Inherited Disorders of the Hair

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GLOSSARY

**Acanthosis nigricans** – an ill-defined, velvety, hyperpigmented plaque involving the fold of the skin, including the axilla, neck and groin

**Atrichia** – absence of hair

**Atrophoderma** – atrophy of the skin

**Blepharitis** – inflammation of the eyelids

**Cicatricial alopecia** – scarring alopecia

**Copy number variations** – DNA segments with 1 kb or more of gains or losses

**Corneodesmosin** – a protein found in corneodesmosomes that is highly expressed in the upper layers of the epidermis, contributing to the skin membrane barrier. Moreover, corneodesmosin in highly expressed in the inner root sheath of the hair follicle

**Desmocollins** – specialized cadherin proteins that interact with themselves and with other proteins contributing to the formation of desmosomes

**Desmogleins** – specialized cadherin proteins that interact with themselves and with other proteins contributing to the formation of desmosomes

**Desmoplakins** – specialized proteins that connect the intermediate filaments to the desmosomal plaque, contributing to cellular integrity

**Desmosomes** – specialized intercellular structures that function in cell–cell adhesion

**Ectodermal dysplasia** – a group of disorders characterized by abnormal development of at least one of the following structures: hair, nails, sweat glands, and teeth

**Ectrodactyly** – also known as split hand foot. It is characterized by loss or defective central hand or foot digits, giving the appearance of lobster claws

**Forelock** – the area above the central part of the forehead

**Hemophagocytosis** – phagocytosis of blood components by histiocytes. It can occur in the bone marrow and other tissues

**Heterochromia** – a difference in color. Most commonly used to describe different iris colors

**Ichthyosis** – dry, thickened, scaly and flaky skin that resembles the skin of fish

**Ichthyosis linearis circumflexa** – migratory polycyclic and serpiginous erythematous plaques with double-edged scale at the margins, which are characteristic of Netherton syndrome

**Keratoderma** – disorders characterized by thickening of the skin of the palms and soles

**Keratosis follicularis** – in the text we used this term to describe erythematous papules arising in follicular regions; distinct from another genetic condition also known as keratosis follicularis, Darier’s disease

**Milia** – white, keratin-filled papules that can appear on skin and mucous membranes

**Moniliform hair** – hair where several regular nodes are formed secondary to defects in the hair cortex

**Pachyderma** – thickening of the skin and particularly of the dermis resembling the thick skin of the elephant

**Pili torti** – twisted hair

**Plakoglobins** – belong to the family of armadillo proteins and are constituents of desmosomes and intermediate junctions

**Plakophilins** – belong to the family of armadillo proteins and are constituents of desmosomes

**Placode** – embryonic thickening of the epithelial layer from which the hair develops

**Steatocystomas** – epidermal cystic lesions that lack a granular layer and contain yellowish oily liquid and frequently hair structures and sweat glands

**Synophrys** – confluence of the eyebrows

**Trichomegaly** – excessive growth of the eyelashes

**Trichorrhexis invaginata** – also known as bamboo hair. A hair shaft anomaly due to intussusception of the hard keratinized part of the hair follicle into the softer non-keratinized portion

**Trichorrhexis nodosa** – weakening of the hair follicle leading to hair follicle splitting, giving the appearance of a broom

**Trichoschisis** – a transverse break of the hair shaft at a region that is devoid of cuticle

**Vesicle** – a fluid-filled membrane-enclosed elevation in the skin
Woolly hair – is characterized by hair shaft anomalies that clinically present with tightly curled hair. Woolly hair is distinct from the tightly curly hair in African populations in that woolly hair shows hair shaft anomalies which can lead to hair loss and hair depigmentation.

152.1 INTRODUCTION AND HAIR ANATOMY

The hair follicle (HF) is an important epidermal structure that plays a role in maintaining adequate internal body temperature control for several species during temperature extremes, and provides the first line of defense against environmental changes, toxins, and infectious agents. The hair is composed of several layers in cross section that work together in maintaining its integrity. The layers from the inside to the outside (Figure 152-1) are as follows. First is the hair shaft, which is made up of three layers: the medulla in the center is surrounded by the hair cortex and the hair shaft cuticle externally. The hair shaft is then surrounded by the inner root sheath (IRS), which itself is made up of three layers: the innermost part is referred to as the IRS cuticle, the middle part Huxley’s layer, and the external part is Henle’s layer. The IRS is then surrounded by a one-cell layer known as the companion layer, which separates the IRS from the next layer, the outer root sheath (ORS) of the HF. During growth and differentiation of the several layers, keratin proteins are being expressed abundantly and differentially, providing a rigid structure for the HF. These keratins interact with the desmosomes formed between the cells, contributing to the integrity of the HF. Importantly, several mutations in keratins, desmosomes, and other proteins regulating their expression have been linked to several phenotypes in human hair disorders.

Longitudinally, the hair can be roughly separated into four regions (Figure 152-2): the bulb, which contains the matrix, the site where melanocytes reside, and which surrounds the dermal papilla (DP); the suprabulbar region, extending up to the site of arrector pili muscle insertion (the area of the bulge that contains the HF stem cells); the isthmus region, extending between the arrector pili muscle and the sebaceous gland; and the infundibular region that extends from the sebaceous gland to the skin surface. All the layers of the HF are derived from the hair matrix except for the ORS, which is contiguous with the basal interfollicular epidermis.

152.2 HF MORPHOGENESIS AND CYCLING

The formation of mammalian HFs occurs during embryogenesis through a series of reciprocal interactions between the ectoderm (epidermis) and the underlying...
mesoderm (dermis) (3). The initial signal for hair development originates from the dermis, which signals to the overlying epithelium to form the placode. It is widely believed that the first signal is related to the Wnt signaling pathway (4). Wnt in the epidermis leads to abundance of β-catenin, which forms the placode (5). The placode then signals to the underlying mesoderm, forming the dermal condensate. Reciprocal signaling between the two compartments leads to the downgrowth of the placode (6,7). The placode then surrounds the dermal condensate, which will later on become the DP, and the cells in the placode proliferate and differentiate to make the several layers of the HF. Wnt/β-catenin expression is required for the activation of its direct transcriptional target, EDA receptor (EDAR), and therefore nuclear factor kappa B (NF-κB) signaling (8). EDAR functions in suppressing the placode inhibitory factors, mainly Dkk1, and thus indirectly potentiates the activity of the Wnt/β-catenin pathway (9).

Once the HF is formed, it begins to cycle. The hair cycle is divided largely into three phases (Figure 152.3), in addition to a recently described fourth phase, exogen (10). The growth phase, regression phase, rest, and shedding phases are termed anagen, catagen, telogen, and exogen, respectively. During cycling, the portion of the HF below the level of the isthmus goes through cyclic growth and regression, while the portion above the isthmus is permanent. The anagen phase is the longest phase, with variable duration depending on the body site. Generally, the anagen phase in the human scalp (longest hair anagen phase in humans) lasts 4–6 years. During the anagen phase, the lower part of the permanent HF (bulge) grows downward and forms the matrix of the HF, which differentiates into the various HF compartments (1). During the telogen phase, the club hair is encased by the permanent portion of the HF, while during catagen the lower part of the HF undergoes apoptosis and regresses toward the permanent portion.

152.3 THE HAIR KERATINS AND THEIR REGULATION

The human genome has 54 functional annotated keratin genes, among which 28 belong to the type I keratin gene cluster and 26 belong to the type II gene cluster. All type II keratin genes cluster together on chromosome 12q13.13, while type I keratin genes cluster on chromosome 17q21.2, with the exception of keratin K18, a type I keratin, which is located in the type II keratin gene domain (11).

Among type I genes, 11 code for type I hair keratins, designated K31–K40 (previously known as Ha1–Ha8, Ka35, Ka36), while 17 code for type I epithelial keratins. Likewise, six of the type II genes encode hair keratins designated K81–K86 (previously known as Hb1–Hb6) while the remaining 20 code for epithelial keratins (12,13).

The main difference between hair and epithelial keratins is that hair keratins possess a greater amount of sulfur in their head and tail domains, which enables them to form tight cross-linking with keratin-associated proteins (KAPs) (14) that contribute to the hard structure of both hair and nails. Hair keratins are mainly expressed in the hair cortex and cuticle, and are structurally divided into three functional regions: the head domain, close to the N-terminus; the α-helical rod domain, which includes the helix initiation and termination motifs; and the tail domain, which is close to the C-terminus. The rod domain is essential for the correct assembly with keratins of the opposite type, and therefore functional intermediate filaments. The head and tail domains are required for the interaction of the keratins with the KAPs (11).
The differentiation of the hair and hair compartments involves the coordinated spatial and temporal expression of a large number of keratin genes. The production of the different keratins is a tightly regulated process that involves several transcription factors and proteins. FOXN1 plays a crucial role in the activation of genes involved in cortex and IRS differentiation. The most commonly affected keratins are keratin 33 and keratins 81, 85, and 86. Moreover, downstream molecules of the Wnt signaling pathway trigger matrix cells toward cortex differentiation. HOXC13 is another transcription factor that is implicated in the regulation of hair keratins. The expression of HOXC13 overlaps with that of keratins 32, 35, 82, and 85. DLX3, a homeobox transcription factor, is another factor which regulates early signaling within the matrix, regulating the expression of hair keratin genes in the hair shaft and IRS. Several human hair phenotypes and syndromes with mutations in keratins or their regulatory proteins have been identified and will be discussed later in the chapter.

**152.4 DESMOSOMES OF THE HF**

Desmosomes are intracellular adhesion structures that are critical for cell–cell attachment in the epithelial and myocardial tissues and in other tissues. The desmosomal cadherin family is a major structural unit of the desmosome. It is composed of desmogleins (DSGs) and desmocollins (DSCs). DSGs and DSCs are glycoproteins containing a single transmembrane domain, through which they interact extracellularly, contributing to intercellular adhesion. Intracellularly, the cadherins bind to plakoglobin, plakophilins, and indirectly to desmoplakin, forming the desmosomal plaque. The desmosomal plaque interacts with the keratin intermediate filaments (KAFs). These interactions impart resilience and strength, and allow the distribution of physical impacts throughout tissues.

DSG(1–4) are all expressed in the human HF. DSG4 is highly expressed in the precortex, keratinizing zone of the cortex, lower hair shaft cuticle, and the upper IRS cuticle. DSG4 expression is regulated by several transcription factors, including HOXC13 and FOXN1. Thus it is perhaps not surprising that mutations in any of these components would be associated with hair disorders.

**152.5 GENETICS OF HYPOTRICHOSIS AND OTHER STRUCTURAL HAIR ABNORMALITIES**

Hypotrichosis denotes loss or reduction of HF density or integrity, and can affect any site on the body in both men and women. We and others have identified several genes associated with different types of hypotrichosis, where...
hypotrichosis occurs as an isolated finding or in the setting of a syndrome.

152.5.1 Disorders Involving the Wnt/β-Catenin Pathway

152.5.1.1 Odonto-Onychodermal Dysplasia and Schopf–Schulz–Passarge Syndrome. Odonto-onychodermal dysplasia (OODD; Online Mendelian Inheritance in Man (OMIM) 257980) is a rare autosomal recessive condition, described first in Lebanese families, and is characterized by hypotrichosis, onychodysplasia, palmar erythema and hyperhidrosis, palmoplantar keratoderma (PPK), oligodontia, and diffuse follicular hyperkeratosis. This condition is associated with deactivating mutations in the \( WNT10A \) gene, which produces an activator ligand of the Wnt/β-catenin signaling pathway (19). In addition to being crucial in hair morphogenesis, the Wnt/β-catenin pathway is also critical in the formation of other ectodermal structures. Not all patients with mutations in the \( WNT10A \) gene will present with hypotrichosis, perhaps due to the presence of several Wnt activator ligands that may compensate for its absence. Schopf–Schulz–Passarge syndrome (SSPS; OMIM 224750) is allelic to OODD, with mutations in the \( WNT10 \) gene. SSPS has a similar presentation to OODD but a distinguishing feature is apocrine hidrocystomas (benign tumors of the sweat glands) that occur around the eyelids (20).

152.5.1.2 Generalized Hereditary Hypotrichosis Simplex. Hereditary hypotrichosis simplex (HSS; OMIM 605389) is an autosomal dominant condition characterized by a progressive hair loss involving the scalp, face, and body hair (Figure 152-4) (21). Patients generally start to lose hair starting in the second half of the first decade, and progress to complete hair loss by the third decade of life. We have recently identified the gene mutated in this condition, \( APCDD1 \), in Pakistani and Italian families (22). We have demonstrated that \( APCDD1 \) is a membrane-tethered protein abundantly expressed in the DP, the matrix, and the hair shaft of human HF. Unlike \( WNT10 \), which functions as an activator of the Wnt/β-catenin pathway, \( APCDD1 \) is an inhibitor of Wnt/β-catenin. Mutations in \( APCDD1 \) are dominant negative against the wild-type allele. Therefore, we suggest that when \( APCDD1 \) is mutated, Wnt/β-catenin is continuously activated, leading to depletion of HF stem cells. This may explain why people initially have normal hair and subsequently develop progressive hair loss.

152.5.2 Human Hair Disorders Involving the EDA-A1/EDAR/EDARADD Signaling Pathway

The EDA-A1/EDAR/EDARADD signaling pathway is part of tumor necrosis factor (TNF) superfamily pathway, and is crucial in hair morphogenesis since it functions to potentiate the activity of Wnt/β-catenin (see Section 152.2). Moreover, the TNF pathway is crucial for the development of other ectodermal structures, including teeth and sweat glands. EDA is a member of the TNF family and is a type II transmembrane protein that consists of three regions. In order to become functionally active, EDA must be cleaved and released out of cells, where it forms a trimer and binds to the EDAR (23). EDAR is a type I transmembrane protein and a member of the TNF receptor superfamily, with a
cysteine-rich domain in the extracellular region as well as a potential death domain in its intracellular region \(^{(18)}\). Usually, EDA-A1 binds to EDAR and activates it, which then interacts with EDARADD through its death domain, resulting in the activation of NF-κB \(^{(24)}\). Activation of NF-κB is essential for the development of the ectodermal structures and therefore mutations in genes along the TNF pathway lead to ectodermal dysplasia syndromes with overlapping clinical features, including sparse hair.

**152.5.2.1 Hypohidrotic Ectodermal Dysplasia.** Hypohidrotic ectodermal dysplasia (HED) is a disorder affecting the hair, teeth, and sweat glands. Clinically, patients show hypotrichosis and characteristic facies with a saddle nose, periorbital wrinkling with hyperpigmentation, conical teeth, and oligodontia (Figure 152-5), (see Chapter 148). Due to the impaired development of sweat glands, patients present with unexplained bouts of recurrent fevers. HED is most commonly inherited in an X-linked pattern (OMIM 305100) due to mutations in the EDA-A1 gene, although autosomal dominant (OMIM 129490) and autosomal recessive (OMIM 224900) inheritance due to mutations in the autosomal EDAR and EDARDD genes have been reported \(^{(18)}\).

**152.5.2.2 X-linked Anhidrotic Ectodermal Dysplasia with Immunodeficiency and Incontinentia Pigmenti.** X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID; OMIM 300291) is an X-linked recessive disorder that occurs mainly in males. This condition is caused by hypomorphic mutations in the \(IKBKG\) (inhibitory κB kinase \(γ\) gene), which encodes NEMO (NF-κB essential modulator). The activity of NEMO is compromised, along with the TNF signaling pathway. Therefore, patients present with many features overlapping those of HED including the characteristic facies, atrichia or hypotrichosis, hypohidrosis, oligodontia, and recurrent bouts of unexplained fevers. The main feature that distinguishes XL-EDA-ID from HED is the recurrent infections beginning early in life, since NF-κB is required for the maturation of the immune system \(^{(25)}\). Incontinentia pigmenti (IP; OMIM 308300) is an X-linked dominant condition which is allelic to XL-EDA-ID. Unlike XL-EDA-ID, IP results from complete loss-of-function mutations in the NEMO gene and therefore this condition occurs almost exclusively in females because most males, except for those who are mosaic or are 47XXY, will die in utero \(^{(26)}\). Clinically, patients present with perturbations in skin pigmentation with a variety of malformations affecting the skin, hair, teeth, eyes, heart, and central nervous system. The characteristic skin signs occur in four highly stereotyped stages: at birth, patients are born inflammatory vesicles; these change few months later into verrucous patches; later on, the verrucous patches will be replaced with a distinctive pattern of hyperpigmentation; and the fourth stage is characterized by dermal scarring \(^{(27)}\).

**152.5.3 Human Hair Disorders Involving the Keratins and Their Regulators**

**152.5.3.1 Monilethrix.** Monilethrix (OMIM 158000) is a condition that affects the hair and sometimes the nails, and is most commonly inherited in an autosomal dominant pattern, though autosomal recessive patterns have recently been reported. It is clinically characterized by dystrophic alopecia that involves most commonly the occipital region of the scalp, but in more severe cases can involve the entire scalp, eyebrows, eyelashes, body hair, and nails (Figure 152-6). Patients may also develop keratosis follicularis and perifollicular erythema. Monilethrix is mostly caused by mutations in the type II hair keratins K81 and K86, and less commonly K83.
The most common site of mutations was localized to the conserved helix termination motifs of K81, K86 and K83, followed by the helix initiation motifs. These keratins are highly expressed within the hair cortex, and are critical to the normal development of the cortex. Mutations in these keratins result in hairs with a beaded appearance because of a periodic decrease in diameter along the hair shaft. To date, no mutations linked to monilethrix have been associated with mutations in type I hair keratins.

**152.5.3.2 Pure Hair and Nail Ectodermal Dysplasia.** Several types of pure hair and nail ectodermal dysplasias (OMIM 602032) with either autosomal recessive or autosomal dominant pattern of inheritance have been reported. To date, only mutations in K85, a type II hair keratin that is critical for the normal development of the HF, have been linked to recessive pure hair and nail ectodermal dysplasia. Patients with autosomal recessive pure hair and nail ectodermal dysplasias are characterized by total alopecia and dystrophic nails (Figure 152-7). K85 is mainly expressed in the matrix of the follicle, which might explain the severe phenotype in these patients.

**152.5.3.3 Autosomal Dominant Woolly Hair.** We and others have recently identified keratin 74, a type II IRS keratin, as the cause of autosomal dominant woolly hair (ADWH; OMIM 194300) in a four-generation Pakistani family. Patients with ADWH report a slowly growing hair which stops growing at few inches. Clinically they are characterized by dry and coarse woolly hair with normal hair density. More recently, Wasif et al. reported mutations in keratin 74 in the setting of hypotrichosis (33). Therefore, within the same family, keratin 74 can cause either woolly hair or hypotrichosis.

**152.5.3.4 Loose Anagen Hair Syndrome.** Loose anagen hair syndrome (LAHS; OMIM 600628) is a sporadic hair disorder but an autosomal dominant pattern of inheritance has been suggested. LAHS is clinically characterized by anagen hairs that are easily plucked from the scalp with no pain. Generally, hair shafts have reduced caliber but are not fragile and not easily broken. It has been proposed that defects in keratin 75, a type II keratin in the companion layer, may underlie LAHS.

**152.5.3.5 Pachyonychia Congenita Type II (Jackson–Lawler Syndrome).** Pachyonychia congenita type II (PCII; OMIM 167210) is a rare genodermatosis characterized by thickened nails, PPK, natal teeth, and steatocystomas. Although not commonly associated with
a hair phenotype, patients can develop pili torti when keratin 17, an ORS keratin, is mutated (1).

152.5.3.6 T-Cell Immunodeficiency with Congenital Alopecia and Nail Dystrophy. T-cell immunodeficiency with congenital alopecia and nail dystrophy (OMIM 601705) is an extremely rare autosomal recessive condition first identified in southern Italy. Patients present with congenital alopecia, nail dystrophy, and severe infections due to T-cell immunodeficiency. Patients usually succumb to the infections during their first year of life. Mutations have been identified in the FOXN1/WHN gene, a regulator of keratin expression (35). FOXN1 plays a critical role in the development of the thymus, the site where T cells mature and become competent, and is a transcriptional regulator of many hair keratin genes.

152.5.3.7 Tricho-Dento-Osseous Syndrome. Tricho-dento-osseous syndrome (TDO; OMIM 190320) is an autosomal dominant condition caused by mutations in the DLX3 gene, a regulator of keratin expression. This condition is associated with very tightly curled hair, enamel hypoplasia, and diffuse bony abnormalities (36).

152.5.4 Human Hair Disorders Involving the Desmosomes

152.5.4.1 Localized Autosomal Recessive Hypotrichosis/Monilethrix. Localized autosomal recessive hypotrichosis (LAH; OMIM 607903) is a rare nonsyndromic hair disorder in which patients present with hypotrichosis involving the scalp, chest, arms, and legs. The eyebrows and beard are partially affected, and the axillary hair, pubic hair, and eyelashes are normal. We and others have identified mutations in the desmoglein 4 (DSG4) gene as the cause of LAH (37). We and others subsequently identified DSG4 mutations in the setting of autosomal recessive monilethrix (38). DSG4 is the only desmoglein member expressed in the keratinizing zone of the hair shaft cortex, overlapping with the expression of the hair keratins K81, K83, and K86 (18). We postulated that abnormal DSG4 proteins alter the switch from the proliferation to the differentiation of trichocytes, leading to abnormal and premature keratinization of the hair shaft, resulting in beaded hair as part of the phenotype in some cases (37).

152.5.4.2 Ectodermal Dysplasia/Skin Fragility Syndrome. Ectodermal dysplasia/skin fragility syndrome (OMIM 604536) is an autosomal recessive genodermatosis that presents clinically with skin fragility (with trauma-induced erosions and blistering), short and sparse hair, PPK, thickened and dystrophic nails, and occasionally hypohidrosis. This condition is caused by mutations in the plakophilin 1 (PKP1) gene (38). Examination of patients’ epidermis under electron microscopy demonstrated aberrant cytoplasmic distribution of desmplakin (DSP) and perinuclear aggregation of KIFs, which indicated that loss of PKP1 led to disruption in DSP distribution and abnormal aggregation of KIFs. Moreover, PKP1 affects the size and number of desmosomes, keratinocyte cell migration, and the calcium stability of desmosomes (39).

152.5.4.3 Cardiocutaneous Diseases: Naxos Disease and Carvajal Syndrome. DSG2 and DSC2 are predominantly expressed in the myocardium of the heart. Heterozygous mutations in the DSG2 or DSC2 genes have been reported to underlie arrhythmogenic right ventricular cardiomyopathy (ARVC) as their only clinical manifestation (OMIM 107970) (40,41). Disruption of the desmosomal plaque components PKG or DSP results in several hereditary diseases involving not only the heart, but also the skin and hair. Naxos (OMIM 601214) and Carvajal (OMIM 605676) syndromes are autosomal recessive human disorders characterized by woolly hair, PPK, and cardiomyopathy, which result from protein truncating mutations in the desmosomal components PG and DP, respectively (42,43). Two homozygous
mutations in the gene encoding PG were also found to underlie skin fragility accompanied by diffuse PPK and woolly hair, without heart abnormalities. Interestingly, one of these mutations resulted in sparse and woolly hair, whereas patients harboring the other mutation had abundant woolly hair (44). Over 40 human mutations in the DSP gene have been shown to cause either skin or heart disease, or a combination of skin, hair, and heart abnormalities, underscoring its importance for the development and integrity of these tissues. Like PG, DSP mutations can be associated with hair abnormalities, with both woolly hair and alopecia being described (45).

152.5.4.4 Hypotrichosis and Recurrent Skin Vesicles. Hypotrichosis with recurrent skin vesicles (OMIM 613102) is a recently described condition with an autosomal recessive pattern of inheritance, first identified in the Pakistani population. Clinically, affected individuals present with sparse scalp, facial, and body hair with fragile hair shafts, as well as recurrent diffuse vesicles involving the scalp and body and non-mucosal surfaces of the body that heal without scarring. The disease was mapped to the DSG–DSC gene cluster on chromosome 18q12.1, and a homozygous nonsense mutation in the DSC3 gene was subsequently identified in all affected individuals (46).

152.5.4.5 Hereditary Hypotrichosis Simplex of the Scalp. Hereditary hypotrichosis simplex of the scalp (HHSS; OMIM 146520) is an autosomal dominant disorder with heterozygous nonsense mutations in the CDSN gene (47). Clinically, patients present with hypotrichosis limited to the scalp. CDSN is expressed in the IRS of the HF. Aggregates of abnormal CDSN can be detected around the HF, as well as in the papillary dermis in patients’ skin, suggesting that they are toxic to the HF. Thus, the mutant CDSN protein appears to function in a dominant negative manner (47). Recently, homozygous mutations in CDSN have also been reported in the setting of generalized inflammatory skin peeling syndrome, an autosomal recessive skin disorder characterized by superficial splitting of the upper layer of the epidermis (48) (OMIM 270300).

152.5.5 Woolly Hair Related to the LIPH/LPA/LPAR6 Signaling Pathway

Lipase H (LIPH) encodes a member of the phospholipase A1 family and is required for the synthesis of lysophosphatidic acid (LPA) (49). LPAR6 (also known as P2RY5) encodes the receptor P2Y5, a seven transmembrane G-protein-coupled receptor (GPCR). Recently, it was found that LPA is a ligand for the receptor P2Y5, which explains the similar phenotypes in patients with either P2RY5 or LIPH gene mutations. Moreover, the expression of P2Y5 overlaps with that of LIPH in the HF (50). These data underscore the important role of the LPA/P2Y5 signaling pathway in the normal development of the HF (51). P2Y5 is mainly expressed in the inner root hair sheath of the HF that arises from the hair matrix and differentiates before the keratinocytes of the central hair matrix. This provides support for the normal development of the hair shaft, and perhaps explains why the hair becomes twisted when LPA/P2Y5 is disrupted, resulting in a woolly hair phenotype. In addition to the scalp hair abnormalities, patients can develop sparse eyebrows, eyelashes, axillary, and body hair, but usually the beard hair is normal.

152.5.5.1 Autosomal Recessive Woolly Hair and Autosomal Recessive Hypotrichosis. We and others have recently shown that mutations in LPAR6 and Lipase H (LIPH) are associated with autosomal recessive woolly hair (ARWH; OMIM 278150) and/or autosomal recessive hypotrichosis (OMIM 611452) (50,52). Mutations in both genes result in a clinically indistinguishable phenotype, which can range from woolly hair to hypotrichosis and complete loss of hair (Figure 152-9) (50). Generally, patients initially present with woolly hair, after which approximately 50% will progress to develop hypotrichosis of variable severity with age. Histology is consistent with decreased number of HFs with miniaturization (53).

152.5.6 Hair Disorders Related to the Hair Cycle Regulator, Hairless (HR)

152.5.6.1 Atrichia with Papular Lesions. Atrichia with papular lesions (APL; OMIM 209500) is a recessive condition due to mutations in the hairless gene on chromosome 8 (54). Patients initially are born with normal hair density and hair loss occurs few months later, leading to complete alopecia without regrowth of the hair. Patients will later develop milia-like papules involving the face, arms, and knees (54) (Figure 152-10). This condition is frequently misdiagnosed as alopecia areata (AA; see Section 152.9.1). A main distinguishing feature from AA is the presence of milia-like papules in APL. Hairless is expressed in the HF, where it plays a pivotal role in the hair cycle (55). During the regression phase (catagen) the lower part of the HF is degenerated, and under certain stimuli probably related to a cross talk between the DP and the bulge, HF stem cells are activated to regenerate the hair and go back to the anagen phase. Hairless appears to mediate the cross talk between the DP and bulge compartments, leading to the progression of the hair cycle from catagen to anagen. Thus, failure of communication between the DP and the bulge will lead to the arrest of hair growth after the first cycle (56). Mutations in the VDR have been associated with vitamin-D-resistant rickets (OMIM 277440) where patients develop hair loss and milia-like papules similar to APL in association rachitic bone changes during mid to late infancy (57).

152.5.6.2 Marie–Unna Hypotrichosis. Marie–Unna hypotrichosis (MUh; OMIM 146550) is a nonsyndromic hereditary hair disease with an autosomal
dominant pattern of inheritance. MUH is clinically characterized by three stages: at birth, affected individuals present with sparse scalp and facial hair, with subsequent development of coarse, wiry, and twisted hairs in early childhood. Later on during adolescence, affected individuals develop complete hair loss, resembling androgenetic alopecia (AGA). Recently, Wen et al. (58) reported that the 5′-untranslated region
(5′-UTR) of the HR gene has four potential upstream open reading frames (uORFs), designated U1HR–U4HR. Sequencing of these four uORFs of 19 families with MUH revealed that affected individuals in all 19 families carried heterozygous nucleotide changes within the U2HR (58).

152.5.7 Hair Disorders with Mutations in the P-Cadherin (CDH3) Gene

152.5.7.1 Hypotrichosis with Juvenile Macular Dystrophy and Ectodermal Dysplasia with Ectrodactyly and Macular Dystrophy. Mutations in the CDH3 gene, encoding P-cadherin, have been shown to underlie two distinct autosomal recessive hereditary diseases in humans. Mutations in CDH3 were identified in families with hypotrichosis with juvenile macular dystrophy (HJMD; OMIM 601553), which is characterized by sparse hair and weak eyesight due to progressive macular dystrophy of the retina (59). Patients will, on average, be completely blind by the age of 40 years. More recently, mutations in CDH3 were also identified in ectodermal dysplasia and ectrodactyly with macular dystrophy (EEM) syndrome (OMIM 225280) (Figure 152-11) (60). For the same mutation, members within the same family will either have HJMD or EEM. Affected individuals with EEM syndrome show common hair and eye phenotypes with HJMD; however, EEM patients also have the additional clinical manifestation of split-hand/foot malformation (SHFM), suggesting crucial roles for P-cadherin in the development not only of hair and the retina but also of the limb. Mutations in p63, a major transcription factor in epithelial tissues, cause several autosomal dominant diseases, such as ectodermal dysplasia, ectrodactyly, and cleft lip/palate (EEC) syndrome, which shows phenotypic overlap with P-cadherin mutations in hair and limbs (61). We have shown that p63 colocalizes with P-cadherin in developing HF placode and limb buds during mouse embryogenesis. Furthermore, we have demonstrated that CDH3 is a direct target gene of p63 (60). Our data underscores the critical role of P-cadherin in the HF, as well as in limb development.

152.5.8 Disorders of Pigmentary Hair

152.5.8.1 Griscelli Syndrome. Griscelli syndrome is divided into three types: Griscelli syndrome I (GS 1; OMIM 214450) is an autosomal recessive condition characterized by light skin, silvery hair, and neurologic impairment. Mutations occur in the MYO5A gene (62). GS 1 is also known as Elejalde syndrome. Griscelli syndrome type 2 (GS 2; OMIM 607624) is the most severe among the three types, inherited in an autosomal recessive pattern, and characterized by light skin, silvery hair, and severe immunodeficiency and lymphohistiocytic hemophagocytosis, requiring bone marrow transplantation (63). GS 2 is associated with mutations in the RAB27A gene. Griscelli syndrome type 3 (GS 3; OMIM) is the most benign of the three types and is characterized exclusively by light skin and silvery hair. Mutations occur either in the MYO5A or the melanophilin gene (64). The skin color defect in GS is not due to impaired synthesis of melanin but is secondary to the impaired delivery of the pigment to the appropriate location in the skin and HF.

152.5.8.2 Chédiak–Higashi Syndrome. Chédiak–Higashi syndrome (CHS; OMIM 214500) is an autosomal recessive condition associated with mutations in the...
LYST gene (65). Clinically, patients present with light-colored skin, silvery hair, photophobia, recurrent infections, and neuropathy. Most individuals will develop an accelerated phase of an uncommon lymphoproliferative disorder characterized by lymphohistiocytic infiltrates, hepatomegaly, hypersplenism, jaundice, and pancytopenia. If not treated with bone marrow transplantation, most patients will die in their first decade of life (66). The most common cause of death is either infection or severe bleeding due to thrombocytopenia. Patients who survive past the first decade will go on to develop progressive neurologic impairment. The gene mutation in CHS affects the synthesis of granules in different types of cells, including immune cells and melanocytes, which explains the clinical features of CHS. 152.5.9.3 Cross Syndrome. Cross syndrome (OMIM 257800), also known as Kramer syndrome or oculocerebro-encephal syndrome with hypopigmentation, is an extremely rare autosomal recessive condition with unknown genetic defect. Clinically, patients present with light-colored skin, silvery hair, microphthalamia, corneal clouding, spastic paraplegia, and developmental delay (67).

152.5.9 Disorders Associated with Light-Colored Hair

152.5.9.1 Albinism. Albinism is divided into four major subtypes according to different genetic basis and clinical features. Type I oculocutaneous albinism (OCA1; OMIM 606952) and type II oculocutaneous albinism (OCA2; OMIM 203200) most commonly present with light-colored hair. OCA1 occurs secondary to mutations in the tyrosinase gene which is required for the synthesis of melanin, while OCA2 occurs secondary to mutations in the P gene which is required for regulating the PH for the normal functioning of tyrosinase. Clinical features associated with albinism include decreased pigmentation in the eyes, decreased visual acuity, and nystagmus (68).

152.5.9.2 Hermansky–Pudlak. Hermansky–Pudlak syndrome (HPS; OMIM 203300) is a rare autosomal recessive disorder, most commonly occurring in the Puerto Rican population, that clinically resembles oculocutaneous albinism, with recurrent episodes of bleeding, granulomatous colitis, cardiomyopathy, kidney failure, and progressive fatal pulmonary fibrosis. At least eight types of HPS exist; HPS3 being the most common, with recurrent episodes of bleeding, granulomatous colitis, cardiomyopathy, kidney failure, and progressive fatal pulmonary fibrosis. At least eight types of HPS exist; HPS3 being the most common, with mutations in the HPS3 gene (69).

152.5.9.3 Waardenburg Syndrome. Waardenburg syndrome (WS) is divided into four types: WS1 (OMIM 193500), WS2 (OMIM 193500), WS3 (OMIM 148820) and WS4 (OMIM 277580). WS1 and WS3 are caused by mutations in the PAX3 gene, type 2 is caused by mutations in the MITF gene, and type 4 is caused by mutations in SOX10 or the endothelin-B receptor gene (EDNRB). All forms of WS are inherited in autosomal dominant pattern. The common clinical features among all types of WS include a characteristic white forelock with premature graying of the hair, heterochromic irides, and sensorineural deafness (70).

152.5.9.4 Piebaldism. Piebaldism (OMIM 172800) is a rare autosomal condition characterized by mutations in the KIT gene. Affected individuals are clinically characterized by a white forelock and depigmented skin patches involving one side of the body that do not cross the midline. The gene defect is presumed to cause abnormal migration of melanocytes from the neural crest during development (71).

152.5.9.5 Phenylketonuria. Phenylketonuria (PKU; OMIM 261600) is an autosomal recessive condition caused by mutations in phenylalanine hydroxylase. Phenylalanine hydroxylase is required for the conversion of phenylalanine to tyrosine that is required for melanin synthesis. Patients usually have light-colored skin and hair, secondary to melanin deficiency, eczema, epilepsy, and severe neurologic and developmental abnormalities (72).

152.5.10 Disorders Associated with Trichorrhexis Nodosa

152.5.10.1 Netherton Syndrome. Netherton syndrome (NS; OMIM 256500) is an autosomal recessive genodermatosis caused by mutations in the SPINK5 gene, which encodes the serine protease inhibitor LEKTI that functions in the formation of the skin membrane barrier. Affected individuals are born with nonspecific erythoderma covered with fine scales. Patients then develop severe atopic dermatitis, hair loss, a characteristic ichthyosis known as ichthyosis linearis circumflexa, and rarely hypernatremic dehydration and failure to thrive. The most common hair abnormality in NS is trichorrhexis nodosa, although trichorrhexis invaginata is diagnostic. The preferred site to examine the hair abnormalities is the eyebrows (73).

152.5.10.2 Menkes Kinky Hair Syndrome. Menkes disease (MNK; OMIM 309400) is an X-linked recessive condition caused by mutations in the ATP7A gene, encoding a copper-ATPase transporter. Patients with MNK have copper deficiency and clinically present with growth retardation, cerebral and cerebellar degeneration, dementia, seizures, and kinky hair that on light microscopy shows pili torti (see below), moniliform hairs (see below) and trichorrhexis nodosa (74).

152.5.10.3 Argininosuccinic Aciduria. Argininosuccinic aciduria (OMIM 207900) is an autosomal recessive condition caused by mutations in the gene encoding argininosuccinate lyase, one of the enzymes in the urea cycle. Affected individuals become symptomatic early after birth and show hyperammonemia, encephalopathy, respiratory alkalosis, convulsions, liver enlargement, dry skin, and brittle hair that reveals trichorrhexis nodosa under light microscopy. It is presumed that the brittle hair is secondary to deficiency in arginine (75).
152.5.10.4 Citrullinemia. Citrullinemia (OMIM 215700) is an autosomal recessive condition caused by mutations in the gene encoding argininosuccinate synthetase, which also forms part of the urea cycle. Patients have similar features to those with argininosuccinic aciduria (76).

152.5.11 Disorders Associated with Pili Torti

152.5.11.1 Bjornstad Syndrome. Bjornstad syndrome (BJS; OMIM 262000) is an autosomal recessive disorder caused by mutations in the BCS1L gene. Clinical features include progressive sensorineural deafness, hair loss secondary to pili torti, and hypogonadism. Mutations in BCS1L lead to accumulation of reactive oxygen species, to which the hair and ears are sensitive (77).

152.5.12 Disorders Associated with Trichoschisis

152.5.12.1 Trichothiodystrophy. Trichothiodystrophy (TTD) is a rare autosomal recessive condition in which the hair is brittle, with trichoschisis and a low sulfur and cysteine content. On polarized microscopy, the hair displays an alternating dark and light banding pattern, which is referred to as tiger tail banding. TTD can be clinically divided into several types. To date, three genes have been implicated in the pathogenesis of TTD: XPB, XPD (mutated in photosensitive TTD), and TTDN1 (mutated in non-photosensitive TTD). XPD and XPD are genes which are implicated in xeroderma pigmentosum, but unlike xeroderma pigmentosum, TTD is not associated with increased risk of skin cancer. TTD clinically presents with variable manifestations including cutaneous, neurologic, and growth abnormalities. Several acronyms are used to describe the clinical manifestations of TTD. PIBIDS (OMIM 278730), IBIDS (OMIM 242170), and BIDS (OMIM 234050) stand for: photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature. Other disorders that are listed under TTD include Sabinas syndrome (OMIM 211390), which is an autosomal recessive condition characterized by hair and nail deformities in association with mental retardation; Pollitt syndrome (OMIM 275550), an autosomal recessive condition characterized by brittle hair and nails, mental retardation, and delayed bone age, with or without dental caries; and Itin syndrome (OMIM 258360), also known as TTD with immunodeficiency, an autosomal recessive disorder characterized by brittle hair and nails, and mental retardation in association with neutropenia and immunoglobulin deficiency. The last subgroup of TTD is TTD with intrauterine growth retardation (IUGR), which is characterized by hair abnormalities, severe IUGR with failure to thrive, developmental delay, recurrent infections, cataracts, and hepatic angioendotheliomas (78,79).

152.6 HAIR ABNORMALITIES IN ASSOCIATION WITH METABOLIC DISEASES

152.6.1 Acrodermatitis Enteropathica

Acrodermatitis enteropathica (OMIM 201100) is a rare autosomal recessive disorder caused by mutations in the SLC39A4 gene, encoding an intestinal zinc transporter. It is clinically characterized by intermittent diarrhea; exfoliative dermatitis that is more pronounced peri-orally, over the finger and toe tips, and in the inguinal area; and alopecia affecting the scalp, eyebrows, and eyelashes (80).

152.6.2 Biotinidase Deficiency

Biotinidase deficiency (OMIM 253260) is a rare autosomal recessive condition caused by mutations in the biotinidase gene. Clinically, patients present with seizure as the most common symptom, in association with ataxia, hearing loss, and skin rash with alopecia resembling that of acrodermatitis enteropathica. Early-onset multiple carboxylase deficiency (OMIM 253270) is a similar disorder, caused by mutation in the holocarboxylase synthetase gene (81).

152.7 OTHER DISORDERS ASSOCIATED WITH HAIR PHENOTYPES

152.7.1 Trichorhinophalangeal Syndrome

Trichorhinophalangeal syndrome type 1 (TRPS1; OMIM 190350) is an autosomal dominant condition caused by mutations in the TRPS1 gene. TRPS1 patients have sparse scalp hair, bulbous tip of the nose, long flat philtrum, thin upper vermilion border, and protruding ears. Skeletal abnormalities include cone-shaped epiphyses at the phalanges, hip malformations, and short stature (82). Similarly, TRPS type 2 (OMIM 150230) and TRPS type 3 (OMIM 190350) are associated with sparse scalp hair.

152.7.2 Keratosis Follicularis Spinulosa Decalvans

Keratosis follicularis spinulosa decalvans (KFS; OMIM 308800) is an X-linked recessive disorder that presents in early childhood with keratotic follicular papules; progressive alopecia of the scalp, eyelashes, and lateral third of the eyebrows; photophobia; corneal dystrophy; blepharitis in association with hyperkeratosis over the elbows, knees, palms, and soles; and nail dystrophy. Recently, mutations have been identified in the MBTPS2 gene, involved in lipid regulation in the skin membrane barrier. Ichthyosis follicularis atrichia photophobia (IFAP; OMIM 308205)
is allelic to KFSD and is clinically characterized by noninflammatory spiny excrescences, hyperkeratosis, and non-cicatricial alopecia and photophobia (83).

152.7.3 Hidrotic Ectodermal Dysplasia

Hidrotic ectodermal dysplasia (HED; OMIM 129500), also known as Clouston syndrome, is an autosomal dominant condition caused by mutations in the connexin 30 gene. Patients usually present with total alopecia and nail dystrophy. Unlike patients with anhidrotic ectodermal dysplasia, patients with HED have normal sweating (84).

152.7.4 Bazex–Dupre–Christol Syndrome

Bazex–Dupre–Christol syndrome (OMIM 301845) is an X-linked dominant disorder of unknown genetic basis. Clinically, it is characterized by congenital hypotrichosis; follicular atrophoderma affecting the dorsa of the hands and feet, the face, and extensor surfaces of the elbows or knees; and the development of basal cell neoplasms by the second decade of life (85).

152.7.5 Hypotrichosis–Lymphedema–Telangiectasia Syndrome

Hypotrichosis–lymphedema–telangiectasia syndrome (HLTS; OMIM 607823) in both dominant and recessive forms has been described, caused by mutations in the SOX 8 gene. Clinically, patients present initially with hypotrichosis with subsequent development of telangiectasias and lymphedema (86).

152.7.6 Chondrodysplasia Punctata Type 2

Chondrodysplasia punctata type 2 (CPXD; OMIM 302960), also known as Conradi–Hunermann syndrome, is an X-linked dominant condition caused by mutations in the EBP gene, coding for sterol isomerase emopamil-binding protein. Affected individuals present with coarse hair, scarring alopecia, striate keratoderma, atrophic whorls of hyperpigmentation, cataracts, skeletal abnormalities including short stature, and epiphyseal stippling and rhizomelic shortening of bones (87).

152.8 HYPERTRICHOSIS

Hypertrichosis describes all forms of hair growth that are excessive for the body and age of the individual, which occur at any site where HFs are present, and are not under the influence of androgens. Inherited hypertrichoses are very rare human disorders, whose incidence as a group has been estimated to be as low as one in 1000 million (18). Here we will divide hypertrichosis conditions into two main groups: the first are conditions with generalized hypertrichosis and the second are inherited conditions with patchy hypertrichosis.

152.8.1 Disorders with Generalized Hypertrichosis

152.8.1.1 Ambras Syndrome. Ambras syndrome (AS; OMIM 145701) is a rare form of generalized CH. Affected individuals present with generalized hypertrichosis that is more pronounced over the upper part of the body, face, and ears, in association with abnormal facial features, such as a triangular, coarse face and long preauricular fissures (Figure 152-12). We studied three patients with AS, and defined an 11.5-Mb candidate interval for AS on chromosome 8q, which includes the TRPS1 gene (82). One of the three patients with AS carries a pericentric inversion with a breakpoint in 8q23.1, which lies 7.3 Mb downstream of TRPS1. We found that the expression of TRPS1 transcript was markedly downregulated in lymphoblasts of the patient (82). We have also detected a significant downregulation of Trps1 expression in Koala mice. The Koa mice are characterized by excess hair on the muzzle and ears, and carry a 51.5-Mb inversion on mouse chromosome 15, of which the proximal breakpoint lies 791 kb upstream of the Trps1 gene (82). Taken together, our data implicate a position effect on the expression of TRPS1, which underlies the hypertrichosis phenotype in both human and mouse.

152.8.1.2 Hypertrichosis with Gingival Hyperplasia. Hypertrichosis with gingival hyperplasia (OMIM 135400) is most commonly inherited in an autosomal dominant pattern. Affected individuals present with generalized hypertrichosis and coarse facial features, including thick lips, wide and flat nasal bridge, large ears, and gingival hyperplasia (Figure 152-13). The genetic basis of hypertrichosis with gingival hyperplasia is unknown, though recently copy number variations (CNVs) in the genome were reported to be implicated in the pathogenesis of the disease. Affected individuals from three Chinese families with autosomal dominant generalized CH with or without gingival hyperplasia were shown to have a heterozygous deletion on chromosome 17q24.2–q24.3 (88). Moreover, a sporadic case of CH with gingival hyperplasia was heterozygous for a duplication of the same region on chromosome 17q (88). Importantly, the SOX9 gene, a crucial transcription factor for HF development (89), is located approximately 2 Mb downstream of these CNVs. The data raise the possibility that the CNVs close to the SOX9 gene may also show a position effect on its expression.

152.8.1.3 Cantu Syndrome. Cantu syndrome (OMIM 239850) is a very rare genetic disorder of unknown etiology and is characterized clinically by congenital hypertrichosis, cardiomegaly, and bone abnormalities. The inheritance pattern is unclear, although autosomal dominant, autosomal recessive, and spontaneous occurrence
have been reported. We have recently identified a 375-kb duplication on chromosome 4q26–27. The region of duplication encompasses three genes: MYOZ2, USP53, and FABP2. MYOZ2 and USP53 are known to be highly expressed in cardiac muscle, and we found that USP53 is expressed in the HF (90).

152.8.1.4 Barber–Say Syndrome. Barber–Say syndrome (OMIM 209885) is a rare congenital condition characterized by severe hypertrichosis, mainly on the back and forehead; atrophic skin with hyperlaxity and redundancy; and facial dysmorphism with hypertelorism, ectropion, telecanthus, abnormal and low-set ears, bulbous nasal tip, small teeth, nystagmus, low frontal hairline, and high arched palate (91).

152.8.1.5 X-linked Hypertrichosis. X-linked hypertrichosis (OMIM 209885) is a rare congenital condition characterized by severe hypertrichosis in an X-linked recessive or dominant form, characterized by congenital generalized hypertrichosis that is associated with dental anomalies and deafness (Figure 152-14). The gene mutated in this condition is still unknown but lies on chromosome Xq24–q27.1 (92).

152.8.1.6 CAHMR Syndrome. CAHMR (OMIM 211770) is an autosomal recessive condition reported in an Egyptian family. Affected individuals present with congenital cataracts and congenital hypertrichosis that is more pronounced on the upper part of the body, in association with mental retardation (93).

152.8.1.7 Amaurosis Congenita, Cone–Rod Type with Congenital Hypertrichosis. Amaurosis congenita, cone–rod type with congenital hypertrichosis (OMIM 204110) is an autosomal recessive form of hypertrichosis characterized by severe retinal dystrophy with visual impairment since birth and profound photophobia in the absence of night blindness. The underlying ophthalmologic pathology suggested a cone–rod type of congenital amaurosis. The ocular defects are accompanied by trichomegaly, bushy eyebrows with synophrys, and excessive facial and body hair with hypertrophied circumareolar hair on the breasts (94).

152.8.1.8 Hypertrichosis and Acromegaly. Hypertrichosis and acromegaly is an autosomal dominant form of generalized hypertrichosis. Affected individuals
characteristically present with generalized hypertrichosis and acromegaloid facies with no intraoral lesions or gingival hyperplasia (95).

**152.8.2 Disorders Associated with Patchy Hypertrichosis**

**152.8.2.1 H Syndrome.** The H syndrome (OMIM 612391) is an autosomal recessive disorder characterized by cutaneous hyperpigmentation, patchy hypertrichosis, hepatosplenomegaly, heart anomalies, progressive sensorineural hearing loss, hypogonadism, short stature, hyperglycemia, hallux valgus, and fixed flexion contractures of the toe and finger joints. The clinical diagnosis relies mainly on the presence of hyperpigmentation and hypertrichosis in the thighs. Mutations occur in the SLC29A3 gene (96).

**152.8.2.2 Winchester Syndrome.** Winchester syndrome (OMIM 259600) is an autosomal recessive condition characterized by multicentric osteolysis, predominantly over the hands and feet, associated with generalized osteoporosis. Radiographically, the osteolysis is accompanied by a characteristic widening of the metacarpal and metatarsal bones. In addition, affected individuals display coarse facial features, corneal opacities, and generalized hypertrichosis. Mutations have been identified in the MMP2 gene, encoding matrix metalloproteinase-2 (97).

**152.8.2.3 Porphyrias.** The four types of porphyria that are characterized by patchy hypertrichosis are porphyria cutanea tarda (PCT; OMIM 176100), hepatosideropoeitic porphyria (HEP; OMIM 176100), variegated porphyria (VP; OMIM 176200), and erythropoeitic protoporphyria (EPP; OMIM 177000). Both PCT and HEP are caused by mutations in urogen decarboxylase, with the former inherited as an autosomal dominant condition while the latter is inherited in an autosomal recessive pattern. VP is inherited as an autosomal recessive condition caused by mutations in protoporphyrinogen oxidase. EPP is an autosomal dominant condition and occasionally autosomal recessive, caused by mutations in ferrochelatase (98).

**152.8.2.4 Schinzel–Giedion Syndrome.** Schinzel–Giedion (SGS; OMIM 269150) syndrome is a condition caused by dominant mutations in the SETBP1 gene. Affected individuals present with severe mental retardation, hypertrichosis, midface retraction, macroglossia, low-set ears, skeletal abnormalities, genitourinary and renal malformations, and cardiac defects (99).

**152.8.2.5 Berardinelli–Seip Syndrome.** Berardinelli–Seip syndrome (OMIM 608594), also known as congenital generalized lipodystrophy, is a rare autosomal recessive metabolic disease characterized by a near absence of adipose tissue from birth or early infancy and severe insulin resistance in association with acanthosis nigricans, hypertrichosis, muscular hypertrophy, hepatomegaly, altered glucose tolerance or diabetes mellitus, and hypertriglyceridemia. Berardinelli–Seip syndrome is caused by mutations in the AGAPT2 gene, encoding 1-acylglycerol-3-phosphate O-acyltransferase-2 (100).

**152.8.2.6 Warburg Micro Syndrome.** Warburg micro syndrome (OMIM 600118) is an autosomal recessive syndrome characterized by facial hypertrichosis, microcephaly, microcornea, congenital cataract, optic atrophy, hypogonitalism, mental retardation, agenesis of the corpus callosum, hypotonia, and spastic palsy. Mutations have been identified in the RAB3GAP gene, encoding the catalytic subunit of the RAB3 GTPase-activating protein complex (101).

**152.8.2.7 Gorlin–Chaudhry–Moss Syndrome.** Gorlin–Chaudhry–Moss syndrome (OMIM 233500) is an autosomal recessive condition characterized by craniosynostosis, flat midface, microphthalmia, conductive hearing loss, hypertrichosis, coarse hair

![Image](image-url)
and low frontal hairline, and short metacarpals and phalanges (102).

**152.8.2.8 Ramon Syndrome.** Ramon syndrome (OMIM 266270) is characterized by maxillary fibrous dysplasia, gingival fibromatosis, epilepsy, neurodevelopmental delay, hypertrichosis, and growth retardation (103).

**152.8.2.9 Zimmermann–Laband Syndrome.** Zimmermann–Laband syndrome (ZLS; OMIM 135500) is an autosomal dominant inherited condition characterized by a coarse facial appearance, gingival fibromatosis, hypoplasia of the terminal phalanges and nails of hands and feet, hypertrichosis, hepatosplenomegaly, and mental retardation. The genetic basis of ZLS is unknown but has been reported in the setting of translocations including t(3;8) and t(3;17) (104).

**152.8.2.10 Cornelia de Lange Syndrome.** Cornelia de Lange syndrome (CDLS1; OMIM 122470) is an autosomal dominant multisystem malformation syndrome characterized by microcephaly, long philtrum, facial dysmorphism, bushy eyebrows with synophrys, anteverted nares, maxillary prognathism, thin lips, upper limb defects, and hypertrichosis, in association with prenatal and postnatal growth and mental retardation. Mutations have been found in around 50% of individuals and they occur in the NIPBL gene, which encodes a component of the cohesin complex (105).

**152.8.2.11 Leprechaunism.** Leprechaunism (OMIM 246200), also known as Donohue syndrome, is an autosomal recessive condition characterized by elfin facial appearance; absence of subcutaneous tissue; low-set ears; large hands, feet, and genitalia; decreased muscle mass; acanthosis nigricans; hypertrichosis and pachyderma; and hypoglycemia, with most patients dying within the first year of life. Mutations have been reported in the insulin receptor gene (106).

**152.8.2.12 Cervical Hypertrichosis with Kyphoscoliosis.** Cervical hypertrichosis with kyphoscoliosis (OMIM 117850) is an autosomal dominant condition characterized by excessive hair growth localized to the cervical area, associated with underlying kyphoscoliosis. Hypertrichosis may also occur at other places along the spine, including the thoracolumbar and sacral regions (107).

**152.8.2.13 Michelin Tire Baby Syndrome.** Michelin tire baby syndrome (OMIM 156100) is an autosomal dominant condition characterized by multiple circumferential deep skin folds on the extremities and gyrus-like on the back, in association with craniofacial anomalies, seizures, mental retardation, esotropia, hemiplegia, congenital heart defect, nevus lipomatosus, and smooth muscle hamartoma, with or without overlying hypertrichosis (108).

**152.8.2.14 Coffin–Siris Syndrome.** Coffin–Siris syndrome (OMIM 135900) is an autosomal recessive condition also known as fifth digit syndrome. Affected individuals show developmental delay, coarse facial features, hypertrichosis, and hypoplastic or absent fifth distal phalanges (109).

### 152.9 GENETICS OF POLYGENIC DISEASES

#### 152.9.1 Alopecia Areata

AA (OMIM 104000) is the second most common cause of hair loss in humans, with a lifetime risk of 1–2%. AA affects about 5.3 million people in the United States alone and shows a broad range of phenotypes from a limited (patchy) non-scarring hair loss on the scalp only to complete hair loss on the whole body, known as alopecia universalis (Figure 152-15). There is no permanent organ destruction, and regrowth of the hair remains possible. Histologically, all types of AA are characterized by the presence of a diffuse lymphocytic infiltrate around the HF bulb sparing the bulge, the site where HF stem cells reside. AA is a tissue-specific autoimmune disease, but its molecular mechanism remains largely unknown. Under normal circumstances, the HF is an immune-privileged organ that expresses low levels of major histocompatibility complex (MHC) proteins (110). The genetic basis

**FIGURE 152-15** AA. Left: Limited (patchy) non-scarring hair loss on the scalp. Right: Complete hair loss on the whole body (alopecia universalis).
of AA is largely unknown. We recently performed a genome-wide association study (GWAS) on patients with AA and identified several loci that are implicated in the pathogenesis of AA. A region of strong association resided in a region of linkage disequilibrium containing genes, the ULBP gene cluster, that encode activating ligands of the natural killer cell receptor NKG2D. We discovered that these ligands are expressed in AA lesional scalp and are markedly upregulated in the HF dermal sheath during active disease. Our findings place AA within the context of shared pathways among autoimmune diseases and implicate a novel disease mechanism, the upregulation of NKG2D ligands, in triggering autoimmunity. Other loci we identified include: CTLA4, IL2/IL21, IL2RA (CD25), Eos (IKZF4), ERBB3, syntaxin 17 (STX17) and peroxiredoxin 5 (PRDX5). Interestingly, many of these genes have been implicated to play some role in immune regulation.

152.9.2 Androgenetic Alopecia

AGA (OMIM 109200) is characterized by shortened anagen phase and HF miniaturization, and is the most common form of hair loss, affecting approximately 40% of men and women (Figure 152-16). AGA is also known as male-pattern baldness in men and female-pattern hair loss in women. Although genetic variations in or close to the androgen receptor have been linked to AGA, until recently not much else was known about this common condition. It was recently shown that the single nucleotide polymorphism (SNP) rs1160312 is associated with AGA. This variant lies on chromosome 20 between the PAX1 and FOXA2 genes. It is still yet unclear whether this variant itself or some other variant nearby is affecting the expression of either gene leading to AGA. With the advance of genetic techniques, such as whole-genome sequencing, it will be possible to pick up many rare variants that were missed with other techniques, and such variants may help us better understand common conditions such as AGA.

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Biographies

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