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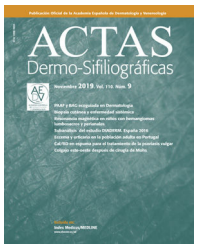

REVIEW

[Translated article] ICHTHYOSIS: Clinical and Molecular Update. Part 1: Introduction and Non-Syndromic Ichthyoses

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Review

Abstract Ichthyoses are a heterogeneous group of diseases sharing symptoms and a common etiopathogenic mechanism. Clinically, these diseases are characterized by the presence of erythema and variable degrees of skin thickening and desquamation. Although the affected area, severity, and molecular substrate are very variable, they are all signs of a disruption of the barrier formed during epidermal differentiation. Ichthyoses follow patterns of Mendelian inheritance and present symptoms since birth or shortly thereafter. Clinically, they can be categorized into non-syndromic (when symptoms are caused exclusively by the epidermal barrier dysfunction) and syndromic ichthyoses (when the causal gene has extracutaneous functions impacting other organs).

Knowledge of molecular mechanisms has improved dramatically over the past few years, and we currently know not only most causal genes, but also the functions of the encoded proteins and their impact on skin barrier formation. In the first part of this review, we'll be introducing ichthyosis physiopathology, along with a clinical and genetic update of non-syndromic entities (those included in the consensus classification and those clinically and/or molecularly characterized since then).

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PALABRAS CLAVE
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Revisión

ICTIOSIS: Actualización clínica y molecular. Parte 1: introducción e ictiosis no sindrómicas

Resumen Las ictiosis son un grupo heterogéneo de enfermedades que comparten síntomas y un mismo mecanismo etiopatogénico. Desde el punto de vista clínico, estas enfermedades se caracterizan por la presencia de eritema y diferentes grados de engrosamiento y descamación cutáneos. Aunque el área afectada, la gravedad y el sustrato molecular son muy variables, todas ellas representan la manifestación de una disrupción de la barrera que se forma durante el proceso de diferenciación epidérmica. Las ictiosis siguen patrones de herencia mendeliana y causan síntomas desde el nacimiento o poco tiempo después. Desde el punto de vista clínico, se dividen en ictiosis no sindrómicas (cuando los síntomas están causados únicamente por el defecto de la barrera epidérmica) e ictiosis sindrómicas (cuando el gen causal también tiene funciones extracutáneas que determinan manifestaciones en otros órganos).

El conocimiento de las bases moleculares ha avanzado extraordinariamente en los últimos años y conocemos no solo la mayoría de los genes que las ocasionan, sino la función de las proteínas que codifican y el impacto en la formación de la barrera cutánea. En la primera parte de este trabajo hacemos una introducción a la fisiopatología de las ictiosis, así como una actualización clínica y genética de las entidades no sindrómicas, tanto las incluidas en la última clasificación consenso como otras que se han caracterizado clínica o molecularmente a lo largo de los últimos años.

Introduction

Ichthyoses are a heterogeneous group of diseases that share symptoms and the same etiopathogenic mechanism. Clinically these diseases are characterized by the presence of erythema and different degrees of cutaneous thickening and desquamation. Although the affected area, severity, and molecular substrate are highly variable, they all represent the manifestation of a disruption of the barrier formed during the process of epidermal differentiation. Therefore, this group of diseases is grouped under the name epidermal differentiation disorders (EDD).[1]

The epidermis is a tissue with a very well-demarcated structure: the constantly dividing stem cells responsible for regenerating the epithelium (keratinocytes) are located in the stratum basale and the cells generated from this division undergo a gradual process of differentiation as they migrate toward the surface.[2] This differentiation process (called cornification) causes morphological changes in keratinocytes due to changes in protein expression patterns, reorganization of the cytoskeleton, lipid secretion, and establishment of intercellular junctions, culminating in the formation of the stratum corneum, which is the most superficial layer of the epidermis, in which keratinocytes have terminally differentiated into corneocytes, cells lacking nuclei and organelles whose cytoplasm is completely filled with structural proteins. Corneocytes form junctions between them called corneodesmosomes and are embedded in a lipid matrix secreted in the lower layers that saturates the intercellular space and in which enzymes capable of degrading the intercellular junctions are immersed[3] (Fig. 1).

The cornification process generates an organic structure that acts as a barrier between the environment and the rest of the organism. Structural proteins give cells mechanical resistance to physical and chemical aggressions; corneodesmosomes bind the cells together and transfer this mechanical resistance to the entire tissue; lipids seal the intercellular spaces, preventing water exchange and, therefore, both the entry of pathogens and water loss through evaporation; and finally, enzymes secreted into the intercellular space are responsible for the orderly degradation of intercellular junctions, allowing the epithelium to desquamate and making it harder for parasites to colonize the skin. In addition, the thinness of the stratum corneum makes the epidermal barrier a very flexible structure, capable of carrying out its functions without limiting the movement of the organism.[4]

An alteration of the epidermal barrier that prevents it from carrying out its functions exposes the organism to physical, chemical, and biological aggressions leading to transepidermal water loss. As a homeostatic response, the body increases the production of differentiated cells and thickens the stratum corneum, which leads to the appearance of the common signs of EDD, hyperkeratosis and increased desquamation. Thickening of the stratum corneum causes loss of skin elasticity, which hinders mobility and can lead to fissure formation. Transepidermal water loss increases the risk of dehydration and, along with the hypohidrosis associated with these disorders, heat intolerance. In addition, the barrier defect increases immune system exposure to pathogens, causing hyperactivation of inflammatory pathways, erythema, and pruritus.[5,6]

When this alteration of the epidermal barrier is caused by extrinsic factors, the disease is called acquired ichthyosis. It is a finding associated with certain tumors (Hodgkin's disease, multiple myeloma and cutaneous T-cell lymphoma), endocrine (renal failure, diabetes, hyperparathyroidism), autoimmune (lupus erythematosus and dermatomyositis), and infectious diseases (leprosy, mycobacterial, or HIV infections), and nutritional disorders (usually lipid or vitamin

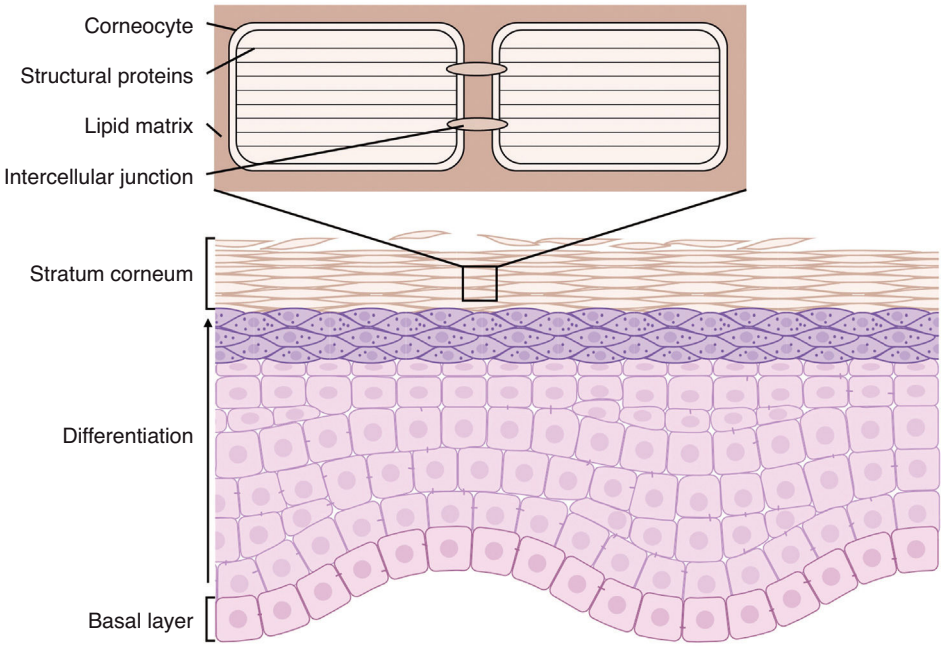

Figure 1 Structure of the epidermis. Stem cells in the stratum basale differentiate to form the stratum corneum, composed of corneocytes packed with structural proteins, anchored by intercellular junctions, and embedded in an extracellular lipid matrix. *Source*: Modified from ''Ichthyosis,'' C. Gutiérrez-Cerrajero et al.[9].

metabolic alterations), or certain drugs (cholesterol-lowering drugs, allopurinol, acitretin, EGFR and BRAF inhibitors). Acquired ichthyosis is a late onset disease—years or decades after birth—its symptoms are usually mild when compared to the other EDD, and its treatment is usually directed against the extrinsic factor causing the disease.[7]

Inherited EDD respond to Mendelian inheritance patterns and cause symptoms since birth or a few months later. At present, more than 100 genes have been described with pathogenic variants causing some type of EDD. The phenotypic presentation of these diseases is very heterogeneous and depends on the functions of the affected protein. Table 1 shows the role of the genes involved in the ichthyosis pathogenesis in epidermal differentiation.[1] Consequently, clinical diagnosis can be difficult, and definitive confirmation of the disease requires molecular confirmation.

According to the consensus classification of congenital ichthyoses published in 2010,[8] congenital ichthyoses are categorized into non-syndromic (when all symptoms are caused by the epidermal barrier defect and there are only cutaneous signs) and syndromic ichthyoses (when the causal gene has extracutaneous functions that determine manifestations in other organs).[9] Following this criterion, we have included diseases described later or that have been better characterized in recent years, updating them both clinically and molecularly.

Non-syndromic ichthyoses

These are ichthyoses whose genetic alterations affect only the differentiation of the epidermis. They are subcategorized based on the time of onset, inheritance pattern, phenotypic spectrum, or type of genetic involvement (Table 2).[8]

Ichthyosis vulgaris (IV)

It is the most common form of ichthyosis in northern European populations, with a prevalence of 1 in 80 in English patient cohorts.[10] IV is characterized, in most cases, by a relatively late presentation, a few months after birth. Patients exhibit a fine, whitish scaling, and, although it is most prominent on the extensor surface of the extremities, it is not uncommon for the entire body surface to be affected. Occasionally, patients have larger, lighter brown scales on the extensor areas of the extremities, especially the lower ones. Another characteristic feature of IV is palmar hyperlinearity, a finding known as filaggrin palm[11] (Fig. 2). Palmoplantar keratoderma is a much less common finding.[12] Additionally, many patients suffer from itching, and scratching leads to very expressive whitish linear lesions. Although IV is frequently associated with atopic dermatitis, only half of the patients with this inflammatory disease associate pathogenic variants in *FLG*.[13] IV is caused by semi-dominant pathogenic variants in *FLG*[14]—a gene encoding the filaggrin protein—the major protein inside corneocytes. Of note, there are 2 rarer forms of ichthyosis that also affect filaggrin metabolism, caused by recessive pathogenic variants in *CASP14*[15] and dominant pathogenic variants in *ASPRV1*.[16] While the first form exhibits a phenotype similar to IV, the second one, exceptionally, exhibits a phenotype similar to lamellar ichthyosis—see below—but with palmar hyperlinearity and no collodion membrane at birth.[16]

Table 1 Function of the main genes involved in congenital ichthyosis pathogenesis.

Gene (MIM code)	Function
Structural proteins	
Keratins	
KRT1 (139350)	Contributes to the intermediate filament cell cytoskeleton in suprabasal epidermal cells
KRT2 (600194)	Contributes to the intermediate filament cell cytoskeleton in the more superficial suprabasal epidermal cells
KRT10 (148080)	Contributes to the intermediate filament cell cytoskeleton in suprabasal epidermal cells, less important in palmoplantar skin
Filaggrin	
ASPRV1 (611765)	Protease involved in filaggrin processing, due to phenotype it probably targets additional proteins
CASP14 (605848)	Protease involved in filaggrin processing
FLG (135940)	Protein that aggregates keratin intermediate filaments through promotion of disulfide-bond formation and liquid-liquid phase separation. It is part of the cornified cell envelope and upon proteolysis contributes to the formation of the epidermal natural moisturizing factor
POMP (613386)	Molecular chaperone responsible for promoting proteasome formation and for the maturation of proteins critical for epidermal differentiation such as filaggrin
Cornified envelope	
LORICRIN (152445)	Precursor protein of the cornified envelope
TGM5 (603805)	Enzyme that crosslinks precursor proteins of and to the cornified envelope
Lipid metabolism	
Ceramides	
ABCA12 (607800)	Enzyme involved in ceramide loading to the lamellar bodies
ABHD5 (604780)	Functions as an acyltransferase and as a coactivator of adipocyte triglyceride lipase
ALDH3A2 (609523)	Enzyme involved in fatty acid synthesis, which some studies suggest are used as ceramide precursors
ALOX12B (603741)	Enzyme involved in ceramide crosslinking to the cornified envelope to form the corneocyte lipid envelope
ALOXE3 (607206)	Enzyme involved in ceramide crosslinking to the cornified envelope to form the corneocyte lipid envelope
CERS3 (615276)	Synthesizes ceramide from modified ultra-long chain fatty acid and dihydrosphingosine
CYP4F22 (611495)	ω-Hydroxylation ultra-long chain fatty acids for acylceramide synthesis
ELOVL1 (611813)	Fatty acid elongase involved in ultra-long chain fatty acid synthesis, which are ceramide precursors
ELOVL4 (605512)	Fatty acid elongase involved in ultra-long chain fatty acid synthesis, which are ceramide precursors
GBA1 (606463)	Catalyzes the breakdown of the glycolipid glucosylceramide to ceramide and glucose
KDSR (136440)	Synthesizes ceramide precursor dihydrosphingosine from serine
LIPN (613924)	Unclear role in ceramide synthesis
NIPAL4 (609383)	Unclear role in ceramide synthesis
PEX7 (601757)	Plays an essential role in peroxisomal protein import (including phytanoyl-coenzyme A hydroxylase)
PHGDH (606879)	Enzyme involved in serine synthesis, which is used as a ceramide precursor
PHYH (602026)	Enzyme involved in synthesis of peroxisomal fatty acids, which are used as ceramide precursors
PNPLA1 (612121)	Catalyzes ω-O-esterification with linoleic acid to form acylceramides
PSAT1 (610936)	Enzyme involved in serine synthesis, which is used as a ceramide precursor
PSPH (172480)	Enzyme involved in serine synthesis, which is used as a ceramide precursor
SDR9C7 (609769)	Enzyme involved in ceramide crosslinking to the cornified envelope to form the corneocyte lipid envelope
SLC27A4 (604194)	Adds coenzyme A to ultra-long chain fatty acids for ceramide synthesis
TGM1 (190195)	Enzyme with poorly understood functions in ceramide crosslinking to the cornified envelope to form the corneocyte lipid envelope
UGCG (602874)	Glycosylates acyl-ceramide
Cholesterol	
EBP (300205)	Enzyme involved in cholesterol synthesis
MBTPS2 (300294)	Membrane metalloprotease involved in activation of transcription factors involved in cholesterol enzyme transcription

Table 1 (*Continued*)

Gene (MIM code)	Function
NSDHL (300275)	Enzyme involved in cholesterol synthesis
SREBF1 (184756)	Transcription factor involved in cholesterol enzyme transcription
STS (300747)	Synthesizes cholesterol from cholesterol sulfate
SULT2B1 (604125)	Responsible for cholesterol sulfation, which plays a major role in the regulation of epidermal differentiation
SUMF1 (607939)	Responsible for modifying various sulfatases
Lamellar bodies	
SNAP29 (604202)	Mediates lamellar body fusion events
VIPAS39 (613401)	Mediates lamellar body fusion events
VPS33B (608552)	Mediates lamellar body fusion events
Dolichol	
DOLK (610746)	Phosphates dolichol
MPDU1 (604041)	Adds mannose to dolichols as preparation for protein O-glycosylation and N-mannosylation
PIGL (605947)	Involved in glycosylphosphatidylinositol anchor synthesis
SRD5A3 (611715)	Involved in dolichol synthesis
Intercellular junctions	
Tight junctions	
CLDN1 (603718)	Tight junction protein, controls paracellular permeability
CLDN10 (617579)	Tight junction protein, controls paracellular permeability
Gap junctions	
GJA1 (121014)	Gap junction protein, controls intercellular communication
GJB2 (220290)	Gap junction protein, controls intercellular communication
GJB3 (603324)	Gap junction protein, controls intercellular communication
GJB4 (605425)	Gap junction protein, controls intercellular communication
GJB6 (604418)	Gap junction protein, controls intercellular communication
Desmosomes	
CDSN (602593)	Component of corneodesmosomes in the *stratum corneum*, increases mechanical resistance
DSG1 (125670)	Desmosome protein, ensures intercellular adhesion
DSP (125647)	Desmosome protein, ensures intercellular adhesion
FLG2 (616284)	Ensures cell-cell adhesion in the upper epidermal layers in a corneodesmosin-dependent fashion
Proteases e inhibitors	
SPINK5 (605010)	Serine protease inhibitor, prevents junction degradation
CAST (114090)	Cysteine protease inhibitor, prevents junction degradation
CSTA (184600)	Cysteine protease inhibitor, prevents junction degradation
SERPINB8 (601697)	Serine protease inhibitor, prevents junction degradation
ST14 (606797)	Functions as an epithelial membrane activator for other proteases and plays a role in profilaggrin processing and hair follicle growth
Transcription/translation	
AARS1 (601065)	Alanyl-tRNA synthetase
ERCC2 (126340)	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription
ERCC3 (133510)	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription
GTF2E2 (189964)	Component of the TFIIE complex involved in type 2 gene transcription
GTF2H5 (608780)	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription
MARS1 (156560)	Methionyl-tRNA synthetase
RNF113A (300951)	Ring finger protein involved in pre-mRNA splicing
TARS1 (187790)	Threonyl-tRNA synthetase

Table 1 (*Continued*)

Gene (MIM code)	Function
Calcium channels	
TRPM4 (606936)	Calcium activated-ion channel, associated with proliferation regulation
Clathrin-coated vesicles	
AP1B1 (600157)	Part of the clathrin-coated vesicle adaptor complex
AP1S1 (603531)	Part of the clathrin-coated vesicle adaptor complex
Miscellaneous	
MPLKIP (609188)	Interacts with cyclin dependent and polo kinases, maintains cell cycle integrity

MIM: gene code in OMIM database.

Table 2 Non-syndromic ichthyosis classification.

Non-syndromic ichthyoses
Ichthyosis vulgaris (IV) (ORPHA: -)
Recessive X-linked ichthyosis (RXLI) (ORPHA: 461)
Autosomal recessive congenital ichthyosis (ARCI) (ORPHA: 281097)
Lamellar ichthyosis (ORPHA: 313)
Congenital ichthyosiform erythroderma (ORPHA: 79394)
Harlequin ichthyosis (ORPHA: 457)
Self-healing collodion baby (ORPHA: 281122)
Acral self-healing collodion baby (ORPHA: 281127)
Bathing suit ichthyosis (ORPHA: 100976)
Keratinopathic ichthyoses (ORPHA: 281103)
Autosomal dominant epidermolytic ichthyosis (ORPHA: 312)
Autosomal recessive epidermolytic ichthyosis (ORPHA: 512103)
Annular epidermolytic ichthyosis (ORPHA: 281139)
Ichthyosis Curth-Macklin (ORPHA: 79503)
Ichthyosis with confetti (ORPHA: 281190)
Superficial epidermolytic ichthyosis (ORPHA: 455)
Epidermolytic nevus (ORPHA: 497737)
Peeling skin syndromes (ORPHA: 817)
Generalized peeling skin syndrome (ORPHA: 263543)
Acral peeling skin syndrome (ORPHA: 263534)
PLACK Syndrome (ORPHA: 44138)
Erythrokeratoderma (ORPHA: 79355)
Loricrin keratoderma (ORPHA: 79395)
KLICK syndrome (ORPHA: 281201)

KLICK: *keratosis linearis, ichthyosis congenita, and sclerosing keratoderma*; ORPHA: código de la enfermedad en la base de datos ORPHANET; PLACK: *peeling skin, leukonychia, acral punctate keratosis, cheilitis, and knuckle pads* (piel descamada, leuconiquia, keratosis puntada acral, queilitis y almohadillas en los nudillos).

Recessive X-linked ichthyosis (RXLI)

RXLI affects only men (with a prevalence of 1 in 5000)[17] as it is caused by deletions of the steroid sulfatase gene (*STS*), located in a distal region of the short arm of the X chromosome that does not undergo inactivation.[18] Although women are carriers of the disease and transmit it, they only manifest it in the rare cases in which the gene deletion occurs in both chromosomes.[19] RXLI is characterized by the presence of dark brown polygonal scales on the extensor surfaces of the extremities (Fig. 3). Although the size of the scales is variable, they tend to be larger on the extensor surfaces of the lower extremities. Involvement of the flexures is variable and probably depends on the severity of desquamation being present in the most clinically expressive subjects. Desquamation affects the scalp, neck, and retroauricular region, giving a false appearance of insufficient hygiene to some of these patients. Palms and soles are usually spared. As

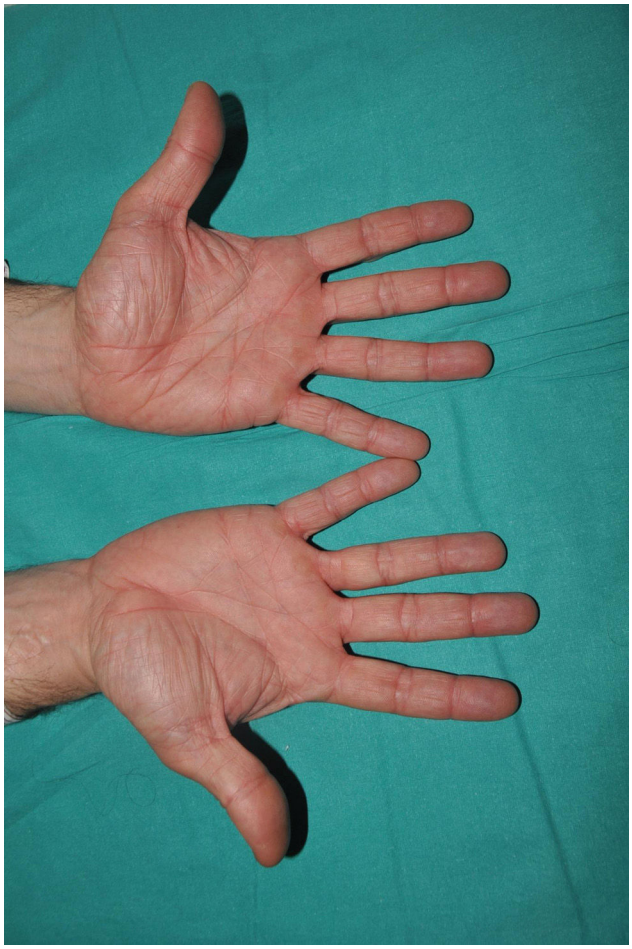

Figure 2 Ichthyosis vulgaris. Palmar hyperlinearity (filaggrin palms) in a patient with a pathogenic variant in *FLG*.

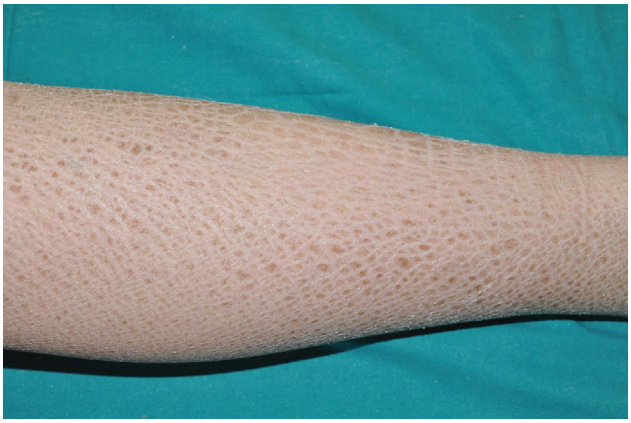

Figure 3 X-linked recessive ichthyosis. Typical dark polygonal scaling on the lower extremity.

with IV, many patients with RXLI are born with a normal skin and manifest the disease after the first few months of life, et some still have some sort of presentation at birth similar to yet much milder than a collodion membrane. The deficit in *STS* function prevents desulfation of cholesterol sulfate in the epidermis, hindering adequate desquamation of the stratum corneum. It also prevents desulfation of dehydroepiandrosterone sulfate, hindering cervical maturation during labor, causing prolonged second stage of labor in carrier women, which can help confirm clinical suspicion.[20] Although RXLI is considered a non-syndromic ichthyosis, 30%-40% of patients present with attention deficit hyperactivity disorder, so it is very likely that some steroid metabolized by the STS enzyme plays a role as a neurotransmitter.[21]

IV and RXLI may have a similar appearance in the more symptomatic IV cases. Family history screening—involvement of maternal grandfather or mother's siblings—normal appearance of palms and soles and sparing of flexures in most patients with RXLI may help differentiate the 2 entities. The confluence of pathogenic variants in *FLG* and *STS* in some patients may significantly increase the expressiveness of desquamation in RXLI patients and facilitate association of palmoplantar hyperlinearity.[22]

Autosomal recessive congenital ichthyosis (ARCI)

ARCI alludes to its inheritance pattern, has a very low prevalence, estimated to be between 7.2 and 16.2 affected per million inhabitants both in Spain[23] and other regions.[24,25] Unlike ichthyoses in the previous group, ARCIs debut at birth. The most typical form of presentation is called collodion baby, which is characterized by a shiny and smooth transparent glue-like membrane that covers the entire body and, in most severe cases, causes ectropion (eversion of the eyelids) and eclabium (eversion of the lips). The col-

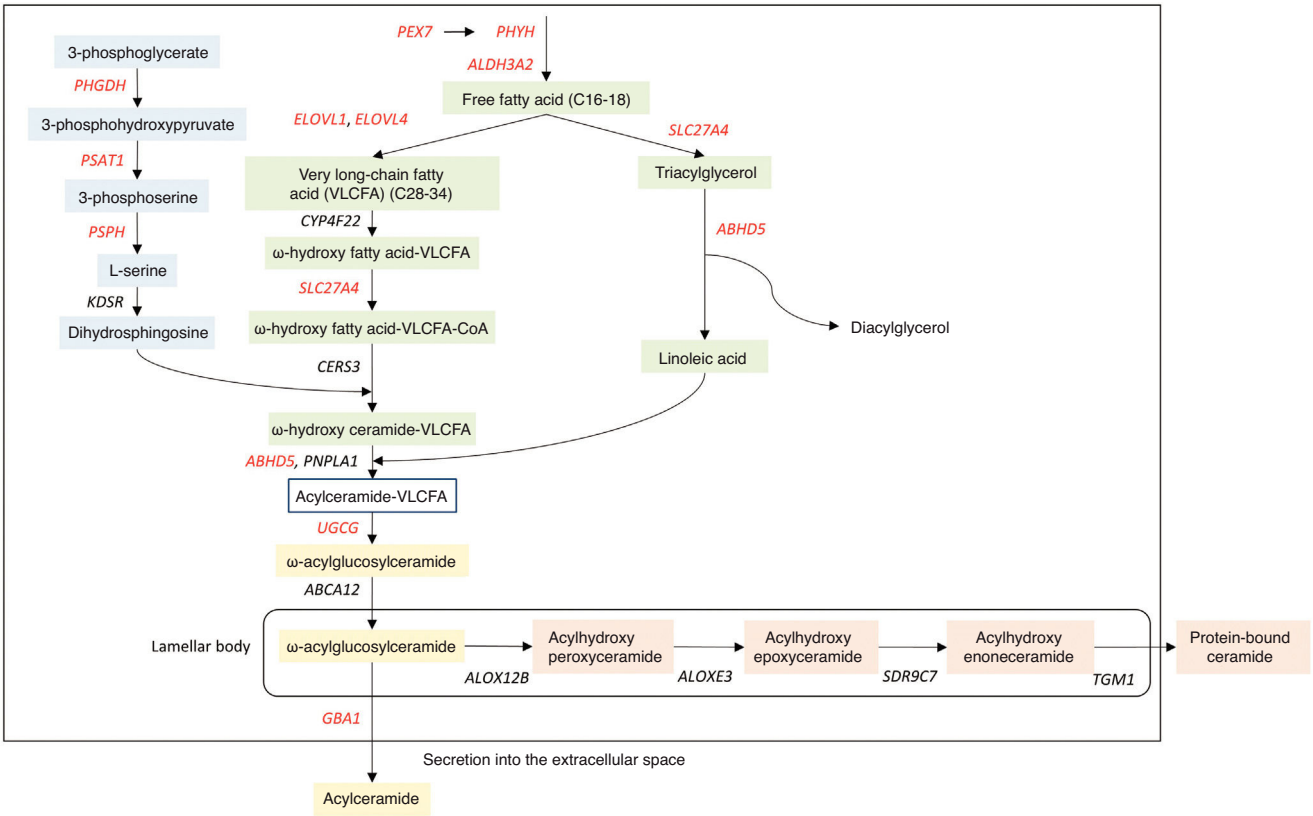

Figure 4 Ceramide synthesis pathway in the epidermis. These reactions involve the union of a sphingoid base (blue) and a fatty acid (green) to form acylceramide, which can be released as a free lipid (yellow) or bound to proteins (orange). Mutations in the genes depicted cause non-syndromic (black) or syndromic (red) ichthyosis.
Source: Modified from ''Ichthyosis,'' C. Gutiérrez-Cerrajero et al.[9].

Table 3 Rare forms of non-syndromic ichthyoses.

Group	Causal genes	Main characteristics
Peeling skin syndromes (PSS, ORPHA: 817)		Characterized by desquamation of the upper layer of the epidermis.[1] They are further subdivided depending on the affected areas
Generalized peeling skin syndrome (generalized PSS, ORPHA: 263543)	*CDSN*[2] (AR, MIM: 270300), *FLG2*[1] (AR, MIM: 618084)	Peeling involves the entire surface of the skin[1] and includes 2 subtypes: Subtype A (non-inflammatory, ORPHA: 263548), caused by *FLG2* Subtype B (inflammatory, ORPHA: 263553), caused by *CDSN*
Acral peeling skin syndrome (acral PSS, ORPHA: 263534)	*CSTA*[3] (AR, MIM: 607936), *TGM5*[4] (AR, MIM: 609796)	The shedding affects primarily the plantar and dorsal surfaces of the hands and feet.[1]
Exfoliative ichthyosis (ORPHA: 289586)	*CSTA*[5] (AR, MIM: 607936), *SERPINB8*[6] (AR, MIM: 617115)	Characterized by shedding of the skin and generalized dry, scaling skin.[5] It is not typically classified as a PSS, but exfoliative ichthyosis shares signs and underlying molecular basis with acral PSS.[5]
Peeling skin-leukonychia-acral punctate keratoses-cheilitis-knuckle pads syndrome (PLACK, ORPHA: 444138)	*CAST*[7] (AR, MIM: 616295)	Characterized by generalized peeling skin with leukonychia (white discoloration of nails), acral punctate keratoses (keratotic patches on the extremities), cheilitis, and knuckle pads.
Others		
Loricrin keratoderma (LK, ORPHA: 79395)	*LORICRIN*[8] (AD, MIM: 604117)	Also known as keratoderma *hereditarium mutilans* with ichthyosis, Camisa disease, or Vohwinkel syndrome with ichthyosis. It is characterized by generalized ichthyosis with honeycomb palmoplantar hyperkeratosis and often constricting bands around the fifth fingers.[8]
Erythrokeratoderma variabilis et progressiva (EKVP, ORPHA: 308166)	*GJA1*[9] (AD, MIM: 617525), *GJB3*[10] (AD o AR, MIM: 133200), *GJB4*[11] (AD, MIM: 617524), *KDSR*[12] (AR, MIM: 617526), *PERP*[13] (AR, MIM: 619209), *TRPM4*[14] (AD, MIM: 618531)	An umbrella term that includes patients with similar clinical findings: migratory erythema and hyperkeratotic lesions, which change size over time[15] (sometimes called *erythrokeratoderma variabilis* (EKV)) and/or fixed brown-red hyperkeratotic plaques[11] (sometimes called progressive symmetric erythrokeratoderma (PSEK)). Individuals and families may show both fixed and migratory plaques caused by mutations in different genes, some of which encode proteins with no apparent functional relationship. EKVP features have also been described in occasional patients with *NIPAL4*[16] or *ABCA12*[17] mutations.

Table 3 (*Continued*)

Group	Causal genes	Main characteristics
Keratosis *linearis*-ichthyosis congenita-sclerosing keratoderma syndrome (KLICK, ORPHA: 281201)	*POMP*[18] (AR, MIM: 601952)	Characterized by congenital ichthyosis, discrete papules on the flexural aspects of large joints, palmoplantar keratoderma, constricting bands around the fingers, and flexural deformities.[18]

AD: autosomal dominant, AR: autosomal recessive.

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lodion membrane is shed within the first few weeks of life, progressing into a phenotypic presentation of variable severity, with varying degrees of erythema and different desquamation morphology. Accordingly, 5 different clinical forms are distinguished and detailed below. In cases where no collodion membrane is seen, neonates present with erythroderma and varying degrees of hyperkeratosis and desquamation. In most cases, the affected genes are involved in the metabolism of ceramides,[8] a lipid component of the intercellular matrix that prevents transepidermal water loss (Fig. 4) (Table 3). Although there is no exact genophenotypic correlation, patients with pathogenic variants in *TGM1* associate alopecia, ectropion, and neonatal presentation as a collodion baby with a significantly higher frequency than the other genes.[8]

According to the current classification of ichthyoses,[8] there are 5 clinical forms of ARCI, including:

- ***Lamellar ichthyosis***: characterized by a moderate-to-severe degree of erythema and desquamation in large

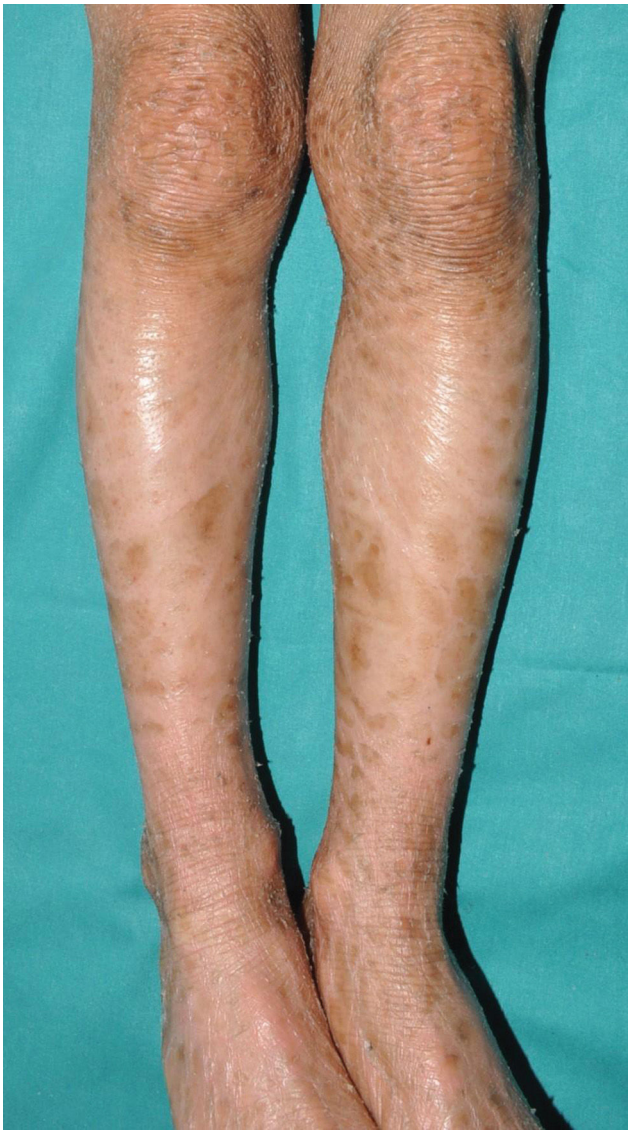

Figure 5 Autosomal recessive congenital ichthyosis. Lamellar desquamation in a patient with the dark phototype *TGM1* variant.

lamellae of somewhat darker tone than the patient's skin, i.e. light brown in light phototypes and dark brown in darker phototypes. Although this large sheet-like desquamation affects the entire body, it is more evident on the lower extremities and the frontal region of the face (Fig. 5). Many patients also present ectropion and a thick adherent scalp desquamation that may precede an almost total cicatricial alopecia.[26] Palmoplantar involvement also presents a laminar aspect, with areas of diffuse thickening and a smooth surface (Fig. 6). Alterations in nail morphology are not a rare finding, such as incurvation of the nail plate, linear areas of leukonychia and increased extension of the lunula.

- ***Congenital ichthyosiform erythroderma***: together with lamellar ichthyosis, it is a classic phenotype of ARCI. Patients present with erythroderma of variable intensity and generalized desquamation with smaller scales than in the lamellar forms (Fig. 7). The scalp is usually less thick

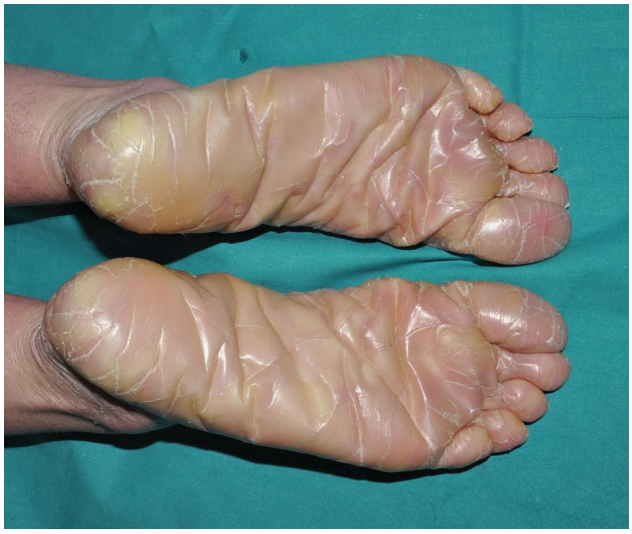

Figure 6 Autosomal recessive congenital ichthyosis. Plantar involvement in a patient with a *TGM1* variant. The surface is thickened, smooth, shiny, and occasionally fissured.

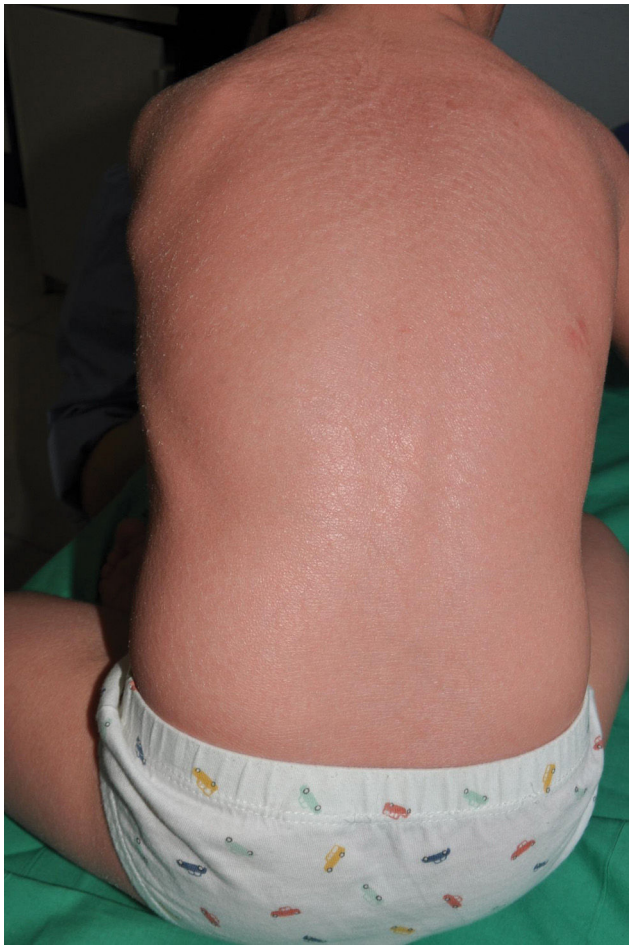

Figure 7 Autosomal recessive congenital ichthyosis. Fine scaling and moderate erythroderma are observed in a patient with an *ABCA12* variant, demonstrating the phenotypic variability of this genetic variant.

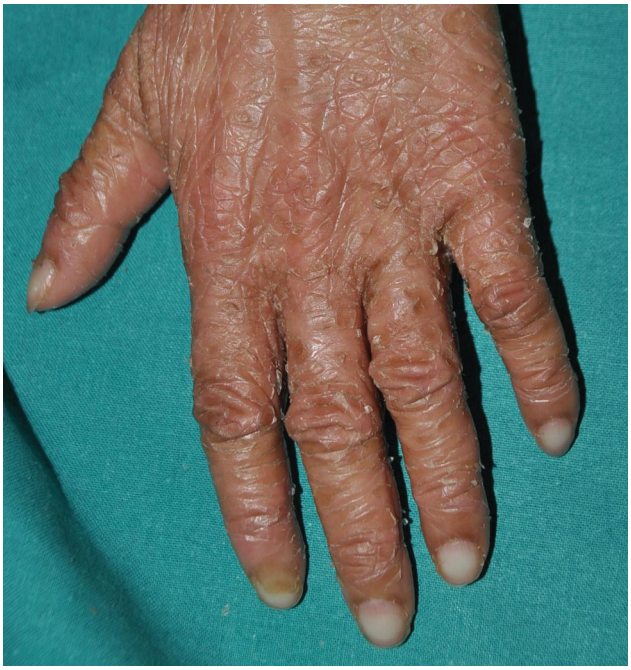

Figure 8 Autosomal recessive congenital ichthyosis. Patient with a pathogenic variant in *TGM1*. Pseudoleukonychia. Note how the loss of elasticity of the skin of the hands causes the nail bed to become vascularized when the patient attempts to stretch his fingers.

and adherent than in the lamellar forms. Characteristically, patients exhibit skin thickening of the dorsum of the hands and feet and a relative loss of elasticity of the skin of the fingers that determines a certain retraction of the fingers and a phenomenon of pseudoleukonychia when stretching them since cutaneous bed is exsanguinated (Fig. 8). Additionally, many patients also present a true leukonychia of probable post-inflammatory origin. Palmoplantar involvement determines a thickening of the palms and soles of leather-like appearance without true hyperkeratosis (Fig. 9). Many patients also exhibit, additionally, a striking facial reddening of the cheeks regardless of the severity of involvement of the rest of the body surface.

- ***Harlequin ichthyosis*** is the severe form of ARCI. It is so named because infants are born with rigid, thickened skin with extensive and deep linear fissures reminiscent of harlequin costumes. The rigidity of the skin integument is such that it restricts respiratory movements and sucking ability, endangering the child's life. Similarly, patients exhibit severe ectropion, eclabium, and severe limitation of the mobility of the fingers, which are enclosed by the corneous shell. This phenotype progresses weeks later to a severe form of congenital ichthyosiform erythroderma which, among other, associates symptoms, alopecia of the scalp, eyebrows and eyelashes, ectropion, anomalies of the auricular pavilions, joint deformities, and permanent mobility limitations[27] (Fig. 10). It is due to recessive pathogenic variants that cause complete loss of function of *ABCA12*,[27] with slightly less severe phenotypes in patients with 2 different heterozygous pathogenic variants.[28]

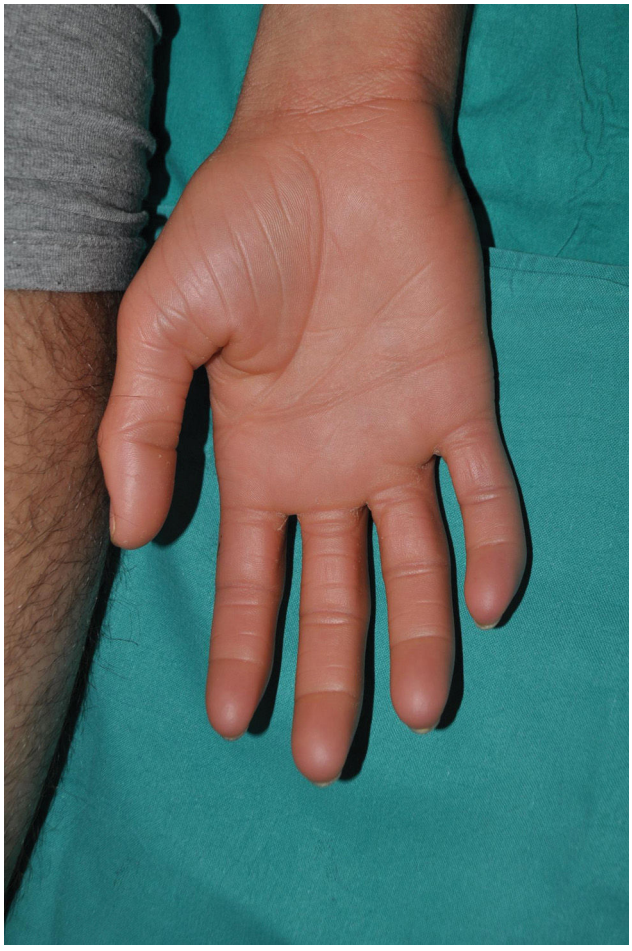

Figure 9 ARCI. Palmar involvement in a patient with a variant in the *ALOX12B* gene. Note the thickened, shiny, and scaly appearance of the palm without the yellowish hue seen in other palmar keratodermas.

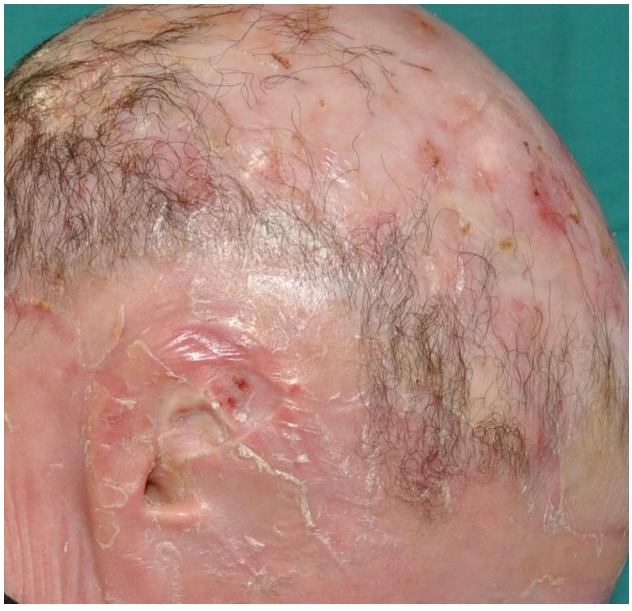

Figure 10 ARCI. Patient with harlequin ichthyosis due to a pathogenic variant in the *ABCA12* gene presenting with severe auricle deformity and scarring alopecia on the scalp.

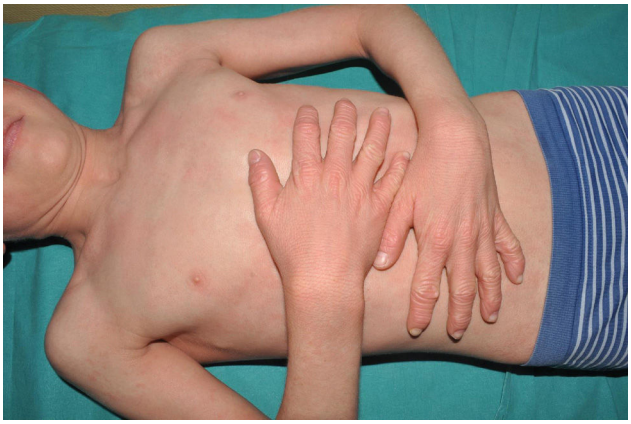

Figure 11 ARCI. Thickening of the skin on the back of the hands in a patient with self-improving ichthyosis due to a *TGM1* variant. The trunk and the rest of the upper extremities appear almost normal.

- ***Self-improving collodion baby***: this is a clinical variant in which the collodion membrane progresses, regardless of its severity, to a mild ARCI phenotype. Although the expressivity of ichthyosis is very faint in some areas such as the trunk and proximal extremities, patients usually present with facial erythema, skin thickening on elbows, knees, and dorsum of hands and feet (Fig. 11), as well as palmoplantar thickening similar in appearance to that described in congenital ichthyosiform erythroderma. Phenotypic progression to self-improving forms is not predictable, which makes prognostic information of collodion infants within the first few days of life difficult to obtain. In fact, it is due to recessive pathogenic variants in *ALOX12B*,[29] *ALOXE3*,[30] *CYP4F22*[31] or *TGM1*,[32] genes that can also determine a much more important clinical involvement and therefore even an immediate molecular diagnosis cannot predict progression.
- ***Acral self-improving collodion baby*** is an exceptional clinical form in which the collodion membrane only affects the distal part of the extremities. It is due to recessive pathogenic variants in *TGM1*.[33]
- ***Bathing suit ichthyosis*** is an ARCI variant in which patients are born with a collodion membrane and progress to a lamellar ichthyosis phenotype of variable expressivity that only affects the trunk and scalp. It is an exceptional form initially described in the North African population[34] and it is due to recessive pathogenic variants in *TGM1*[35] that generate a thermosensitive protein that loses activity in warmer areas of the body.

Keratinopathic ichthyosis

They receive the name *keratinopathic ichthyoses* because they are caused by pathogenic variants in genes encoding keratins. They have a very low prevalence, estimated at 1.1 per million.[24] Different clinical forms are distinguished according to the inheritance pattern and phenotypic features.

- ***Autosomal dominant keratinopathic ichthyosis***: the most common form of keratinopathic ichthyosis. Its main characteristic is intercellular separation, which is why it is also called epidermolytic ichthyosis. Patients are born with erythroderma, blisters, and erosions so extensive that differential diagnosis with epidermolysis bullosa can be difficult to establish. As the weeks go by, patients suffer from less erosions and a diffuse hyperkeratosis grows, which will eventually become more accentuated on the flexor surfaces of the large folds and, later, on elbows and knees. Patients exhibit throughout their lives a variable degree of erythema and skin fragility that makes them prone to erosions with minimal trauma (Fig. 12). This group of ichthyoses is caused by dominant variants in *KRT1*[36] or *KRT10*.[36] Those caused by variants in *KRT1* commonly present palmoplantar keratoderma (Fig. 13), usually absent in those associated with pathogenic variants in *KRT10*, since in palmoplantar skin *KRT9* can partially rescue the phenotype of a loss of *KRT10*.[36]
- ***Autosomal recessive keratinopathic ichthyosis***: clinically very similar to the above. It is caused by pathogenic

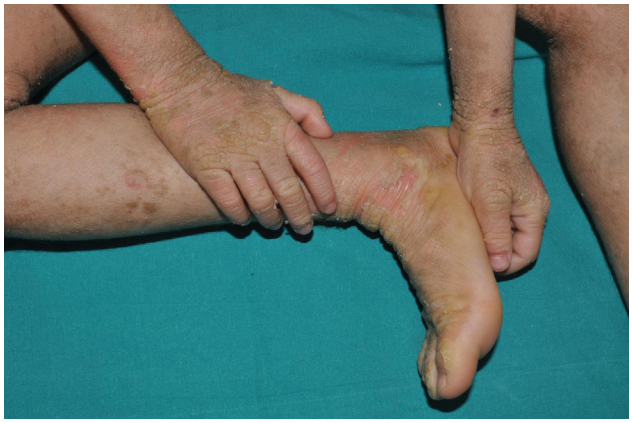

Figure 12 Epidermolytic keratinopathic ichthyosis due to a pathogenic variant in the *KRT10* gene. Generalized involvement is observed with extensive areas of thickening in the upper and lower extremities and areas of skin fragility in the pretibial and lateral regions of the feet. The involvement stops at the palmoplantar border and spares the palms and soles.

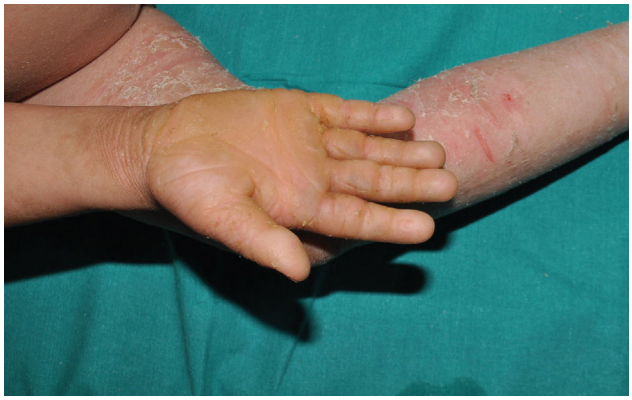

Figure 13 Epidermolytic keratinopathic ichthyosis due to a pathogenic variant in the *KRT1* gene. Diffuse palmar thickening and involvement of the lower extremity are observed, with evident areas of cutaneous fragility.

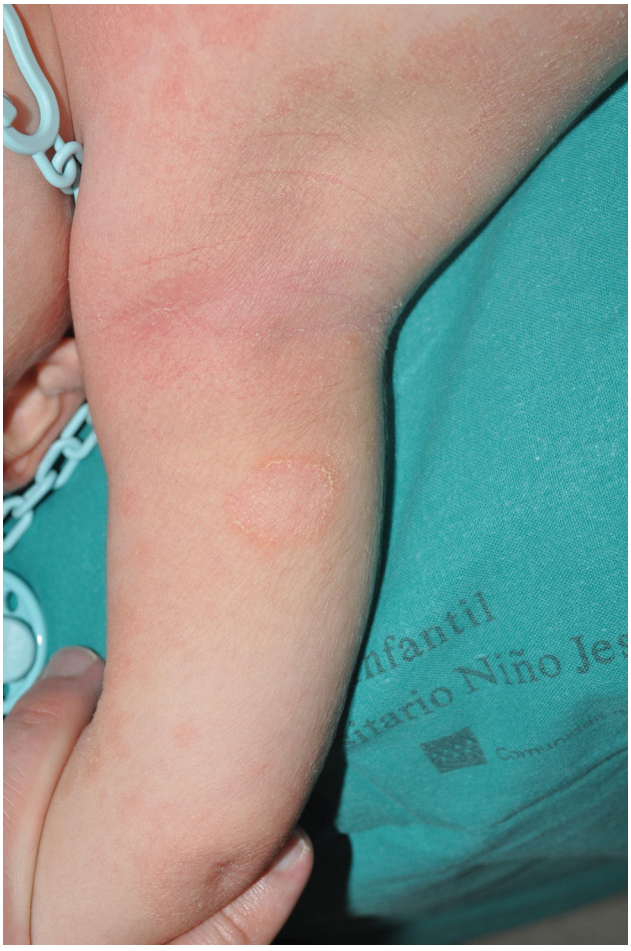

Figure 14 Annular epidermolytic keratinopathic ichthyosis due to a variant in the *KRT10* gene. An annular lesion with superficial peripheral desquamation typical of certain *KRT10* variants that result in this peculiar clinical form is observed.

recessive variants in *KRT10*.[37] Its prevalence is much lower than the dominant forms.

- ***Annular keratinopathic ichthyosis***: a special subtype in which patients are born with an appearance similar to that of other keratinopathic ichthyoses, but subsequently progress to a less severe clinical form in which, in addition to diffuse hyperkeratosis at the level of the large folds, transient annular lesions with superficial desquamation are observed[38] (Fig. 14). It is caused by dominant pathogenic variants in *KRT1*[39] or *KRT10*.[40]
- ***Superficial keratinopathic ichthyosis*** shows a milder phenotype than the 2 previous ones and does not present erythroderma at birth. It is characterized by mild-to-moderate diffuse hyperkeratosis showing predilection for articular surfaces. There may be focal detachment of the hyperkeratosis, a phenomenon called ''mauserung'' or ''molting'' in the international literature (Fig. 15). It is caused by dominant pathogenic variants in *KRT2*.[41] This keratin is expressed in superficial layers of the epidermis and probably for this reason the clinical manifestation and the phenomena of epidermolysis and focal detachment of hyperkeratosis are less expressive vs cases related to pathogenic variants in *KRT1* and *KRT10*.

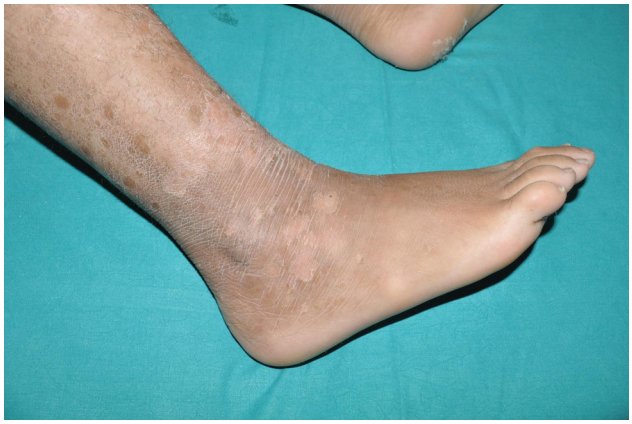

Figure 15 Superficial epidermolytic keratinopathic ichthyosis due to a *KRT2* variant, where patchy superficial detachment of the epidermis (''flaking'') is observed.

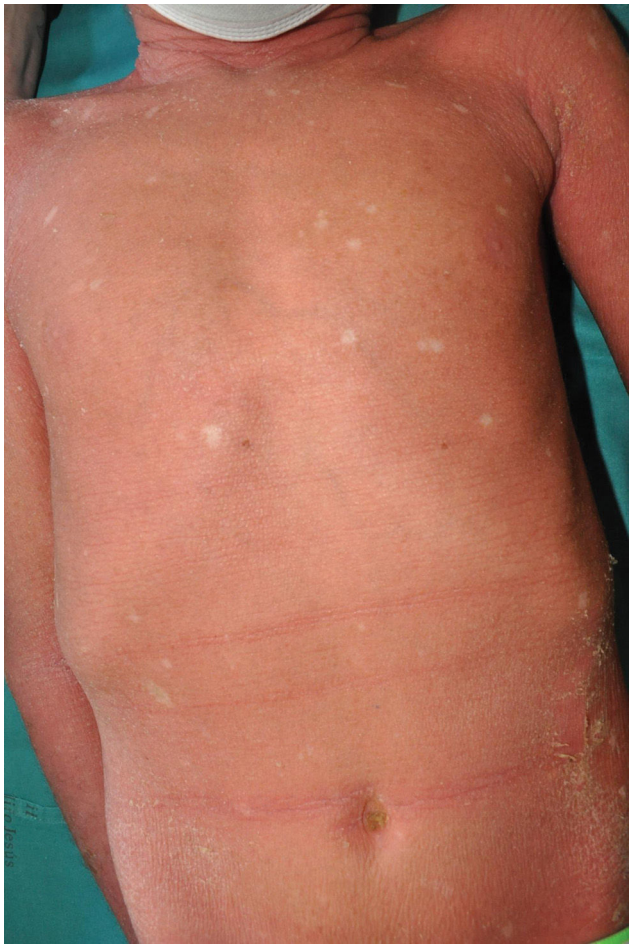

Figure 16 Non-epidermolytic keratinopathic ichthyosis with reverse mosaicism due to *KRT10* variant. Note the lenticular lesions resembling normal skin on the anterior trunk.

- ***Mosaic keratinopathic ichthyoses*** are characterized by hyperkeratotic lesions of Blaschkoid distribution whose extent is variable, ranging from a few centimeters (epidermolytic nevus) to hemicorporal, uni or bilateral involvement. They are due to postzygotic pathogenic

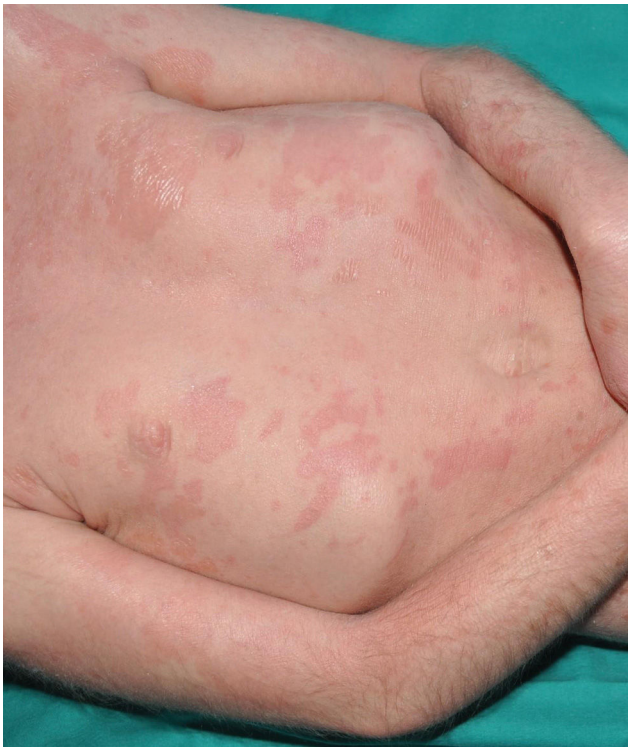

Figure 17 Skin exfoliation syndrome due to a pathogenetic variant in *CDSN*. The patient presents with diffuse erythema with patchy areas of superficial exfoliation.

variants in *KRT1*,[42] *KRT10*,[43] or *KRT2*,[44] in which the disease-causing mutation only affects some epidermal progenitors. The area of affected skin varies depending on the timing of mutation, the earlier the mutation occurs, the more extensive it is. In cases where the mosaic affects the gonads, the disease can be transmitted to the patient's children as generalized keratinopathic ichthyosis.

- ***Keratinopathic ichthyosis with reversion patches (in confetti)***: a particular type of non-epidermolytic keratinopathic ichthyosis in which there is no epidermolysis and therefore the typical histological findings of intercellular separation are not observed. Clinically, patients present with severe ichthyosiform erythroderma and variable palmoplantar involvement. At school age, small lenticular areas of healthy skin begin to be observed on the trunk, which increase in number and size with age (Fig. 16). Patients may also present ectropion, scalp alopecia, nail changes, hypertrichosis, and abnormal gait, among other symptoms.[45] It is caused by dominant variants in *KRT10*[46] or, much less frequently, in *KRT1*, whose reversions appear in adulthood.[47] Healthy skin patches are caused by loss of heterozygosity of the mutated allele due to mitotic recombination events whose triggering factor is unknown, but is thought to be related to aberrant import of mutated keratins to the nucleus.[45]
- Other non-syndromic ichthyoses are shown in Table 3. Although they are very rare, some have prominent clinical data that may facilitate diagnosis, such as superficial desquamation and underlying erythema in peeling skin syndromes (Fig. 17) or cribriform keratoderma produced by loricrin variants (Fig. 18).

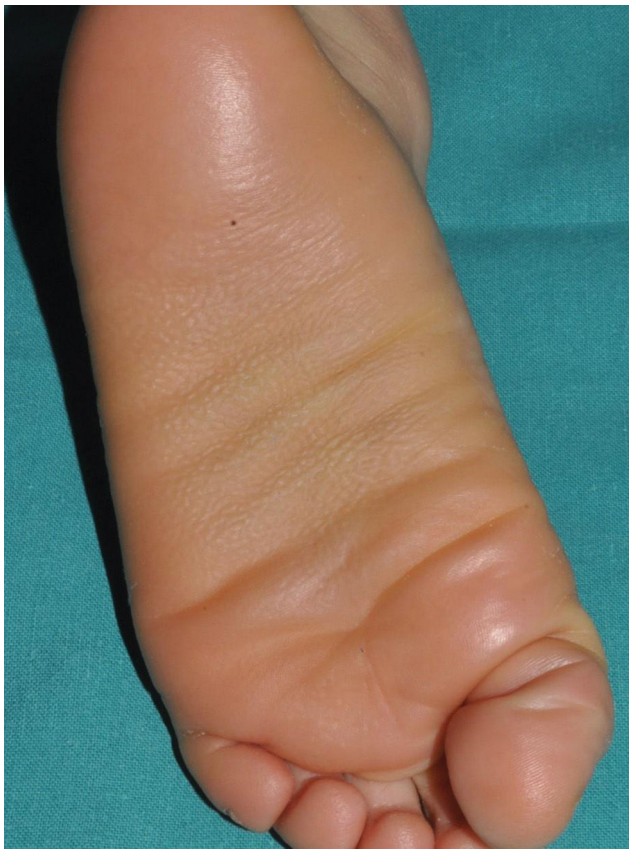

Figure 18 Loricrin keratoderma. Diffuse plantar involvement in an affected individual, showing small, cribriform depressions.

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