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Review Article

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

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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

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	

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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.

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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.

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