Received: 30 December 2022 | Accepted: 10 February 2023

DOI: 10.1111/ddg.15054

MINIREVIEW

Selected genodermatoses – Status quo and future prospects

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Summary
Genodermatoses are monogenetic disorders, which may manifest with symptoms either exclusively on the skin or also involve other organs in the context of an associated syndrome. Over the past 30 years, numerous hereditary hair, tumor, blistering, and keratinization diseases have been characterized both clinically and genetically. This has resulted in the continuous development of disease-specific classifications as well as diagnostic algorithms and examination techniques, and has also led to new pathogenesis-based therapeutic approaches. While the deciphering of the underlying genetic defects of these diseases is already well advanced, there is still much room for the development of new translationally motivated treatment strategies.

KEYWORDS
Basal cell carcinoma, epidermolysis bullosa, genodermatoses, hair disorders, keratinization disorders

INTRODUCTION

Genodermatoses are rare monogenic disorders that can manifest either with symptoms exclusively on the skin or also affect other organs in the context of a primary syndrome. Based on this definition, they can be classified into ten subgroups: *(1)* blistering diseases, *(2)* keratinization diseases, *(3)* diseases of ectodermal structures, *(4)* vascular and lymphatic diseases, *(5)* nevi and nevoid malformations, *(6)* pigmentation diseases, *(7)* tumor diseases, *(8)* metabolic diseases, *(9)* neurocutaneous syndromes, and *(10)* complex genetic diseases with skin involvement.[1]

The continuous development and refinement of molecular biology techniques has enabled the deciphering of numerous new gene defects in genodermatoses in recent years. The identification of these genetic variants forms the basis for a better understanding of these diseases and the development of pathogenesis-based, causal therapeutic strategies.

GENE DEFECTS IN HEREDITARY HAIR DISORDERS

At first glance, subtle changes on the scalp seem to be harmless and are therefore often underestimated. They may be associated with hypotrichosis and complete alopecia resulting in psychic distress, especially in girls and women due to the visible abnormalities. Research into the involved genes may lead to a better understanding of the pathophysiology of hair growth and hair loss.

Monogenic isolated alopecias comprise a group of clinically and genetically heterogeneous types of hair loss (Table 1). These include inherited alopecias (atrichias), such as atrichia congenita, and alopecias developing in childhood or adulthood, such as hypotrichosis simplex. Alopecias may also be differentiated based on the localization of hair loss or potential structural changes of the remaining hair, for example in case of monilethrix and uncombable hair syndrome.[2]

Autosomal dominant types of hypotrichosis simplex (HS) have been described only rarely in the last two decades (less than 50 families worldwide). In these cases, pathogenic variants in the genes *CDSN*, *APCDD1*, and *SNRPE* are responsible.[3–5]

Autosomal recessive hypotrichoses, however, have been described markedly more often, even though they are rare. They are caused by mutations in the genes *LPAR6*, *LIPH*, *LSS*, *DSG4, C3orf52*, and *CDH3*.[6] Apart from hypotrichosis, patients with pathogenic variants in *CDH3* usually also present with macular degeneration.[7] In cases with pathogenic variants of *LSS*, not only the isolated forms,

TABLE 1 Overview of monogenic hereditary isolated hypotrichoses. Mode of inheritance, chromosomal localization, and proteins/genes affected (modified from Betz, 2014).

Disease	Inheritance	Chromosome	Protein(s)/gene(s)
Monilethrix	AD	12q13	Keratins (KRT81, KRT83, KRT86)
Monilethrix(-like)	AR	18q12	Desmoglein 4 (DSG4)
Marie Unna hereditary hypotrichosis	AD	8p21	U2HR
Alopecia (atrichia) universalis congenita	AR	8p21-p22	Hairless (HR)
		12q12-q14	Vitamin D (1,25-dihydroxyvitamin D3) receptor (VDR)
Hypotrichosis simplex	AD	6p21.3	Corneodesmosin (CDSN)
		18p11	*Adenomatosis polyposis down-regulated 1* (APCDD1)
		2p25-2p23	*Small nuclear ribonucleoprotein E* (SNRPE)
	AR	18q12	Desmoglein 4 (DSG4)
		21q22.3	Lanosterol synthase (*LSS*)
		3q27	Lipase H (LIPH)
		13q14-q21	G protein-coupled receptor P2Y5 (LPAR6 alias P2RY5)
Hypotrichosis and vellus hair	AD	12q13	Keratins (KRT71, KRT74)
Uncombable hair syndrome	AR	1p36.13; 20p13; 1q21.3	Peptidylarginine deiminase 3 (*PADI3*), transglutaminase 3 (*TGM3*), trichohyalin (*TCHH*)

Abbr.: AD, autosomal dominant; AR, autosomal recessive.

but also patients with HS and intellectual impairment have been described.[8–10]

Another autosomal recessive hair loss disease is alopecia universalis congenita with pathogenic variants in the *HR* gene.[11,12] Characteristically, patients lose all their hair approximately 4 to 8 weeks after birth and do not regrow it later. This disease is often confused with alopecia universalis, the maximum variant of alopecia areata, which has a multifactorial inheritance and usually starts with a circumscribed loss of hair.[13]

The *HR* gene also plays a role in Marie Unna hereditary hypotrichosis, although the mutations are localized in *U2HR*, one of four open reading frames (U1HR–U4HR) upstream of the *HR* gene coding region. *U2HR* encodes a small signaling peptide that modulates and controls the expression of the downstream *HR* gene.[14] At birth, affected individuals usually have normal or slightly sparse hair, and only rarely is hair completely absent. In the first two years of life, the hair remains thin and sparse. Approximately from the third year of life, the hairs develop a markedly coarsened and wiry structure, becoming irregularly twisted and difficult to comb (bristles). After puberty, a progressive loss of hair follicles occurs beginning from the vortex.[15]

Monilethrix is one of the more common types of monogenic alopecias and is caused by mutations in the keratin genes *KRT81*, *KRT83*, and *KRT86*, as well as, rarely, in *DSG4*.[16–18] Due to a defect in hair structure, dystrophic alopecia occurs, mainly at the back of the head. Nail changes have also been described.

The uncombable hair syndrome, also known as Struwwelpeter syndrome in German-speaking countries, is also characterized by structural changes of the hair. Recently, pathogenic variants in the genes *PADI3*, *TGM3*, and *TCHH* have been identified. If one of the proteins encoded by these genes is malfunctional, this has fundamental effects on the structure and stability of the hairs, since the three proteins are involved in the same metabolic pathway and the subsequent cross-linking of hair proteins is no longer ensured.[19] Clinically, affected children present with shaggy and tousled silvery-blonde to light brown hair that cannot be combed (Figure 1). Recently, a study with more than 100 affected individuals demonstrated that two common variants in *PADI3* are predominantly responsible for the uncombable hair syndrome.[20]

Although an increasing number of studies on loose anagen syndrome have been published in recent years, the underlying gene defect is not yet known. In this disease, young girls are primarily affected, presenting with fine and brittle hair.[21]

Despite the increasing number of newly detected gene defects, treatment options for rare hair diseases are currently highly unsatisfying and gene therapeutic strategies are either still in their infancy or remain as visions of the future.

FIGURE 1 Female patient with uncombable hair syndrome. Shaggy and tousled hair that cannot be combed.

HEREDITARY TUMOR DISEASES WITH BASAL CELL CARCINOMAS

Tumors of the skin usually show a solitary and sporadic manifestation. However, if they appear in the form of multiple and disseminated neoplasms with high familial incidence, the diagnosis of a genetic tumor disease seems evident. The various types of skin tumors are highly diverse with respect to their clinical and histopathological features, as well as their malignancy. Basal cell carcinoma is by far the most common malignant tumor worldwide and may occur in basal cell nevus syndrome, Bazex-Dupré-Christol syndrome, Rombo syndrome, Oley syndrome, and xeroderma pigmentosum.[22,23]

Whereas the genetic causes of basal cell nevus syndrome and xeroderma pigmentosum are well understood and characterized and it is still unknown whether Rombo and Oley syndromes really represent independent entities, Bazex-Dupré-Christol syndrome in particular has been the focus of scientific interest since the gene defect was first mapped on chromosome Xq24-27.1 in 1995. Apart from basal cell carcinomas, affected individuals may also develop hypotrichosis, follicular atrophoderma, milias, hypohidrosis, facial hyperpigmentation, and trichoepithelioma. However, following the publication in 2017 by a French research group suggesting that mutations in the *ACTRT1* gene are responsible for the disease,[24] a recent publication has shown that this gene is not associated with disease development. Rather, large noncoding intergenic duplications on chromosome Xq26.1 result in dysregulation of *ARHGAP36* gene expression via a position effect.[25] The protein, also called ARHGAP36, regulates as an effector molecule the activity of the sonic hedgehog signaling route, which is constitutively upregulated in almost all basal cell carcinomas, thereby contributing decisively to tumor growth.[26] Accordingly, ARHGAP36 represents a new, attractive therapeutic target for the treatment of basal cell carcinomas.

NEW THERAPEUTIC APPROACHES IN BLISTERING GENODERMATOSES AND KERATINIZATION DISEASES

The prototype of blistering genodermatoses is the group of inherited epidermolysis bullosa characterized by localized or generalized tendency of skin and mucous membranes to spontaneously or traumatically induced fragility and blister formation, reclassified in 2020 (Table 2).[27] Significant therapeutic developments have been occurring for these disorders for some time, culminating most recently in the first European approval of a drug for topical wound management in severe junctional and dystrophic forms of inherited epidermolysis bullosa (https://ausderwelt.de/amryt-verfolgt-formalen-fda-beschluss-fuer-oleogel-s10/).[28] In addition, gene therapy treatment approaches for this group of diseases have also recently been shown to be very effective after years of development. For example, the chronic, non-healing, extensive wounds of a patient with *LAMB3*-mutated junctional epidermolysis bullosa were successfully treated by combining *ex vivo* gene therapy with stem cell therapy using extensive skin grafts, demonstrating that the grafted, genetically modified skin remained structurally and functionally intact in the long term.[29,30] Recently, reconstitution of functional collagen VII, the major structural protein of anchoring fibrils of the skin, was achieved by topical *in vivo COL7A1* gene therapy based on herpes simplex virus type 1 (HSV-1).[31] In a clinical phase III trial with beremagene geperpavec (B-VEC) based on this technique, complete healing of more than two thirds of all treated wounds was achieved, whereas only approximately one fifth of the wounds healed after treatment with placebo.[32]

Hereditary keratinization diseases are clinically and genetically heterogeneous.[33] In recent years, a paradigm shift has been observed with respect to treatment concepts. Based on gene expression analyses in four of the more common ichthyoses (epidermolytic ichthyosis, Netherton syndrome, lamellar ichthyosis, and congenital ichthyosiform erythroderma), common features were found with respect to the immune signature of the cutaneous inflammatory reaction and/or the barrier dysfunction associated with these diseases. While all subtypes exhibited a significant T helper (Th) 22/Th17-mediated immune response, additional changes were found in the Th2-mediated immune response especially in Netherton syndrome and a changed Th1 immune response in congenital ichthyosiform erythroderma.[34] Upregulation of interleukin (IL)-36α and IL-36γ had already been demonstrated in harlequin ichthyosis.[35] For this reason, several biologics primarily approved for psoriasis, psoriasis arthritis, and atopic eczema that exhibit inhibitory effects on specific cytokines have recently been used in various types of

TABLE 2 Current classification of hereditary epidermolysis bullosa (EB) into four main forms (modified from Has et al.).

Main EB type	Level of blistering	EB subtypes	Affected (target) proteins
EB simplex	Intraepidermal (epidermolytic)	Autosomal dominant EBS Autosomal recessive EBS	Keratin 5/14; plectin, kelch-like Protein 24 Keratin 5/14, plectin, exophilin 5 (Slac2-b), bullous pemphigoid antigen 1 (BP230), CD151 antigen (tetraspanin 24)
Junctional EB	Intra-lamina lucida (lamina lucidolytic)	Severe Intermediate Intermediate Gastric atresia Localized Inversa type Late manifestation LOC syndrome With interstitial lung disease and nephrotic syndrome	Laminin 332a Laminin 332 Type XVII collagen $\alpha6\beta4$ integrin Laminin 332, type XVII collagen, $\alpha6\beta4$ integrin, $\alpha3$ integrin Laminin 332 Type XVII collagen Laminin $\alpha3A$ $\alpha3$ integrin
Dystrophic EB	Sub-lamina densa (dermolytic)	Autosomal dominant DEB Intermediate Localized Pruriginosa Self-limiting Autosomal recessive DEB Severe Intermediate Inversa type Localized Pruriginosa Self-limiting Compound heterozygous DEB, severe	Type VII collagen
Kindler syndrome	Mixed	–	Kindlin 1

Abbr.: DEB, dystrophic EB; EBS, EB simplex; JEB, junctional EB.

hereditary ichthyosis associated with moderate to severe inflammation of the skin. Among these biologics were infliximab, ixekizumab, ustekinumab, secukinumab, and dupilumab.[36] The therapeutic results, however, have been variable,[37] possibly due to the heterogeneous underlying genetic defects and/or because in the pathology of hereditary keratinization diseases, the interplay of several proinflammatory molecules, rather than a single cytokine, is likely to be contribute significantly to the phenotypic manifestation.[38] Thus, biologics are no "silver bullet" in genetic ichthyoses.

CONCLUSION AND OUTLOOK

Developments in the field of molecular and cell biology over the past three decades have led to major changes and new strategies in diagnosis, prevention, and therapy of monogenetically inherited skin diseases. Because of this, it was possible to characterize various disease groups not only based on their clinical and/or histopathological criteria, but for the first time also based on the underlying gene defects. This also enabled the precise differentiation of individual diseases with overlapping symptoms and histologic features. The identification and continued exploration of these genes and their interplay within molecular signaling routes provides the starting point for the development of targeted pathogenesis-based treatment concepts that are urgently needed,[27,33], given that the current therapy of genodermatoses is still predominantly orientated towards the symptoms.

ACKNOWLEDGEMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

None.

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How to cite this article: Frank J, Has C, Betz RC. Selected genodermatoses – Status quo and future prospects. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2023;21:337–341. https://doi.org/10.1111/ddg.15054