Int J BioMed Public Health. 2020; 3(2):46-57
10.22631/ijbmph.2019.185074.1108

International Journal
of
BioMedicine and Public Health
http://www.ijbmph.com

Review Article

A review on the pathophysiology of nonsyndromic ichthyosis as an epidermal genodermatosis

Open Access

Farzane Saeidi[1], Ehsan Sohrabi[2], Elham Behrangi[3], Pouria Khani[4*]

ARTICLE INFO

Article History:
Received 10 May 2019
Revised 27 May 2020
Accepted 28 November 2019

Keywords:
Ichthyosis
Genodermatosis
Keratinization
Skin disorder

[1]Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran; [2]Department of Medical Genetics and Molecular Biology, Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran; [3]Department of Dermatology and Laser Surgery, Clinical Research Center, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran; [4]Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran.

Correspondence:
Pouria Khani. Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran.
Email: Pouriakhani70@gmail.com

ABSTRACT

Ichthyoses as epidermal genodermatoses are a large group of keratinization disorders that affect the entire integument, which is typically characterized by visible scaling and inflammation on the skin. Nowadays, in addition to clinical criteria, new molecular diagnostic methods, such as next-generation sequencing, can help to differentiate the subgroups of ichthyoses more precisely. These disorders are mostly classified based on clinical and histologic features and molecular markers. Inherited ichthyoses were divided into two groups: non-syndromic ichthyosis and syndromic ichthyosis. Non-syndromic ichthyosis is a group of various skin diseases with genetic and clinical heterogeneity. In this group, ichthyosis vulgaris and recessive X-linked ichthyosis are common and are often of delayed onset. Correct diagnosis of the molecular defects resulted from ichthyosis is useful for the prediction of the prognosis, genetic counseling (accurate risk assessment), prenatal diagnosis, and a better understanding of skin biology. However, the most essential and promising advantage of a precise molecular diagnosis is using gene therapy for its treatment, which may be considered as a subcategory of personalized medicine. This review is focused on the different aspects of non-syndromic ichthyoses pathophysiology.

Introduction

Ichthyoses also known as disorders of keratinization (DOK), include a heterogeneous group of Mendelian disorders. These disorders characterized by generalized dry skin accompanied by the frequent finding of abnormal barrier function, which starts a default compensatory pathway of hyperproliferation. It causes the characteristic clinical manifestation of localized and/or generalized scaling (1-3). The inherited ichthyoses are typically present at birth, but the consequent disease development and the outcome can be highly variable. For example, some affected children with harlequin ichthyosis often die in the neonatal period (4), but the children affected with other types of disease may survive to adulthood.

Manifestations of the disease are mainly because of mutations in genes that mostly create skin barrier structures. The ichthyosis Consensus Conference, which was held in

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

2009, formed a general agreement on classification for DOK based on their pathophysiology, mode of inheritance, and clinical appearances. This classification system generates the two main groups for DOK: 1) nonsyndromic forms, with clinical findings limited to the skin, and 2) syndromic forms, which affects other organ systems (2). According to clinical, histopathological, and electron microscopy assessment, the diagnosis does not reflect the molecular defects of the disease (5). Identification of the molecular defects of congenital ichthyosis is essential for (6): a) Obtaining vital information about the prognosis. b) Assessing different response to one treatment in different genetic subgroups (personalized medicine). c) Genetic counseling (accurate risk assessment) and prenatal diagnosis. d) Achieving a better understanding of skin biology to use in targeted therapy and drug development.
Syndromic ichthyoses phenotypes are because of underlying genetic abnormalities that are present at the skin and other organs (7). Among disorders causing ichthyosis, as one of their symptoms, some diseases induce abnormalities in organs other than the skin. These diseases with characteristic signs are considered as syndromes which their prevalence is insignificant and include Netherton, Sjo¨ gren–Larsson, Conradi–H€unermann–Happle, Dorfman–Chanarin, ichthyosis follicularis, atrichia and photophobia (IFAP), and Refsum (7).
In this review, we summarize the various aspects of molecular mechanisms and genotype-phenotype correlations in non-syndromic ichthyosis. This study aims to highlight novel genetic findings that involve in disease pathogenesis.

Non-syndromic Ichthyosis

Non-syndromic ichthyoses are identified by the phenotypic appearance of the disorder that manifested only in the skin. Non-syndromic ichthyoses comprise ichthyosis vulgaris, recessive X-linked ichthyosis, autosomal recessive congenital ichthyosis, keratinopathic ichthyosis, and other forms (1) (Table 1). Ichthyosis Vulgaris (IV) and X-linked recessive ichthyosis (XLRI) are considered as the "common ichthyoses", given their high prevalence (1, 2). Non-syndromic ichthyoses are genetically heterogeneous. Genes involved in non-syndromic ichthyoses and their features listed in Table 2. In order to achieve a molecular diagnosis, Next-generation sequencing (NGS) technologies can be recruited. Initial reports approved the NGS utility for the molecular investigation of various genodermatoses in the clinic (8, 9).

Table 1. Non-syndromic ichthyoses phenotypes and related genes

Ichthyosis Phenotype			Relevant genes	Ref
Common ichthyosis		Ichthyosis vulgaris	FLG	(14)
		Recessive X-linked ichthyosis	STS	(30)
Autosomal recessive congenital ichthyosis	Major types	Harlequin ichthyosis	ABCA12	(42, 43)
		Lamellar ichthyosis	ABCA12, ALOXE3, ALOX12B, CERS3, CYP4F22, NIPAL4/ICHTHYIN, PNPLA1, TGM1	(44)
		Congenital ichthyosiform erythroderma	ABCA12, ALOXE3, ALOX12B, CERS3, CYP4F22, LIPN, NIPAL4/ICHTHYIN, PNPLA1, TGM1	(45)
	Minor types	Self-healing collodion baby	ALOXE3, ALOX12B, TGM1	(34, 35)
		Acral self-healing collodion baby	TGM1	(36)
		Bathing suit ichthyosis	TGM1	(1)
Keratinopathic ichthyosis	Major types	Epidermolytic ichthyosis	KRT1, KRT10	(1, 46, 47)
		Superficial epidermolytic ichthyosis	KRT2	(1)
	Minor types	Annular epidermolytic ichthyosis	KRT1, KRT10	(48, 49)
		Ichthyosis Curth-Macklin	KRT1	(50)
		Autosomal recessive epidermolytic ichthyosis	KRT10	(41)
		Epidermolytic nevi	KRT1, KRT10	(51, 52)
		Congenital reticular ichthyosiform erythroderma	KRT1, KRT10	(53, 54)
Other forms		Loricrin keratoderma	LOR	(55)
		Erythrokeratoderma variabilis	GJB3, GJB4	(56, 57)
		Peeling skin disease	CDSN	(58)
		Keratosis linearis with ichthyosis congenita and sclerosing keratoderma	POMP	(59)

Ichthyosis Vulgaris (IV)

Ichthyosis vulgaris (IV), with an estimated prevalence of one in 100, is the most prevalent itchthyosis. IV is the mildest form of heritable non-syndromic ichthyosis (10).

Clinical symptoms

Ichthyosis vulgaris characterized by xerosis, scaling, pruritus, and eczema, which is strongly connected to atopic manifestations. The phenotypic manifestations usually appear from the age of 2 months. They are most pronounced in winter or cold, dry climates, and often get better in summer. Typically the extensor sides of the lower legs and the back are mostly affected. Keratosis pilaris and palmoplantar hyperlinearity are common features of IV. Phenotypically, IV is a mild form of ichthyosis. In contrast to many other forms of ichthyosis, IV does not tend to be present at birth (11). Moreover, it includes generalized xerosis and fine white to grayscale that is best observed on the abdomen, chest, and extensor surfaces of the extremities (3, 12, 13).

Table 2. Genes involved in non-syndromic ichthyoses and their features

Gene	Other names	Gene OMIM	Protein or complete name	Features	Reference
FLG	▪ ATOD2 epidermal filaggrin	135940	Filaggrin	▪ Cytogenetic Location: 1q21.3 ▪ The FLG gene consists of 3 exons ▪ Profilaggrin is a key protein element of the keratohyalin granules of mammalian epidermis ▪ This protein display wide species variations ▪ FLG gene is made up of repeats with the same length Filaggrin of human contains a heterogeneous molecules population from the point of view sizes, charges, and sequences	(11, 60-62)
LOR	▪ LORI_HUMAN	152445	Loricrin	▪ Cytogenetic location: 1q21.3 ▪ Yoneda et al. (1992) revealed that this gene has a single intron with 1,188 bp in the 5-prime UTR and there is no intron in the coding sequence. ▪ Loricrin also known as the epidermal differentiation complex ▪ Loricrin is a major constituent of the cornified envelope ▪ Transgenic mice functional studies have revealed that the mutant loricrin accretion in the nucleus appears to interfere with the later stages of differentiation of epiderm	(63-66)
GJB3	▪ connexin 31 ▪ CX31 ▪ CXB3_HUMAN ▪ DFNA2 ▪ gap junction protein, beta 3, 31kDa ▪ PNHI	603324	Gap Junction Protein, Beta-3	▪ Cytogenetic location: 1p34.3 ▪ Gap junctions facilitate intercellular metabolic and electrical communication ▪ Connexin protein subunits in gap junction channels are encoded by a multigene family that comprises GJB3 ▪ This protein is found in the outermost skin layer (the epidermis) ▪ Intercellular communication facilitated by Cx31 is essential for differentiation of epiderm (growth and maturation of cells) and cell response to external factors.	(67-69)
GJB4	▪ connexin 30.3 ▪ connexin-30.3 ▪ CX30.3 ▪ CXB4_HUMAN ▪ EKV ▪ gap junction beta-4 protein gap junction protein, beta 4, 30.3kDa	605425	Gap Junction Protein, Beta-4	▪ Cytogenetic location: 1p34.3 ▪ more frequently known as connexin 30.3 ▪ This protein is found in the outermost skin layer (the epidermis). ▪ This protein seems to has a role in the growth and maturation of epidermal cells. ▪ M van Geel and et al. have revealed connexin 30.3 is not essential in humans for the normal function of the skin or embryonic development.	(57, 70)
ABCA12	▪ ABCAC_HUMAN ▪ ATP-binding cassette 12 ▪ ATP-binding cassette transporter 12 ▪ ATP-binding cassette, sub-family A (ABC1), member 12 ▪ ATP-binding cassette, sub-family A, member 12 ▪ ICR2B	607800	Atp-Binding Cassette, Subfamily A, Member 12	▪ Cytogenetic Location: 2q35 ▪ ABCA12 gene comprises 53 exons and spans 206 kb of the genome ▪ This gene show 36% Similarity of the sequence with ABCA1 and ABCA7 (highest similarity in their ATP-binding domains) ▪ This gene is expressed in normal human keratinocytes ▪ ABCA12 protein concentrates to lamellar granules in the upper epidermal human skin keratinocytes ▪ ABCA12 may has a critical role in the lipid discharge into the intercellular spaces (an explanation for the epidermal barrier defect seen in related disorder)	(42, 43, 71)

Genetic changes and molecular pathogenesis

Ichthyosis vulgaris (IV) is a result of autosomal dominant mutations in the filaggrin gene (*FLG*), which has a critical role in epidermal differentiation and formation of the skin barrier. Autosomal semi-dominant inheritance is also described. Individuals with heterozygous mutations show a mild phenotype in contrast to patients with homozygous or compound heterozygous mutations that have more severe forms of ichthyosis (14-17). Moreover, the patient's penetrance is incomplete (90% in homozygotes) (15).

Table 2. Continued

Gene OMIM	Protein or complete name	Features	Reference	Chromosome
609383	Nipa-Like Domain-Containing 4	▪ Cytogenetic location: 5q33.3 ▪ The NIPAL4 gene comprises 6 exons ▪ Ichthyin gene expressed at high levels in brain, lung, stomach, skin, and leukocytes ▪ Expression of this gene has not been detectable in the liver, thyroid, and fetal brain ▪ In the same normal skin biopsies analysis, the strong expression has been observed in cultured keratinocytes and weaker expression of NIPAL4 has been seen in cultured fibroblasts	(72)	1
612121	Patatin-Like Phospholipase Domain-Containing Protein 1	▪ Cytogenetic Location: 6p21.31 ▪ This protein belongs to the patatin-like phospholipase (PNPLA) family (the presence of a highly conserved patatin domain in this family is a prominence feature) ▪ Metabolic stimuli have a role in the induction of this protein ▪ This protein has a role in the regulation of differentiation of adipocyte and in glycerophospholipid metabolism in the barrier of cutaneous ▪ This gene is expressed in the skin epidermal keratinocytes(in the granular layer)	(73, 74)	1
602593	Corneodesmosin	▪ Cytogenetic location: 6p21.33 ▪ This gene is situated in the major histocompatibility complex (MHC) class I region ▪ The CDSN gene comprises 2 exons and spans 4.5 kb of genome ▪ Another name is 'S gene' because the gene Is expressed only in the skin ▪ Protein encoded by this gene has been found in corneodesmosomes ▪ This protein tolerates a cleavage series during corneocyte maturation ▪ CDSN gene is highly polymorphic in populations of human.	(75-79)	1
613924	Lipase Family, Member N	▪ Cytogenetic location: 10q23.31 ▪ The LIPN gene includes 9 exons and spans 16.84 kb of the genome ▪ Lipase encoded by this gene is highly expressed in granular keratinocytes in the epidermis ▪ This enzyme has a role in the keratinocytes differentiation ▪ Probably lipase N is a part of the differentiation of human keratinocytes program	(80, 81)	1
139350	Keratin 1	▪ Cytogenetic location: 12q13.13 ▪ Keratin 1 is created in keratinocytes in the outer layer of the skin ▪ K1 and K10 are coexpressed in ultimately differentiated epidermis	(82, 83)	2

Table 2. Continued

Gene OMIM	Protein or complete name	Features	Reference
600194	Keratin 2	▪ Cytogenetic location: 12q13.13 ▪ The KRT2 gene comprises 9 exons and spanning 7,634 bp of genome ▪ The major epidermal type II class keratins are KRT1 , KRT2, KRT5 ,KRT6A, and KRT6B ▪ KRT2 and KRT9 are expressed in the cells of the upper spinous layer	(84-86)
613386	Proteasome Maturation Protein	▪ Cytogenetic Location: 6p21.31 ▪ Cytogenetic location: 13q12.3 ▪ The 20S proteasome as a proteolytically the active constituent of the 26S proteasome complex has a 4-ring structure (2 outer rings with 7 alpha subunit structures and 2 inner rings with 7 beta subunit structures). The assemblage of this structure arises through specific intermediates of roughly 13S and 16S. The protein produced by POMP gene is a molecular chaperone that is associated especially with these precursor intermediates and facilitates the sequential assembly of beta subunits onto the preformed alpha subunit rings ▪ A variant in the 5' UTR of this gene has been related to KLICK syndrome	(87-89)
190195	Transglutaminase 1	▪ Cytogenetic location: 14q12 ▪ The TGM1 gene comprises 15 exons and spans 14.3 kb of the genome ▪ The start codon is situated in the second exon. The exon sizes from 3 to 14 are distinctly conserved between the human TGM1 gene and factor XIIIA gene ▪ This enzyme is found in cells that make up the outermost layer of the skin (the epidermis) and has a role in the development of the epidermal cornified cell envelope ▪ The enzyme is encoded in keratinocyte is most similar to factor XIII, while the band-4.2 protein is most similar to transglutaminase that is encoded in tissue. ▪ This enzyme also called transglutaminase K	(90-93)
615276	Ceramide Synthase 3	▪ Cytogenetic Location: 15q26.3 ▪ The human CERS3 gene has a single exon ▪ This gene is a member of the ceramide synthase gene family ▪ The protein encoded by human CERS3 have 5 or 6 transmembrane domains ▪ Radner et al. showed the existence of the CERS3 protein at the interface between the stratum corneum and the stratum granulosum in the epidermis ▪ This protein is involved in the synthesis of ultra-long-chain acyl moieties ceramides (ULC-Cers) ▪ This protein has also been involved in the lipid structures modification required for spermatogenesis. ▪ Gene Mutations have been related to defects of male fertility and defects of the epidermis, comprising ichthyosis	(94-96)

Chromosome	Gene	Other names
5	NIPAL4	▪ ARCI6 ▪ ICHTHYIN ▪ ICHYN
5	PNPLA1	▪ ARCI10 ▪ dJ50J22.1
6	CDSN	▪ HTSS ▪ HTSS1 ▪ HYPT2 ▪ PSS ▪ PSS1 ▪ S
10	LIPN	▪ ARCI8 ▪ bA186O14.3 ▪ LI4 ▪ LIPL4
12	KRT1	▪ 67 kDa cytokeratin ▪ CK-1 ▪ CK1 ▪ cytokeratin 1 ▪ cytokeratin-1 ▪ EHK1 ▪ hair alpha protein ▪ K1 ▪ K2C1_HUMAN ▪ keratin 1, type II ▪ keratin, type II cytoskeletal 1 ▪ KRT1A ▪ type-II keratin Kb1

Table 2. Continued

Gene OMIM	Protein or complete name	Features	Reference
607206	Arachidonate Lipoxygenase 3	▪ Cytogenetic location: 12q13.13 ▪ Cytogenetic Location: 17p13.1 ▪ The ALOXE3 gene comprises 15 exons and spans 22 kb of the genome ▪ ALOXE3 has one more exon than other lipoxygenase genes ▪ ALOXE3 is a member of a gene cluster which also encompasses ALOX12B, ALOX15B and a novel pseudogene, ALOX15P. ▪ Although ALOXE3 named LOX based on its gene sequence lacks the typical catalytic activity of the lipoxygenase class of enzymes and instead represents a unique type of epoxy alcohol synthase	(97, 98)
603741	Arachidonate 12-Lipoxygenase, R Type	▪ Cytogenetic location: 17p13.1 ▪ ALOX12B gene comprises 15 exons and spans 12.5 kb of the genome ▪ ALOX12B has one more exon than other lipoxygenase genes ▪ the conversion of arachidonic acid to 12R-hydroxyeicosatetraenoic acid (12R-HETE) catalyzed by 12R-lipoxygenase ▪ this gene is expressed in keratinocytes and psoriatic scales	(97, 99, 100)
148080	Keratin 10	▪ Cytogenetic Location: 17q21.2 ▪ KRT10 gene is expressed in ultimately differentiated epidermal cells ▪ Keratin 10 is a member of the acidic type I family	(82, 101, 102)
611495	Cytochrome P450, Family 4, Subfamily F, Polypeptide 22	▪ Cytogenetic location: 19p13.12 ▪ the CYP4F22 gene comprises 12 exons ▪ The CYP4F22 gene is part of a cytochrome P450 genes cluster which encodes an enzyme which has a role in the pathway of 12(R)-lipoxygenase ▪ The cytochrome P450 protein is a monooxygenase. This enzyme has a role in catalyzing many reactions such as metabolism of drug and cholesterol synthesis, steroids and other lipids ▪ CYP4F22 is evolutionarily conserved (86% homology of protein with rodent orthologs and 67% homology of amino acid with CYP4F2 and CYP4F3) ▪ High expression of the gene has seen in the culture keratinocytes ▪ Cytogenetic location: Xp22.31 ▪ The STS gene comprises 10 exons and spans about 146 kb of the genome ▪ Presence of a pseudogene of STS on human Yq chromosome, suggested a recent pericentric inversion ▪ steroid sulfatase is a membrane-bound microsomal enzyme with generally expression and plays a role in hydrolyzes several 3-beta-hydroxysteroid sulfates (as metabolic precursors for the synthesis of estrogens, androgens, and cholesterol) ▪ Steroid sulfatase activity in normal females is higher than normal males because lionization don't affect the locus of the STS gene ▪ There are large deletions involving the entire STS gene and flanking sequences in more than 80% of patients with X-linked ichthyosis	(103)
12	KRT2	▪ K2 ▪ KB2 ▪ KERATIN 2A; KRT2A ▪ KERATIN 2e; KRT2E	
13	POMP	▪ C13orf12 ▪ HSPC014 ▪ PNAS-110 ▪ UMP1	
14	TGM1	▪ epidermal TGase ▪ ICR2 ▪ protein-glutamine gamma-glutamyltransferase K ▪ TGASE ▪ TGase-1 ▪ TGase K ▪ TGK ▪ TGM1_HUMAN ▪ transglutaminase-1 ▪ transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase) ▪ transglutaminase K ▪ transglutaminase, keratinocyte	
15	CERS3	▪ ARCI9 ▪ LASS3	

Int J BioMed Public Health. 2020; 3(2):46-57 DOI: 10.22631/ijbmph.2019.185074.1108 http://www.ijbmph.com

Chromosome	Gene	Other names
17	ALOX E3	▪ E-LOX ▪ e-LOX-3 ▪ eLOX3 ▪ epidermal lipoxygenase ▪ LOXE3_HUMAN ▪ MGC119694 ▪ MGC119695 ▪ MGC119696
17	ALOX1 2B	▪ 12R-lipoxygenase ▪ 12R-LOX ▪ arachidonate 12-lipoxygenase, 12R-type ▪ epidermis-type lipoxygenase 12 ▪ LX12B_HUMAN
17	KRT10	▪ CK-10 ▪ CK10 ▪ cytokeratin 10 ▪ K1C10_HUMAN ▪ K10 ▪ keratin-10 ▪ keratin 10, type I ▪ keratin, type I cytoskeletal 10
19	CYP4F2 2	▪ ARCI5 ▪ INLNE ▪ LI3
X	STS	

Histologically, a decrease in the size and number or a complete absence of keratohyalin granules in biopsies from patients with IV, was first observed in the 1980s (18). However, the specific nature of the filaggrin gene, including its extended length and highly repetitive sequence, caused difficulty in its sequencing using conventional polymerase chain reaction techniques, which, in turn, delayed detection of loss-of-function mutations in the FLG gene until 2006 (19).

The filaggrin gene (FLG) is located on the human chromosome 1q21.3. Filaggrin is synthesized as a large, complex, insoluble, and highly phosphorylated polypeptide precursor protein, profilaggrin, that specifically interacts with intermediate filaments, particularly keratins. Profilaggrin is the main constituent of keratohyalin granules (visible in the granular cell layer of the epidermis). During epidermal terminal differentiation and development of the cornified cell envelope, dephosphorylation and proteolysis of profilaggrin create multiple filaggrin monomers (20, 21). It is noteworthy that, in addition to the null mutations in the pro-FLG gene, variation in enzymes processing pro-filaggrin or filaggrin result in a lack of filaggrin (22).

Filaggrin protein has an essential role in facilitating the terminal differentiation of the epidermis and the formation of the protective skin barrier. Filaggrin is connected to keratin intermediate filaments in the outer granular layer of the epidermis, which helps their packing into bundles. Filaggrin also is cross-linked to the cornified cell envelope in terminal differentiation, which makes an insoluble barrier in the stratum corneum to guard the organism against environmental agents and prevent epidermal water loss (16, 23).

Patients who have IV are at increased risk for asthma, atopic dermatitis, and allergies, which is probably because of the disruption of barrier function that may cause greater penetration of the epidermis by potential allergens (24, 25).

Recessive X-linked ichthyosis

The second most common ichthyosis is recessive X-linked ichthyosis (RXLI), which its prevalence is of 1:4000 (10). Clinical findings in XLRI are often impossible to differentiate it from IV.

Clinical symptoms

First appearances commonly happen in the neonatal period with widespread desquamation, xerosis, and progress to fine scaling of the trunk and extremities in infancy. Brownish, polygonal, plate-like scale that is tightly adhered to the skin will gradually appear over time. RXLI is a more severe form of ichthyotic than IV. This disease causes large, dark brown scales form, and the lesion affects the whole body (26, 27).

Table 3. Features of Autosomal recessive congenital ichthyosis

Ichthyosis Phenotype			Features	Ref
Autosomal recessive congenital ichthyosis	Major types	Harlequin Ichthyosis (HI)	▪ Most phenotypically severe ▪ Occasionally fatal ▪ Thick, plate-like scales with severe ectropion, eclabium, and flattening of the ears ▪ Skin development is altered in utero.	(31, 110, 111)
		Lamellar Ichthyosis (LI)	▪ Milder than HI ▪ Hyperkeratosis and scales varies from patient to patient ▪ Scales are large, thickened and dark gray or brown ▪ LI does not include erythroderma ▪ several cases with very mild erythema have been reported	(32)
		Congenital ichthyosiform erythroderma	▪ Scales are typically fine and white or light gray ▪ In severe cases the erythroderma is systemic and persistent ▪ In milder cases the erythroderma improves in infancy ▪ Skin biopsy shows marked to moderate hyperkeratosis, a normal or moderately thickened granular cell layer, slight acanthosis, and variable parakeratosis.	(32, 33, 112)
	Minor types	Self-healing collodion baby	▪ A minor variant of ARCI ▪ Accounts for approximately 10% of all ARCI cases	(34, 35)

	Acral self-healing collodion baby	▪ Collodion baby phenotype is characterized by the presence of a tight, translucent membrane that covers the entire skin at birth. This membrane usually sheds around 10 to 14 days and reveals the underlying disease ▪ Acral self-healing collodion baby is a rare variant of this phenotype. The patients are born with the typical membrane but limited to the hands and feet only, and after it sheds, the skin appears entirely normal.	(113)
	Bathing suit ichthyosis	▪ Characterized by a unique distribution of lesions on the trunk, the most proximal parts of the upper limbs, the scalp and the neck, but not the central face and extremities	(1)

Genetic changes and molecular pathogenesis

Recently it is suggested that STS gene deletions may be the reason for milder skin abnormalities than most classic forms of RXLI; Those cases incidentally found to have an STS deletion by whole-genome chromosomal microarray (CMA) typically did not have the polygonal or "dirty" scale which is a hallmark of RXLI. In these cases, the milder complications consisted of dry or peeling skin and eczema (2, 28-30).
STS gene (other names: ARSC, ARSC1, ASC, ES, SSDD) encodes a multi-pass membrane protein that is related to the endoplasmic reticulum. It is a member of the sulfatase family and hydrolyzes several 3-beta-hydroxysteroid sulfates, which are metabolic precursors for estrogens, androgens, and cholesterol (26).

Autosomal Recessive Congenital Ichthyosis (ARCI)

Autosomal recessive congenital ichthyosis (ARCI) (Table 3) is a genetically and phenotypically heterogeneous group of diseases. It is clinically divided into three major phenotypes and three minor subtypes. Major ones consisted of Harlequin ichthyosis, Lamellar ichthyosis, and Congenital ichthyosiform erythroderma (31-33). The minor types include Self-healing collodion baby, Acral self-healing collodion baby, and Bathing suit ichthyosis (34-36).

Keratinopathic ichthyosis

Keratinopathic ichthyosis (KI) (Table 4) is considered as an umbrella term for epidermolytic ichthyosis (EI), superficial epidermolytic ichthyosis (SEI), annular epidermolytic iichthyosis (AEI), ichthyosis curth-macklin (ICM), autosomal recessive epidermolytic ichthyosis (AREI), epidermolytic nevi (EN) and congenital reticular ichthyosiform erythroderma (CRIE). All types of KI are formed because of mutations in the keratin family genes KRT1, KRT2 and KRT10 (3, 37-41).

Table 4. Features of keratinopathic ichthyosis

Ichthyosis Phenotype			Features	Ref
Keratinopathic ichthyosis	Major types	Epidermolytic ichthyosis	▪ The most prevalent keratinopathic ichthyosis ▪ Generalized blister and multiple erosions with erythroderma ▪ The patients show blistering and erythema at birth, which diminishes with age, and generalized epidermolytic hyperkeratosis in adulthood ▪ Skin biopsy shows marked epidermal acanthosis and hyperkeratosis and granular degeneration (most characteristic feature)	(37, 114)
		Superficial epidermolytic ichthyosis	▪ More superficial pattern of epidermolysis ▪ Mild epidermal hyperkeratosis over flexural areas ▪ Blister formation ▪ The development of superficially denuded areas of hyperkeratotic skin	(38)
	Minor types	Annular epidermolytic ichthyosis	▪ Intermittent development of annular, polycyclic, erythematous, scaly plaques over the proximal extremities and the trunk	(39)
		Ichthyosis Curth-Macklin	▪ Autosomal dominant ▪ Extensive and spiky or verrucous hyperkeratosis (affects the large joints and the trunk, with or without palmoplantar keratoderma)	(40, 115)
		Autosomal recessive epidermolytic ichthyosis	▪ Autosomal recessive form of epidermolytic ichthyosis ▪ Caused by KRT10 mutation	(116)
		Epidermolytic nevus	▪ Circumscribed verrucous lesions of any size presenting singly or multiply ▪ Can occur at any site ▪ Histologically, papilloma-like proliferation and granular degeneration occur in the epidermis	(51, 117)
		Congenital reticular ichthyosiform erythroderma	▪ Very rare ▪ Erythroderma on almost the entire body surface ▪ Prominent scales and palmoplantar keratoderma ▪ Hundreds to thousands of pale confetti- like spots appear across the body surface and increase in number and size with age	(118-120)

Conclusion

Nowadays, the molecular diagnosis of most diseases, such as genodermatoses, is possible. New molecular diagnostic techniques such as next-generation sequencing technologies and using precise clinical criteria are very beneficial in determining the correct diagnosis of non-syndromic ichthyosis. Understanding the structure of involved proteins and their features can be very effective in understanding the pathophysiology of these diseases, which provides new therapeutic avenues for its treatment. Gene editing, correcting inherited mutation technologies, and the exploitation of stem cells raises the flag of hope to the development of gene therapy for genodermatoses such as non-syndromi Ichthyoses. Moreover, the exact diagnosis is also crucial for the determination of the prognosis and provision of accurate genetic counseling for future pregnancies.

Ethical disclosure

Not applicable.

Acknowledgment

We would like to thanks the editors and referees whose constructive criticism led us to develop the presentation and maintain the quality of the paper.

Author contributions

All authors read and approved the final manuscript and have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Conflict of interest

The authors do not have any conflict of interest.

Funding/Support

None declared.

References

1. Takeichi T, Akiyama M. Inherited ichthyosis: Non-syndromic forms. J Dermatol. 2016; 43(3):242-51. doi:10.1111/1346-8138.13243
2. Marukian NV, Choate KA. Recent advances in understanding ichthyosis pathogenesis. F1000Res. 2016; 5:1-9. doi:10.12688/f1000research.8584.1
3. Oji V, Tadini G, Akiyama M, Bardon CB, Bodemer C, Bourrat E, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Soreze 2009. J Am Acad Dermatol. 2010; 63(4):607-41. doi:10.1016/j.jaad.2009.11.020
4. Theiler M, Mann C, Weibel L. Self-healing collodion baby. J Pediatr. 2010; 157(1):169- e1. doi:10.1016/j.jpeds.2010.01.031
5. Saito R, Boyce A, Hsu CK, Rashidghamat E, Hide M, Wedgeworth E, et al. Predictive phenotyping of inherited ichthyosis by next-generation DNA sequencing. Brit J Dermatol. 2017; 176(1):249-51. doi:10.1111/bjd.14807
6. Sitek J, Kulseth M, Rypdal K, Skodje T, Sheng Y, Retterstøl L. Whole-exome sequencing for diagnosis of hereditary ichthyosis. J Eur Acad Dermatol Venereol. 2018; 32(6):1022-7. doi:10.1111/jdv.14870
7. Yoneda K. Inherited ichthyosis: Syndromic forms. J Dermatol. 2016; 43(3):252-63. doi:10.1111/1346-8138.13284
8. Scott CA, Plagnol V, Nitoiu D, Bland PJ, Blaydon DC, Chronnell CM, et al. Targeted sequence capture and high-throughput sequencing in the molecular diagnosis of ichthyosis and other skin diseases. J Invest Dermatol. 2013; 133(2):573.
9. Takeichi T, Nanda A, Liu L, Salam A, Campbell P, Fong K, et al. Impact of next generation sequencing on diagnostics in a genetic skin disease clinic. Exp Dermatol. 2013; 22(12):825-31. doi:10.1111/exd.12276
10. Traupe H, Fischer J, Oji V. Nonsyndromic types of ichthyoses–an update. J Dtsch Dermatol Ges. 2014; 12(2):109-21. doi:10.1111/ddg.12229
11. Sybert VP, Dale BA, Holbrook KA. Ichthyosis vulgaris: identification of a defect in synthesis of filaggrin correlated with an absence of keratohyaline granules. J Invest Dermatol. 1985; 84(3):191-4. doi:10.1111/1523-1747.ep12264813
12. Numata S, Teye K, Krol RP, Karashima T, Fukuda S, Matsuda M, et al. Mutation study for 9 genes in 23 unrelated patients with autosomal recessive congenital ichthyosis in Japan and Malaysia. J Dermatol Sci. 2015; 78(1):82. doi:10.1016/j.jdermsci.2015.02.006
13. Okulicz JF, Schwartz RA. Hereditary and acquired ichthyosis vulgaris. Int J Dermatol. 2003; 42(2):95-8. doi:10.1046/j.1365-4362.2003.01308.x
14. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet. 2006; 38(3):337-42. doi:10.1038/ng1743
15. Thyssen J, Godoy-Gijon E, Elias P. Ichthyosis vulgaris: the filaggrin mutation disease. Brit J Dermatol. 2013; 168(6):1155-66. doi:10.1111/bjd.12219
16. Brown SJ, McLean WI. One remarkable molecule: filaggrin. J Invest Dermatol. 2012; 132(3):751-62. doi:10.1038/jid.2011.393
17. Irvine AD, McLean WI, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011; 365(14):1315-27. doi:10.1056/NEJMra1011040
18. Fleckman P, Brumbaugh S. Absence of the granular layer and keratohyalin define a morphologically distinct subset of individuals with ichthyosis vulgaris. Exp Dermatol. 2002; 11(4):327-36. doi:10.1034/j.1600-0625.2002.110406.x
19. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet. 2006; 38(3):337. doi:10.1038/ng1743
20. Rawlings AV, Harding CR. Moisturization and skin barrier function. Dermatol Ther. 2004; 17(s1):43-8. doi:10.1111/j.1396-0296.2004.04S1005.x
21. Brown S, Relton C, Liao H, Zhao Y, Sandilands A, McLean W, et al. Filaggrin haploinsufficiency is highly penetrant and is associated with increased severity of eczema: further delineation of the skin phenotype in a prospective epidemiological study of 792 school children. Brit J Dermatol. 2009; 161(4):884-9. doi:10.1111/j.1365-2133.2009.09339.x
22. Sandilands A, Sutherland C, Irvine AD, McLean WI. Filaggrin in the frontline: role in skin barrier function and disease. J Cell Sci. 2009; 122(9):1285-94. doi:10.1242/jcs.033969
23. Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. Nat Rev Mol Cell Bio. 2005; 6(4):328-40. doi:10.1038/nrm1619
24. Osawa R, Akiyama M, Shimizu H. Filaggrin gene defects and the risk of developing allergic disorders. Allergol Int. 2011; 60(1):1-9. doi:10.2332/allergolint.10-RAI-0270
25. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet. 2007; 39(5):650-4. doi:10.1038/ng2020
26. Elias PM, Williams ML, Choi E-H, Feingold KR. Role of cholesterol sulfate in epidermal structure and function: lessons from X-linked ichthyosis. BBA-Mol Cell Biol L. 2014; 1841(3):353-61. doi:10.1016/j.bbalip.2013.11.009
27. Hand JL, Runke CK, Hodge JC. The phenotype spectrum of X-linked ichthyosis identified by chromosomal microarray. J Am Acad Dermatol. 2015; 72(4):617-27. doi:10.1016/j.jaad.2014.12.020
28. Vega MdRR, Murillo-Vilches MR, Toral-Lopez J, Sanchez EG, Sanchez AT, González-Huerta LM, et al. X-linked ichthyosis in a patient with a novel nonsense mutation in the STS gene. J Dermatol Sci. 2015; 80(2):160-2. doi:10.1016/j.jdermsci.2015.09.004
29. Mitsutake S, Suzuki C, Akiyama M, Tsuji K, Yanagi T, Shimizu H, et al. ABCA12 dysfunction causes a disorder in glucosylceramide accumulation during keratinocyte differentiation. J Dermatol Sci. 2010; 60(2):128-9. doi.org/10.1016/j.jdermsci.2010.08.012
30. Takeichi T, Sugiura K, Hsu C-K, Tanahashi K, Takama H, Simpson MA, et al. Novel indel mutation of STS underlies a new phenotype of self-healing recessive X-linked ichthyosis. J

Dermatol Sci. 2015; 79(3):317. doi:10.1016/j.jdermsci.2015.07.001
31. Williams M, Elias P. Genetically transmitted, generalized disorders of cornification: The ichthyoses. Dermatol Clin. 1987; 5(1):155-78. doi:10.1016/S0733-8635(18)30772-1
32. Akiyama M, Sawamura D, Shimizu H. The clinical spectrum of nonbullous congenital ichthyosiform erythroderma and lamellar ichthyosis. Clin Exp Dermatol. 2003; 28(3):235-40. doi:10.1046/j.1365-2230.2003.01295.x
33. Williams ML, Elias PM. Heterogeneity in autosomal recessive ichthyosis: clinical and biochemical differentiation of lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. Arch Dermatol. 1985; 121(4):477-88. doi:10.1001/archderm.1985.01660040061013
34. Frenk E. A spontaneously healing collodion baby: a light and electron microscopical study. ACTA Derm-Venereol. 1980; 61(2):168-71. PMID:6165200
35. Raghunath M, Hennies H-C, Ahvazi B, Vogel M, Reis A, Steinert PM, et al. Self-healing collodion baby: a dynamic phenotype explained by a particular transglutaminase-1 mutation. J Invest Dermatol. 2003; 120(2):224-8. doi:10.1046/j.1523-1747.2003.12032.x
36. Mazereeuw-Hautier J, Aufenvenne K, Deraison C, Ahvazi B, Oji V, Traupe H, et al. Acral self-healing collodion baby: report of a new clinical phenotype caused by a novel TGM1 mutation. Brit J Dermatol. 2009; 161(2):456-63. doi:10.1111/j.1365-2133.2009.09277.x
37. Brocq L. Erythrodermie congénitale ichthyosiforme avec hyperépidermotrophie. Ann Derm Syph. 1902;3:1-31.
38. Akiyama M, Tsuji-Abe Y, Yanagihara M, Nakajima K, Kodama H, Yaosaka M, et al. Ichthyosis bullosa of Siemens: its correct diagnosis facilitated by molecular genetic testing. Brit J Dermatol. 2005; 152(6):1353-6. doi:10.1111/j.1365-2133.2005.06598.x
39. Sahn EE, Weimer CE, Garen PD. Annular epidermolytic ichthyosis: a unique phenotype. J Am Acad Dermatol. 1992; 27(2):348-55. doi:10.1016/0190-9622(92)70198-O
40. Curth HO, Macklin MT. The genetic basis of various types of ichthyosis in a family group. Am J Hum Genet. 1954; 6(4):371-82. PMID:14349943
41. Müller FB, Huber M, Kinaciyan T, Hausser I, Schaffrath C, Krieg T, et al. A human keratin 10 knockout causes recessive epidermolytic hyperkeratosis. Hum Mol Genet. 2006; 15(7):1133-41. doi:10.1093/hmg/ddl028
42. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, McMillan JR, Goto M, Arita K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. J Clin Invest. 2005; 115(7):1777-84. doi:10.1172/JCI24834
43. Kelsell PD, Norgett EE, Unsworth H, Teh M-T, Cullup T, Mein CA, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet. 2005; 76(5):794-803. doi:10.1086/429844
44. Sugiura K, Takeichi T, Tanahashi K, Ito Y, Kosho T, Saida K, et al. Lamellar ichthyosis in a collodion baby caused by CYP4F22 mutations in a non-consanguineous family outside the Mediterranean. J Dermatol Sci. 2013; 72(2):193-5. doi:10.1016/j.jdermsci.2013.06.008
45. Sugiura K, Akiyama M. Lamellar ichthyosis caused by a previously unreported homozygous ALOXE3 mutation in East Asia. Acta Derm Venereol. 2015;95:858-9. doi:10.2340/00015555-2022
46. DiGiovanna JJ, Bale SJ. Clinical heterogeneity in epidermolytic hyperkeratosis. Arch Dermatol. 1994; 130(8):1026-35. doi:10.1001/archderm.1994.01690080092014
47. Arin MJ, Longley MA, Anton-Lamprecht I, Kurze G, Huber M, Hohl D, et al. A novel substitution in keratin 10 in epidermolytic hyperkeratosis. J Invest Dermatol. 1999; 112(4):506-8. doi:10.1046/j.1523-1747.1999.00557.x
48. Yang J-M, Yoneda K, Morita E, Imamura S, Nam K, Lee E-S, et al. An alanine to proline mutation in the 1A rod domain of the keratin 10 chain in epidermolytic hyperkeratosis. J Invest Dermatol. 1997; 109(5):692-4. doi:10.1111/1523-1747.ep12338320
49. Yoneda K. Annular epidermolytic ichthyosis. Brit J Dermatol. 1999; 141(4):748-50. doi10.1046/j.1365-2133.1999.03125.x
50. Kubo Y, Urano Y, Matsuda R, Ishigami T, Murao K, Arase S, et al. Ichthyosis hystrix, Curth-Macklin type: a new sporadic case with a novel mutation of keratin 1. Arch Dermatol. 2011; 147(8):999-1001. doi:10.1001/archdermatol.2011.217
51. Paller AS, Syder AJ, Chan Y-M, Yu Q-C, Hutton E, Tadini G, et al. Genetic and clinical mosaicism in a type of epidermal nevus. N Engl J Med. 1994; 331(21):1408-15. doi:10.1056/NEJM199411243312103
52. Tsubota A, Akiyama M, Sakai K, Goto M, Nomura Y, Ando S, et al. Keratin 1 gene mutation detected in epidermal nevus with epidermolytic hyperkeratosis. J Invest Dermatol. 2007; 127(6):1371-4. doi:10.1038/sj.jid.5700712
53. Choate KA, Lu Y, Zhou J, Choi M, Elias PM, Farhi A, et al. Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in KRT10. Sci. 2010; 330(6000):94-7. doi:10.1126/science.1192280
54. Choate KA, Lu Y, Zhou J, Elias PM, Zaidi S, Paller AS, et al. Frequent somatic reversion of KRT1 mutations in ichthyosis with confetti. J Clin Invest. 2015; 125(4):1703-7. doi:10.1172/JCI64415
55. Maestrini E, Monaco AP, McGrath JA, Ishida-Yamamoto A, Camisa C, Hovnanian A, et al. A molecular defect in loricrin, the major component of the cornified cell envelope, underlies Vohwinkel's syndrome. Nat Genet. 1996; 13(1):70-7. doi:10.1038/ng0596-70
56. Richard G, Smith LE, Bailey RA, Itin P, Hohl D, Epstein EH, et al. Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis. Nat Genet. 1998; 20(4):366-9. doi:10.1038/3840
57. Macari F, Landau M, Cousin P, Mevorah B, Brenner S, Panizzon R, et al. Mutation in the gene for connexin 30.3 in a family with erythrokeratodermia variabilis. Am J Hum Genet. 2000; 67(5):1296-301. doi:10.1016/S0002-9297(07)62957-7
58. Wateren A, Cormane R. Oral retinoic acid as therapy for erythrokeratoderma variabilis. Brit J of Dermatol. 1977; 97(1):83-5. doi:10.1111/j.1365-2133.1977.tb15432.x
59. Dahlqvist J, Klar J, Tiwari N, Schuster J, Törmä H, Badhai J, et al. A single-nucleotide deletion in the POMP 5′ UTR causes a transcriptional switch and altered epidermal proteasome distribution in KLICK genodermatosis. Am J Hum Genet. 2010; 86(4):596-603. doi:10.1016/j.ajhg.2010.02.018
60. Baden H, Roth S, Goldsmith L, Baden S, Lee L. Keratohyalin protein in disorders of keratinization. J Invest Dermatol. 1974;62(4):411-4. doi:10.1111/1523-1747.ep12701666
61. Gan SQ, McBride OW, Idler WW, Markova N, Steinert PM. Organization, structure, and polymorphisms of the human profilaggrin gene. Biochem. 1990; 29(40):9432-40. doi:10.1021/bi00492a018
62. Presland RB, Haydock PV, Fleckman P, Nirunsuksiri W, Dale BA. Characterization of the human epidermal profilaggrin gene. Genomic organization and identification of an S-100-like calcium binding domain at the amino terminus. J Biol Chem. 1992; 267(33):23772-81.
63. Yoneda K, Hohl D, McBride O, Wang M, Cehrs K, Idler W, et al. The human loricrin gene. J Biol Chem. 1992; 267(25):18060-6.

64. Hohl D, Mehrel T, Lichti U, Turner M, Roop D, Steinert P. Characterization of human loricrin. Structure and function of a new class of epidermal cell envelope proteins. J Biol Chem. 1991; 266(10):6626-36.
65. Gedicke M, Traupe H, Fischer B, Tinschert S, Hennies HC. Towards characterization of palmoplantar keratoderma caused by gain-of-function mutation in loricrin: analysis of a family and review of the literature. Brit J Dermatol. 2006; 154(1):167-71. doi:10.1111/j.1365-2133.2005.06995.x
66. O'driscoll J, Muston G, McGrath J, Lam H, Ashworth J, Christiano A. A recurrent mutation in the loricrin gene underlies the ichthyotic variant of Vohwinkel syndrome. Clin Exp Dermatol. 2002; 27(3):243-6. doi:10.1046/j.1365-2230.2002.01031.x
67. Xia J-h, Liu C-y, Tang B-s, Pan Q, Huang L, Dai H-p, et al. Mutations in the gene encoding gap junction protein β-3 associated with autosomal dominant hearing impairment. Nat Genet. 1998; 20(4):370-3. doi:10.1038/3845
68. Gottfried I, Landau M, Glaser F, Di W-L, Ophir J, Mevorah B, et al. A mutation in GJB3 is associated with recessive erythrokeratodermia variabilis (EKV) and leads to defective trafficking of the connexin 31 protein. Human molecular genetics. 2002;11(11):1311-6.
69. Wenzel K, Manthey D, Willecke K, Grzeschik K-H, Traub O. Human gap junction protein connexin31: molecular cloning and expression analysis. Biochem Bioph Res Co. 1998; 248(3):910-5. doi:10.1006/bbrc.1998.9070
70. Van Geel M, Van Steensel M, Steijlen P. Connexin 30.3 (GJB4) is not required for normal skin function in humans. Br J Dermatol. 2002; 147(6):1275-7. doi:10.1046/j.1365-2133.2002.05000_9.x
71. Annilo T, Shulenin S, Chen Z, Arnould I, Prades C, Lemoine C, et al. Identification and characterization of a novel ABCA subfamily member, ABCA12, located in the lamellar ichthyosis region on 2q34. Cytogenet Genome Res. 2002; 98(2-3):169-76. doi:10.1159/000069811
72. Lefèvre C, Bouadjar B, Karaduman A, Jobard F, Saker S, Özguc M, et al. Mutations in ichthyin a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. Hum Mol Genet. 2004; 13(20):2473-82. doi:10.1093/hmg/ddh263
73. Wilson PA, Gardner SD, Lambie NM, Commans SA, Crowther DJ. Characterization of the human patatin-like phospholipase family. J lipid Res. 2006; 47(9):1940-9. doi:10.1194/jlr.M600185-JLR200
74. Grall A, Guaguère E, Planchais S, Grond S, Bourrat E, Hausser I, et al. PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nat Genet. 2012; 44(2):140. doi:10.1038/ng.1056
75. Simon M, Montézin M, Guerrin M, Durieux J-J, Serre G. Characterization and purification of human corneodesmosin, an epidermal basic glycoprotein associated with corneocyte-specific modified desmosomes. J Biol Chem. 1997; 272(50):31770-6.
76. Serre G, Mils V, Haftek M, Vincent C, Croute F, Réano A, et al. Identification of late differentiation antigens of human cornified epithelia, expressed in re-organized desmosomes and bound to cross-linked envelope. J Invest Dermatol. 1991; 97(6):1061-72. doi:10.1111/1523-1747.ep12492589
77. Holm SJ, Carlen LM, Mallbris L, Ståhle-Bäckdahl M, O'brien KP. Polymorphisms in the SEEK1 and SPR1 genes on 6p21. 3 associate with psoriasis in the Swedish population. Exp Dermatol. 2003; 12(4):435-44. doi:10.1034/j.1600-0625.2003.00048.x
78. Zhou Y, Chaplin DD. Identification in the HLA class I region of a gene expressed late in keratinocyte differentiation. Proc Natl Acad Sci USA. 1993; 90(20):9470-4. doi:10.1073/pnas.90.20.9470
79. Wada T, Matsuda Y, Muraoka M, Toma T, Takehara K, Fujimoto M, et al. Alu-mediated large deletion of the CDSN gene as a cause of peeling skin disease. Clin Genet. 2014; 86(4):383-6. doi:10.1111/cge.12294
80. Israeli S, Khamaysi Z, Fuchs-Telem D, Nousbeck J, Bergman R, Sarig O, et al. A mutation in LIPN, encoding epidermal lipase N, causes a late-onset form of autosomal-recessive congenital ichthyosis. Am J Hum Genet. 2011; 88(4):482-7. doi:10.1016/j.ajhg.2011.02.011
81. Toulza E, Mattiuzzo NR, Galliano M-F, Jonca N, Dossat C, Jacob D, et al. Large-scale identification of human genes implicated in epidermal barrier function. Genome Biol. 2007; 8(6):R107. doi:10.1186/gb-2007-8-6-r107
82. Lessin SR, Huebner K, Isobe M, Croce CM, Steinert PM. Chromosomal mapping of human keratin genes: evidence of non-linkage. J Invest Dermatol. 1988; 91(6):572-8. doi:10.1111/1523-1747.ep12477087
83. Popescu N, Bowden P, DiPaolo J. Two type II keratin genes are localized on human chromosome 12. Hum Genet. 1989; 82(2):109-12. doi:10.1007/BF00284039
84. Smith FJ, Maingi C, Covello SP, Higgins C, Schmidt M, Lane EB, et al. Genomic organization and fine mapping of the keratin 2e gene (KRT2E): K2e V1 domain polymorphism and novel mutations in ichthyosis bullosa of Siemens. J Invest Dermatol. 1998; 111(5):817-21. doi:10.1046/j.1523-1747.1998.00371.x
85. Collin C, Moll R, Kubicka S, Ouhayoun J-P, Franke WW. Characterization of human cytokeratin 2, an epidermal cytoskeletal protein synthesized late during differentiation. Exp cell Res. 1992; 202(1):132-41. doi:10.1016/0014-4827(92)90412-2
86. McLean WI, Morley SM, Lane EB, Eady RA, Griffiths WAD, Paige DG, et al. Ichthyosis bullosa of Siemens–a disease involving keratin 2e. J Invest Dermatol. 1994; 103(3):277-81.
87. Fricke B, Heink S, Steffen J, Kloetzel PM, Krüger E. The proteasome maturation protein POMP facilitates major steps of 20S proteasome formation at the endoplasmic reticulum. EMBO Rep. 2007; 8(12):1170-5. doi:10.1038/sj.embor.7401091
88. Witt E, Zantopf D, Schmidt M, Kraft R, Kloetzel P-M, KruÈger E. Characterisation of the newly identified human Ump1 homologue POMP and analysis of LMP7 (β5i) incorporation into 20 S proteasomes. J Mol Biol. 2000; 301(1):1-9. doi:10.1006/jmbi.2000.3959
89. Chondrogianni N, Gonos ES. Overexpression of hUMP1/POMP proteasome accessory protein enhances proteasome-mediated antioxidant defence. Exp Gerontol. 2007; 42(9):899-903. doi:10.1016/j.exger.2007.01.012
90. Polakowska RR, Eickbush T, Falciano V, Razvi F, Goldsmith LA. Organization and evolution of the human epidermal keratinocyte transglutaminase I gene. Proc Natl Acad Sci USA. 1992; 89(10):4476-80. doi:10.1073/pnas.89.10.4476
91. Kim I-G, McBride O, Wang M, Kim S, Idler W, Steinert P. Structure and organization of the human transglutaminase 1 gene. J Biol Chem. 1992; 267(11):7710-7.
92. Yamanishi K, Inazawa J, Liew F, Nonomura K, Ariyama T, Yasuno H, et al. Structure of the gene for human transglutaminase 1. J Biol Chem. 1992; 267(25):17858-63.
93. Nemes Z, Marekov LN, Fésüs L, Steinert PM. A novel function for transglutaminase 1: attachment of long-chain ω-hydroxyceramides to involucrin by ester bond formation. Proc Natl Acad Sci. 1999; 96(15):8402-7. doi:10.1073/pnas.96.15.8402
94. Mizutani Y, Kihara A, Igarashi Y. LASS3 (longevity assurance homologue 3) is a mainly testis-specific (dihydro) ceramide synthase with relatively broad substrate specificity. Biochem J. 2006; 398(3):531-8. doi:10.1042/BJ20060379

95. Radner FP, Marrakchi S, Kirchmeier P, Kim GJ, Ribierre F, Kamoun B, et al. Mutations in CERS3 cause autosomal recessive congenital ichthyosis in humans. PLoS Genet. 2013; 9(6):e1003536. PMID: 23754960
96. Rabionet Roig M. Ceramide Synthase 3 and its Essential Role in Skin Barrier Function and Male Fertility 2010. doi:10.11588/heidok.00013239
97. Krieg P, Marks F, Fürstenberger G. A gene cluster encoding human epidermis-type lipoxygenases at chromosome 17p13. 1: cloning, physical mapping, and expression. Genomics. 2001; 73(3):323-30. doi:10.1006/geno.2001.6519
98. Yu Z, Schneider C, Boeglin WE, Marnett LJ, Brash AR. The lipoxygenase gene ALOXE3 implicated in skin differentiation encodes a hydroperoxide isomerase. Proc Natl Acad Sci. 2003; 100(16):9162-7. doi:10.1073/pnas.1633612100
99. Sun D, McDonnell M, Chen X-S, Lakkis MM, Li H, Isaacs SN, et al. Human 12 (R)-lipoxygenase and the mouse ortholog molecular cloning, expression, and gene chromosomal assignment. J Biol Chem. 1998; 273(50):33540-7.
100. Boeglin WE, Kim RB, Brash AR. A 12R-lipoxygenase in human skin: mechanistic evidence, molecular cloning, and expression. Proc Natl Acad Sci. 1998; 95(12):6744-9. doi:10.1073/pnas.95.12.6744
101. Darmon MY, Sémat A, Darmon MC, Vasseur M. Sequence of a cDNA encoding human keratin No 10 selected according to structural homologies of keratins and their tissue-specific expression. Mol Biol Rep. 1987;12(4):277-83. doi:10.1007/BF00444680
102. Zhou X-M, Idler WW, Steven A, Roop D, Steinert P. The complete sequence of the human intermediate filament chain keratin 10. Subdomainal divisions and model for folding of end domain sequences. J Biol Chem. 1988; 263(30):15584-9.
103. Lefèvre C, Bouadjar B, Ferrand V, Tadini G, Mégarbané A, Lathrop M, et al. Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. Hum Mol Genet. 2006; 15(5):767-76. doi:10.1093/hmg/ddi491
104. Stein C, Hille A, Seidel J, Rijnbout S, Waheed A, Schmidt B, et al. Cloning and expression of human steroid-sulfatase. Membrane topology, glycosylation, and subcellular distribution in BHK-21 cells. J Biol Chem. 1989; 264(23):13865-72.
105. Alperin ES, Shapiro LJ. Characterization of Point Mutations in Patients with X-linked Ichthyosis Effects on the structure and function of the steroid sulfatas protein. J Biol Chem. 1997; 272(33):20756-63.
106. Yen PH, Allen E, Marsh B, Mohandas T, Wang N, Taggart RT, et al. Cloning and expression of steroid sulfatase cDNA and the frequent occurrence of deletions in STS deficiency: implications for XY interchange. Cell. 1987; 49(4):443-54. doi:10.1016/0092-8674(87)90447-8
107. Müller C, Migl B, Traupe H, Ropers H. X-linked steroid sulfatase: evidence for different gene-dosage in males and females. Hum Genet. 1980; 54(2):197-9. doi:10.1007/BF00278971
108. Shapiro LJ, Mohandas T, Weiss R, Romeo G. Non-inactivation of an X-chromosome locus in man. Sci. 1979; 204(4398):1224-6. doi:10.1126/science.156396
109. Basler E, Grompe M, Parenti G, Yates J, Ballabio A. Identification of point mutations in the steroid sulfatase gene of three patients with X-linked ichthyosis. Am J Hum Genet. 1992; 50(3):483. PMID:1539590
110. Dale BA, Holbrook KA, Fleckman P, Kimball JR, Brumbaugh S, Sybert VP. Heterogeneity in harlequin ichthyosis, an inborn error of epidermal keratinization: variable morphology and structural protein expression and a defect in lamellar granules. J Invest Dermatol. 1990;94(1):6-18.
111. Akiyama M, Kim D-K, Main DM, Otto CE, Holbrook KA. Characteristic morphologic abnormality of harlequin ichthyosis detected in amniotic fluid cells. J Invest Dermatol. 1994; 102(2):210-3.
112. Akiyama M. Severe congenital ichthyosis of the neonate. Int J Dermatol. 1998; 37(10):722-8. doi:10.1046/j.1365-4362.1998.00488.x
113. Ferrari B, Martínez JP, Luna PC, Larralde M. Acral self-healing collodion baby: A case series. Int J Womens Dermatol. 2016; 2(4):140-2. doi:10.1016/j.ijwd.2016.09.004
114. Judge M, McLean W, Munro C. Disorders of keratinization. Rook's Textbook of Dermatology, Eighth Edition. 2010:1-122.
115. Niemi K-M, Virtanen I, Kanerva L, Muttilainen M. Altered keratin expression in ichthyosis hystrix Curth-Macklin. Arch Dermatol Res. 1990; 282(4):227-33. doi:10.1007/BF00371641
116. Covaciu C, Castori M, De Luca N, Ghirri P, Nannipieri A, Ragone G, et al. Lethal autosomal recessive epidermolytic ichthyosis due to a novel donor splice-site mutation in KRT10. Brit J Dermatol. 2010; 162(6):1384-7. doi:10.1111/j.1365-2133.2010.09665.x
117. Nazzaro V, Ermacora E, Santucci B, Caputo R. Epidermolytic hyperkeratosis: generalized form in children from parents with systematized linear form. Brit J Dermatol. 1990; 122(3):417-22. doi:10.1111/j.1365-2133.1990.tb08292.x
118. Marghescu S, Anton-Lamprecht I, Rudolph P, Kaste R. Congenital reticular ichthyosiform erythroderma. Hautarzt. 1984; 35(10):522-9. PMID: 6500934
119. Camenzind M, Harms M, Chavaz P, Saurat J, editors. Confetti ichthyosis. Ann Dermatol Vener. 1983; 11(8):675-6. PMID: 6529087
120. Brusasco A, Tadini G, Cambiaghi S, Ermacora E, Grimalt R, Caputo R. A case of congenital reticular ichthyosiform erythroderma–ichthyosis 'en confettis'. Dermatol. 1994; 188(1):40-5. doi:10.1159/000247084