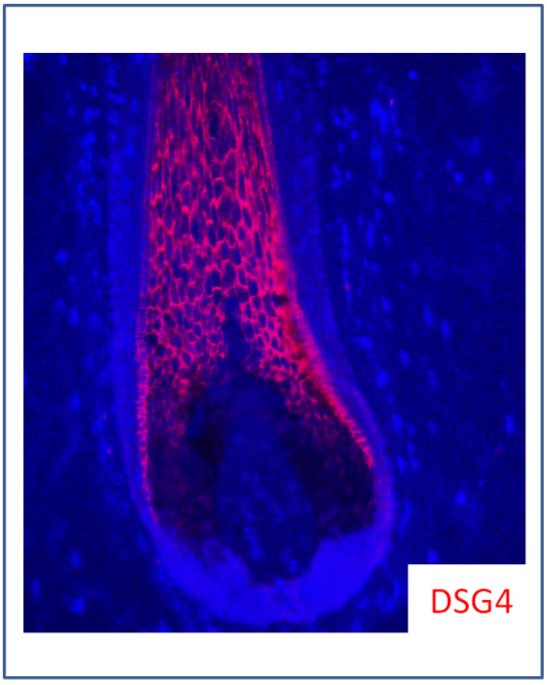

Figure 9. Expression of desmoglein 4 (DSG4) in the human hair shaft.

proteases, such as kallikrein-related peptidases, which leads to the loss of cell-cell adhesivity in the SC and causes desquamation [42]. CDSN is also expressed predominantly in the IRS of the HF, and thus is considered to be important for terminal differentiation, as well as subsequent degradation of the IRS [43]. In 2003, heterozygous nonsense mutations in the *CDSN* gene have been identified in patients with hereditary hypotrichosis simplex of the scalp (HHSS; MIM 146520), which is an autosomal dominant disorder characterized by sparse hairs limited to the scalp region without any obvious hair shaft anomalies (Figure 10) [44]. Histologically, the IRS of the patients' HF was disturbed, which was consistent with the expression of CDSN in the IRS. Furthermore, aggregates of abnormal CDSN were detected around the HF, as well as in the papillary dermis in patients' skin [44]. These aggregates have recently been shown to be an amyloid protein derived from the mutant CDSN, which is likely to be toxic to the HF cells [45]. Therefore, the mutant CDSN protein appears to function in a dominant negative manner, affect growth of the HF, and lead to HHSS. In addition to HHSS, it has been reported that mutations in other genes functionally related with CDSN can show some hair phenotypes associated with congenital ichthyosis. Of these, Netherton syndrome (NS; MIM 256500) is a rare autosomal recessive condition characterized by ichthyosiform erythroderma, atopic manifestation, and the hair shaft anomaly, known as bamboo hair (trichorrhexis invaginata) (Figure 11). The NS is caused by loss of function mutations in *SPINK5* gene which encodes a serine protease inhibitor named LEKTI (lymphoepithelial Kazal-type-related inhibitor) [46]. Disruption of LEKTI has been shown to result in upregulation of serine proteases and excess desquamation due to premature proteolysis of CDSN [47, 48]. Furthermore, it has been reported that recessively-inherited mutations in *ST14* gene, which encodes a member of serine proteases (matriptase), underlie ichthyosis with hypotrichosis syndrome (MIM 610765) [49]. Sum of these genetic data suggest that balanced expression of CDSN, serine proteases, and their inhibitors is critical for the HF differentiation.

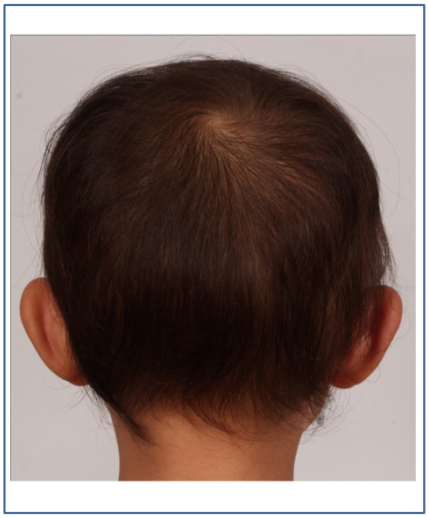

Figure 10. Clinical features of hypotrichosis simplex of the scalp.

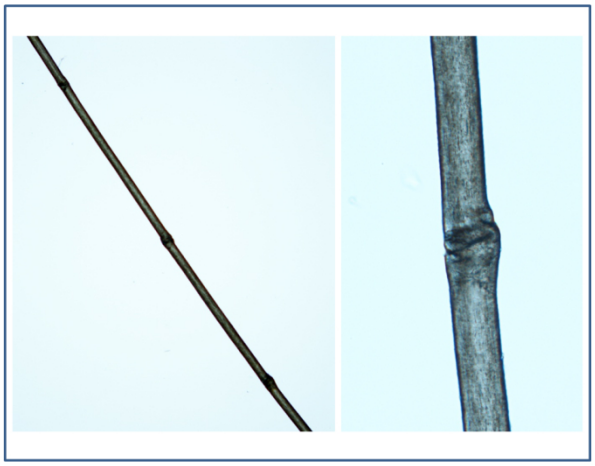

Figure 11. Bamboo hair (trichorrhexis invaginata).

E- and P-cadherins are classical cadherins which are a major component of adherens junctions in the HF. When the HF placode is formed during embryogenesis, the expression of E-cadherin is markedly downregulated, while P-cadherin is simultaneously upregulated, and prominant expression of P-cadherin persists in the proximal portion of the HF. This phenomenon, known as cadherin switching, is believed to be essential for the HF morphogenesis [50]. In addition, P-cadherin has recently been shown to be important for postnatal hair growth and cycling as well [51]. The critical role of these classical cadherins in the HF has been further supported by two hereditary diseases resulting from mutations in the P-cadherin gene (*CDH3*). First, mutations in the *CDH3* gene are known to underlie hypotrichosis with juvenile macular dystrophy (HJMD; MIM 601553), which is an autosomal recessive disease characterized by sparse hair and weak eyesight due to macular dystrophy of the retina [52]. In addition, it has been reported that another disease, ectodermal dysplasia, ectrodactyly and macular dystrophy (EEM syndrome; MIM 225280), is also caused by recessively-inherited mutations in the *CDH3* gene [53]. Affected individuals with EEM syndrome show common hair and eye phenotype with HJMD. However, EEM patients also shows split hand/foot malformation (ectrodactyly), suggesting crucial roles of P-cadherin in the development of not only hair and retina, but also the limbs in humans. There are no clear genotype-phenotype correlations in *CDH3* mutations, as it has been reported that a same mutation in the *CDH3* gene caused HJMD in one family [54], while EEM syndrome in another family [53]. Identification of modifier gene(s) may reveal this paradox in the future.

Gap junction (GJ) is a specialized intercellular structure that provides a pathway for both metabolic and ionic coupling between adjacent cells and maintains tissue homeostasis [55]. Connexins (Cxs) are 4-pass transmembrane proteins and the major component of the GJs. Clouston syndrome (MIM 129500), also known as hidrotic ectodermal dysplasia, is an autosomal dominant condition characterized by hypotrichosis, nail dystrophy, and

palmoplantar keratoderma. The disease is caused by mutations in *GJB6* gene which encodes Cx30 [56]. In addition, mutations in *GJB2* gene encoding Cx26 are known to underlie keratitis-ichthyosis-deafness syndrome (KID; MIM 148210) [57]. The triad of KID is vascularizing keratitis, profound sensorial hearing loss, and erythrokeratoderma. Additionally, patients with KID show severe hypotrichosis in high frequency. Interestingly, it has been reported that a mutation in the *GJB6* gene (V37E) can show phenotypes resembling KID [58]. These Cx proteins are mainly expressed in the ORS of the HF (Figure 12) [59, 60], and thus they may play some roles in maintaining the function of the HF stem cells.

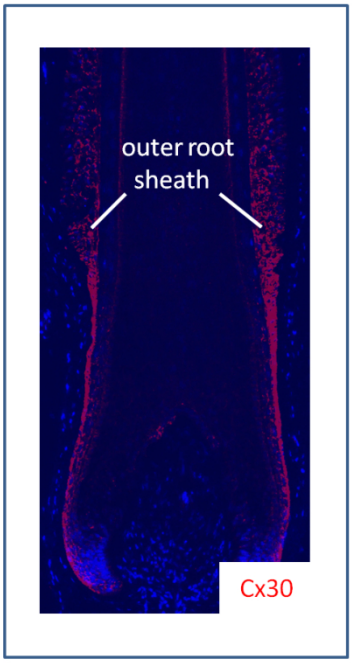

Figure 12. Cx30 expression in the human hair follicle.

In addition to the cell-cell adhesion structures described above, tight junction (TJ) also exists in the HF epithelium and expression patterns of TJ-associated proteins in the HF have previously been characterized [61]. Disruption of *CLDN1* gene encoding claudin 1, a major structural component of TJ, has recently been shown to cause a severe autosomal recessive syndrome, known as ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis (MIM 607626) [62].

5. Hereditary hair disorders associated with transcription factors

During the past 20 years, numerous genes that are expressed in the HF have been identified, and various transcription factors have been shown to be involved in transcriptional

regulation of these genes. Of these, p63 is one of the main transcription factors expressed in the HF. During the HF morphogenesis, p63 is abundantly expressed in the HF placode (Figure 13). In the postnatal stage, it is strongly expressed in the ORS and the matrix region of the HF (Figure 14). It has previously been reported that mutations in *TP63* gene encoding p63 cause several autosomal dominant diseases including ectodermal dysplasia, ectrodactyly, cleft lip/palate (EEC) syndrome (MIM 604292), ankyloblepharon, ectodermal defects, and cleft lip/palate (AEC) syndrome (MIM 106260) and Rapp-Hodgkin syndrome (MIM 129400) (Table 3) [63-65]. In most cases, patients with these syndromes result in scarring alopecia, and their hair shafts are coarse and twisted (Figure 15). It is noteworthy that affected individuals with *TP63* mutations show large phenotypic overlaps in hair and limbs with P-cadherin (*CDH3*) mutations. p63 colocalizes with P-cadherin in developing HF placode and limb buds during mouse embryogenesis. Importantly, it has been demonstrated that the *CDH3* is a direct target gene of p63 [66].

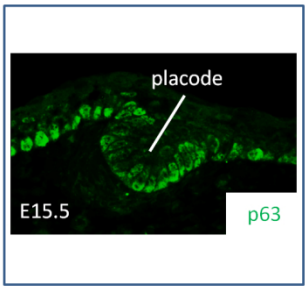

Figure 13. P63 expression in the developing mouse hair follicle placode.

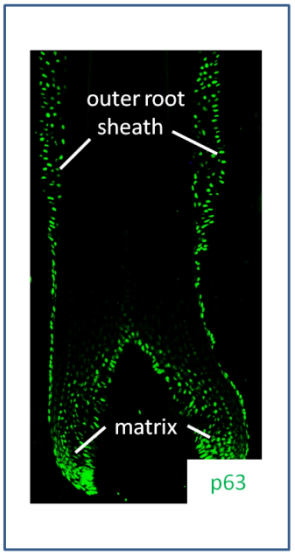

Figure 14. p63 expression in the human hair follicle.

disease	inheritance pattern	OMIM#	main symptoms	gene	Protein, function
Ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC) syndrome	AD	604292	hypotrichosis, ectrodactyly, cleft lip/palate, hypodontia	*TP63*	tumor protein p63
Ankyloblepharon, ectodermal defects, and cleft lip/palate (AEC) syndrome	AD	106260	hypotrichosis, ankyloblepharon, skin erosion, cleft lip/palate, hypodontia	*TP63*	tumor protein p63
Rapp-Hodgkin syndrome	AD	129400	hypotrichosis, cleft lip/palate, hypodontia	*TP63*	tumor protein p63
T cell immunodeficiency, congenital alopecia, and nail dystrophy (human nude phenotype)	AR	601705	atrichia, nail dystrophy, T-cell immuodeficiency	*FOXN1*	Forkhead box N1
Atrichia with papular lesions	AR	209500	atrichia, papules	*HR*	Hair less (transcriptional corepressor)
Marie-Unna hereditary hypotrichosis	AD	146550	Hypotrichosis, wiry hair	*U2HR*	Small peptide that regulates translation of the HR protein
Trichorhinophalangeal syndrome type I/type III	AD	190350/190351	Hypotrichosis, peer-shaped nose, brachydactyly, clinodactyly	*TRPS1*	Zing finger transcription factor
Hypotrichosis-lymphedema-telangiectasia syndrome	AD/AR	607823	Hypotrichosis, lymphedema, telangiectasia (easily visible blood vessels)	*SOX18*	SRY-BOX 18
Trichodontoosseous syndrome	AD	190320	WH, hypodontia, bone anomalies	*DLX3*	Distal-less homeobox 3

AD, autosomal dominant; AR, autosomal recessive; WH, woolly hair.

Table 3. Hereditary hair disorders resulting from mutations in transcription factors.

FOXN1, also known as WHN, is a transcription factor expressed in the matrix and the hair shaft of the HF, and has been shown to regulate the expression of several hair keratin genes [67]. FOXN1 is expressed in not only the HF, but also in the nail units and thymus. Mutations in the *FOXN1* gene have been reported to underlie T-cell immunodeficiency, congenital alopecia, and nail dystrophy (MIM 601705), which is an autosomal recessive disease and represents the human counterpart of the nude mouse phenotype, suggesting the crucial roles of FOXN1 in development of skin appendages, as well as thymus in both humans and mice [68].

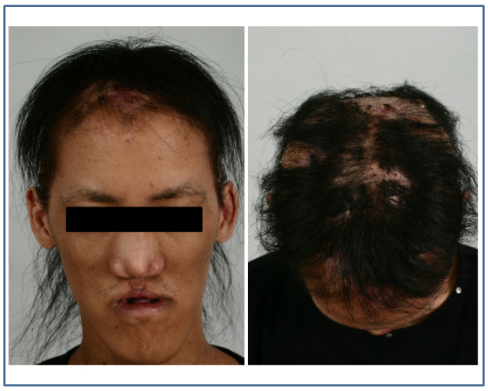

Figure 15. Clinical features of Rapp-Hodgkin syndrome.

Hairless (*HR*) is a putative single zinc-finger transcription factor which is known to regulate the catagen phase of the hair cycle [69]. Recessively-inherited mutations in the *HR* gene have been shown to underlie atrichia with popular lesions (APL; MIM 209500) [70]. APL is characterized by early onset of generalized complete hair loss (atrichia), which is followed by papular eruptions due to formation of dermal cyst after an abnormal first catagen phase [71]. Mutations responsible for APL have been found in coding exons or exon-intron boundary sequences of the *HR* gene, all of which were predicted to result in loss of expression and/or function of the HR protein. Recently, another disease, known as Marie-Unna hypotrichosis (MUH; MIM 146550), has been shown to be associated with the *HR* gene. MUH is a non-syndromic hereditary hair disorder showing an autosomal dominant inheritance pattern. Affected individuals with MUH typically exhibit sparse scalp and facial hair at birth. Subsequently, coarse, wiry, and twisted hairs develop in early childhood. Hair loss progresses with aging, which leads to a complete alopecia or a phenotype just like androgenetic alopecia. MUH was previously mapped to the *HR* locus on chromosome 8p21.3 [72]. However, direct sequencing analysis of coding sequences of the *HR* gene failed to detect mutations. Later on, Wen et al. found that the promoter region of the *HR* gene has four potential upstream open reading frames (uORFs), which were designated *U1HR-U4HR*. Strikingly, direct sequencing analysis of the *U1HR-U4HR* in patients with MUH has led to the identification of mutations within the *U2HR* sequences, which encode a small peptide of 34 amino acid residues [73]. *In vitro* studies have suggested that this small peptide encoded by the *U2HR* downregulates the *HR* expression at the translational level, and loss-of-function mutations in the *U2HR* results in overexpression of the HR protein [73]. Besides these findings, actual consequences resulting from *U2HR* mutations *in vivo* remain elusive.

TRPS1 is a transcription factor with GATA-type and Ikaros-type zinc finger domains, which has been shown to be abundantly expressed in both epithelial and mesenchymal components in the developing mouse HFs [74]. Furthermore, it has recently been reported that Trps1 plays crucial roles in regulating the expression of several Wnt inhibitors and various transcription factors during vibrissa follicle morphogenesis in mice [75]. In humans,

mutations in the *TRPS1* gene are known to cause trichorhinophalangeal syndrome type I (TRPS I; MIM 190350) or type III (TRPS III; MIM 190351), both of which show an autosomal dominant inheritance trait, and are characterized by sparse hair and a number of craniofacial and skeletal abnormalities, such as peer-shaped nose and brachydactyly. Hypotrichosis is the most prominent in the temporal region of the scalp (Figure 16) [76, 77].

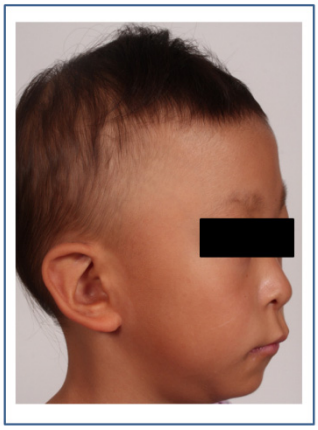

Figure 16. Clinical features of TRPS I.

In addition to the transcription factors described above, several other members are also associated with hereditary hair diseases. For instance, both dominantly- and recessively-inherited mutations in *SOX18* gene underlie hypotrichosis-lymphedema-telangiectasia syndrome (MIM 607823) [78] and dominantly-inherited mutations in *DLX3* gene cause trichodontoosseous syndrome (MIM 190320), respectively (Table 3) [79].

6. Hereditary hair disorders caused by disruption in signaling pathways

It has been shown via analyses using mice models that several signaling pathways play crucial roles in the HF morphogenesis and development. In humans, disruption of these signaling pathways has been demonstrated to underlie various hereditary hair disorders (Table 4). In addition, information obtained from the analysis of hereditary hair diseases has highlighted a novel signaling pathway that had not previously been known to play a role in the HF development.

Hypohidrotic ectodermal dysplasia (HED), also known as Christ-Siemens-Touraine syndrome, is a rare genetic disease characterized by abnormal development of hair, teeth, and sweat glands. Most cases of HED show an X-linked recessive inheritance pattern (MIM 305100), while a minority of HED is inherited as either an autosomal dominant (MIM 129490) or an autosomal recessive trait (MIM 224900). During the last 15 years, the molecular basis for HED has gradually been disclosed. X-linked HED is caused by mutations in ectodysplasin (*EDA*) gene [80], and autosomal forms of HED are resulting from mutations in either EDA-receptor (*EDAR*) [81] or EDAR-associated death domain

disease	inheritance pattern	OMIM#	main symptoms	gene	protein, function
Hypohidrotic ectodermal dysplasia	XR	305100	Hypotrichosis, hypohidrosis, hypodontia	EDA	ectodysplasin A1 (EDA-A1)
	AD	129490		EDAR EDARADD TRAF6	EDA-A1 receptor EDAR-associated death domain TNF receptor-associated factor 6
	AR	224900		EDAR EDARADD	EDA-A1 receptor EDAR-associated death domain
Odontoonychodermal dysplasia	AR	257980	Hypotrichosis, hypodontia, nail dystrophy, PPK	WNT10A	Wnt ligand
Generalized hereditary hypotrichosis simplex	AD	605389	hypotrichosis	APCDD1	Wnt inhibitor
Localized autosomal recessive hypotrichosis 2 (LAH2)/autosomal recessive woolly hair 2 (ARWH2)	AR	604379	WH, hypotrichosis	LIPH	phosphatidic acid-selective phospholipase A1α (PA-PLA1α)
LAH3/ARWH1	AR	611452/278150	WH, hypotrichosis	LPAR6	LPA6 (LPA receptor)
Inflammatory skin and bowel disease	AR	614328	erythema, diarrhea, WH	ADAM17	Tumor necrosis factor converting enzyme (TACE)

XR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive; PPK, palmoplantar keratoderma; LPA, lysophosphatidic acid.

Table 4. Hereditary hair disorders associated with disruption of signaling pathways.

(*EDARADD*) [82] genes. The *EDA* gene encodes several isoforms of a type II transmembrane protein via alternative splicing [83]. Of these, ectodysplasin-A1 (EDA-A1) is the longest isoform which belongs to the tumor necrosis factor (TNF) ligand superfamily. EDAR, the receptor of EDA-A1 [84], is a type I transmembrane protein and a member of the TNF receptor superfamily with a potential death domain in its intracellular region. During the development of ectoderm-derived organs, EDA-A1 binds to its receptor EDAR, which subsequently associates with its adaptor EDARADD. Additionally, EDARADD protein

interacts with TNF receptor-associated factor 6 (TRAF6), which further forms a complex with TGFβ-activated kinase 1 (TAK1) and TAK1-binding protein 2 (TAB2) within the cytoplasm, leading to activate the downstream NF-κB [85]. Most recently, a heterozygous mutation in the *TRAF6* gene has been identified in a patient showing typical clinical features of HED [86]. Since EDA-A1, EDAR, EDARADD, and TRAF6 are closely related to each other in a signaling pathway, mutations in any of these four pathway components result in identical phenotypic characteristics among patients.

Odontoonychodermal dysplasia (OODD; MIM 257980) is an autosomal recessive disease which is characterized by various ectodermal abnormalities including hypotrichosis, hypodontia, nail dystrophy, and palmoplantar keratoderma. It has recently been shown that OODD is caused by loss of function mutations in the *WNT10A* gene, which encodes a WNT ligand [87]. It is noted that some affected individuals with *WNT10A* mutations can show phenotypes resembling HED [88], indicating the close relationship between EDA-A1/EDAR signaling and Wnt signaling, which has also been suggested by experiments in mice models [89].

In addition to Wnt ligands, abnormal function of Wnt inhibitors has recently been shown to cause a hereditary hair disorder in humans. Generalized hypotrichosis simplex (GHS; MIM 605389) is an autosomal dominant non-syndromic hair disorder which is characterized by progressive loss of scalp and body hairs starting in the middle of the first decade of life and almost complete baldness by the third decade [90]. In several families with GHS, an identical heterozygous missense mutation (L9R) has been identified in *APCDD1* gene on chromosome 18p11.22 [91, 92]. The *APCDD1* gene encodes a single-pass transmembrane protein which is abundantly expressed in the dermal papilla, the matrix and the hair shaft of human HF. Functional studies in cultured cells, chick embryos, and xenopus have revealed that APCDD1 inhibits Wnt signaling potentially via interacting Wnt ligands and their co-receptors LRPs [91]. In addition, it has been demonstrated that the L9R-mutant APCDD1 protein functions in a dominant negative manner against wild-type APCDD1 protein [91]. Therefore, Wnt activity is predicted to be upregulated in patients' HFs. It is postulated that chronic stimulation by Wnt signaling may result in depletion of stem cell pool in the HF bulge, leading to GHS.

Recently, a signaling of lipid mediators has been shown to play essential roles in hair growth. About a decade ago, phosphatidic acid, has been demonstrated to promote hair growth in organ culture system, suggesting a potential role of lipids in hair growth [93]. Later on, it has been reported that mutations in lipase H (*LIPH*) gene underlies an autosomal recessively-inherited hypotrichosis (Localized autosomal recessive hypotrichosis 2 (LAH2); MIM 604379) [94]. Affected individuals with LAH2 show sparse hair on their scalp and extremities, whereas facial and sexual hairs look normal. In addition, it is noteworthy that patients with *LIPH* mutations show woolly hair (WH) in high frequency (Figure 17) [95], thus the *LIPH* can be regarded as a causative gene responsible for autosomal recessive WH (ARWH). Most affected individuals with *LIPH* mutations showed mainly WH during early childhood, and then exhibited wide variability in the hypotrichosis phenotype with aging [96].

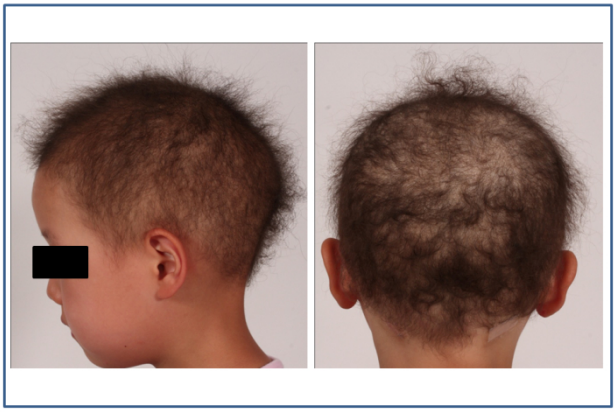

Figure 17. Clinical features of LAH2/woolly hair caused by mutations in the *LIPH* gene.

The *LIPH* gene encodes cell membrane-associated phosphatidic acid-selective phospholipase A$_1\alpha$ (PA-PLA$_1\alpha$) which produces 2-acyl lysophosphatidic acid (LPA) from phosphatidic acid [97]. As LPA activates cells through binding with its receptor, the existence of LPA receptor(s) in the HF had been expected, which has been idenitified by the analyses of additional families with ARWH/hypotrichosis without carrying mutations in the *LIPH* gene. Affected individuals in these families showed WH and associated hypotrichosis (Localized autosomal recessive hypotrichosis 3 (LAH3); MIM611452), which were almost identical phenotypes to those with *LIPH* mutations. Linkage studies and positional cloning have led to the identification of mutations in *LPAR6* gene, also known as *P2RY5*, in these families [98, 99]. The *LPAR6* gene encodes a G protein-coupled receptor LPA$_6$ (P2Y5), which has clearly been proved to be a receptor of LPA [100]. Both PA-PLA$_1\alpha$ and LPA$_6$ are mainly expressed in the IRS of human HF [24, 99]. Importantly, their expression overlaps with K71 and K74, of which mutations underlie autosomal dominant WH/hypotrichosis. Sum of these data strongly suggest the crucial roles of PA-PLA$_1\alpha$/LPA/LPA$_6$ pathway in the HF differentiation and hair growth, and its downstream signaling may be involved in regulating expression of the IRS-specific keratins. More recently, significant findings have been reported, which have revealed the downstream signaling of the PA-PLA$_1\alpha$/LPA/LPA$_6$ pathway. Inoue et al. have produced *Liph*-knockout (KO) mice which exhibited a wavy coat phenotype resembling WH in humans [101]. In addition, a series of expression studies in the mutant mice, as well as detailed *in vitro* analyses, have demonstrated that the PA-PLA$_1\alpha$/LPA/LPA$_6$ axis regulates differentiation and maturation of mouse HF via a signaling pathway composed of tumor necrosis factor converting enzyme (TACE), transforming growth facor (TGF)-α, and epidermal growth factor receptor (EGFR) [101]. It has been shown that LPA produced by PA-PLA$_1\alpha$ stimulated its receptor LPA$_6$, which subsequently activated TACE. Then, TACE induced ectodomain shedding of TGF-α, which resulted in transactivation of EGFR (Figure 18) [101]. Notably, in the HF of the *Liph*-KO mice, the expression of cleaved TGF-α, tyrosine-phosphorylated EGFR, LPA, and the IRS-specific K71, were significantly reduced [101]. Most recently, a recessively-inherited mutation in *ADAM17* gene encoding TACE have been shown to cause inflammatory skin and bowel

disease (MIM 614328) in humans, and affected individuals with the *ADAM17* mutation appear to show WH phenotypes, similar to patients with *LIPH* or *LPAR6* mutations [102]. These findings strongly suggest that the PA-PLA1α/LPA/LPA6 signaling can be involved in activating TACE in humans as well.

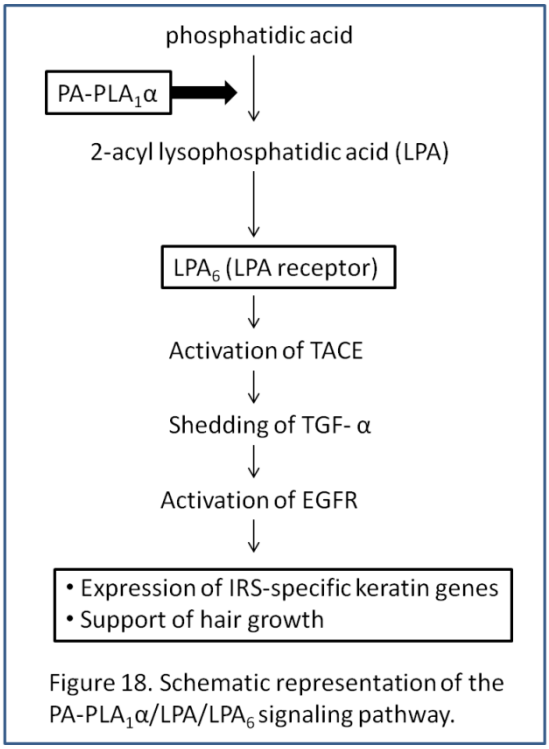

Figure 18. Schematic representation of the PA-PLA1α/LPA/LPA6 signaling pathway.

7. Conclusions

To identify causative genes responsible for hereditary hair disorders, as well as to disclose the functional relationship between these genes, has provided precious information to better understand the complex mechanisms for the HF development and cycling in humans. It is highly expected that recently-established methods in molecular genetics, especially whole genome sequencing [103], will enable us to find additional causative genes for the diseases. These genes may be associated with not only rare hair disorders, but also determining the hair texture in healthy individuals and/or more common hair diseases, such as alopecia areata and androgenetic alopecia.

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