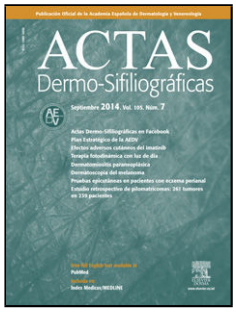
Journal Pre-proof



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

C. Gutiérrez-Cerrajero R. González Sarmiento Á. Hernández Martín

PII: S0001-7310(25)00143-7

DOI: https://doi.org/doi:10.1016/j.ad.2025.03.012

Reference: AD 4313

To appear in: *Actas dermosifiliograficas*

Received Date: 2 July 2024

Accepted Date: 1 September 2024

Please cite this article as: Gutiérrez-Cerrajero C, González Sarmiento R, Hernández Martín Á, ICTIOSIS: Actualización clínica y molecular. Parte 1: introducción e ictiosis no sindrómicas, *Actas dermosifiliograficas* (2025), doi: https://doi.org/10.1016/j.ad.2025.03.012

Refers to AD_4220

Revisión

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

[[Translated article]]ICHTHYOSIS: Clinical and molecular update. Part 1: Introduction and non-syndromic ichthyoses

C. Gutiérrez-Cerrajero[a,b], R. González Sarmiento[a,b] , Á. Hernández Martín[c,*]

[a]. Departamento de Medicina, Facultad de Medicina, Universidad de Salamanca, Salamanca, España)

[b]. Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, España)

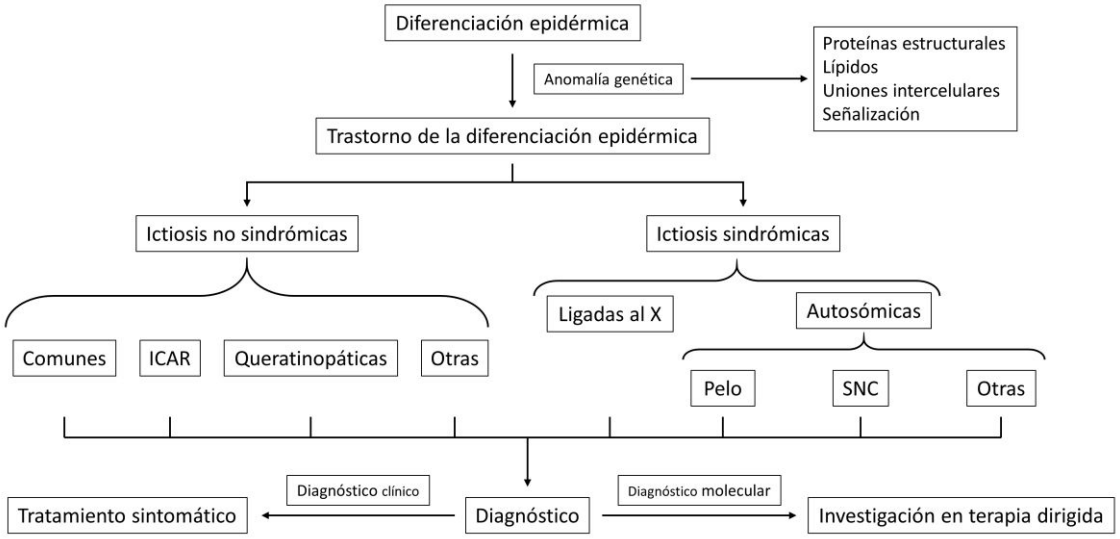
[c]. Servicio de Dermatología, Hospital Infantil Niño Jesús, Madrid, España)

[*]. Autor de correspondencia

ahernandez@aedv.es

Graphical abstract

fx1



1.1 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 cutáneas. 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 sólo 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 y/o molecularmente a lo largo de los últimos años.

1.2 Palabras clave

Ictiosis, desórdenes de la cornificación, genodermatosis, revisión

1.3 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).

1.4 Keywords

Ichthyosis, disorders of cornification, genodermatosis, review

1.5 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 disorders of epidermal differentiation (DED)[1].

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 towards 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] (Figure 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 lost 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 sign of DED, hyperkeratosis and increased desquamation. Thickening of the stratum corneum causes skin elasticity loss, 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 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 vs all the other DED, and its treatment is usually directed against the extrinsic factor causing the disease[7].

Inherited DED 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 DED. 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 appearance of ichthyoses 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.

a. 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].

i. 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] (Figure 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 more 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].

ii. 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 (Figure 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 with IV, many patients with RXLI are born with a normal skin and manifest the disease after the first few months of life, yet they still some 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 horny layer. 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].

iii. 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 10^6 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 collodion 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 (Figure 4) (Table 3). Although there is no exact geno-phenotypic 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 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 (Figure 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 (Figure 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 (Figure 7). The scalp is usually less thick 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 (Figure 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 (Figure 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] (Figure 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].
- ***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 (Figure 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.

iv. Keratinopathic ichthyosis

They receive the name *keratinopathic ichthyoses* because they are caused by pathogenic variants in genes encoding keratins, 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 (Figure 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 (Figure 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 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] (Figure 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 (Figure 15). It is caused by dominant pathogenic variants in *KRT2*[41]. This keratin is expressed in superficial layers of the stratum corneum 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*.

- ***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 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 (Figure 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 (Figure 17) or cribriform keratoderma produced by loricrin variants (Figure 18).

Bibliografía

<BIBL>

<BIB>

1

S Oji F V.

S Metze F D.

S Traupe F H.

BT Inherited Disorders of Cornification

PN Wiley

D 2016

P 1-L 97

DOI 10.1002/9781118441213.rtd0066

<original_ref>Oji V., Metze D., Traupe H., Inherited Disorders of Cornification, Wiley, 2016, 1- 97, 10.1002/9781118441213.rtd0066</original_ref>

</BIB>

<BIB>

2

S Kolarsick F P.A.

S Ann Kolarsick F M.

S Goodwin F C.

AT Anatomy and Physiology of the Skin

JT J Dermatol Nurses Assoc

V 3

D 2011

P 203-L 213

DOI 10.1097/JDN.0b013e3182274a98

<original_ref>Kolarsick P.A., Ann Kolarsick M., Goodwin C., Anatomy and Physiology of the Skin, J Dermatol Nurses Assoc, 3, 2011, 203- 213, 10.1097/JDN.0b013e3182274a98</original_ref>

</BIB>

<BIB>

3

S Moreci F R.S.

S Lechler F T.

AT Epidermal structure and differentiation

JT Curr Biol

V 30

D 2020

P R144-L R149

DOI 10.1016/J.CUB. 2020.01.004

<original_ref>Moreci R.S., Lechler T., Epidermal structure and differentiation, Curr Biol, 30, 2020, R144- R149, 10.1016/J.CUB. 2020.01.004</original_ref>

</BIB>

<BIB>

4

S Murata F T.

S Honda F T.

S Mostafa F A.

S Kabashima F K.

AT Stratum corneum as polymer sheet: Concept and cornification processes

JT Trends Mol Med

V 28

D 2022

P 350-L 359

DOI 10.1016/j.molmed.2022.02.008

<original_ref>Murata T., Honda T., Mostafa A., Kabashima K., Stratum corneum as polymer sheet: Concept and cornification processes, Trends Mol Med, 28, 2022, 350- 359, 10.1016/j.molmed.2022.02.008</original_ref>

</BIB>

<BIB>

5

S Mazereeuw-Hautier F J.

S Vahlquist F A.

S Traupe F H.

S Bygum F A.

S Amaro F C.

S Aldwin F M.<ET-AL>

AT Management of congenital ichthyoses: European guidelines of care, part one

JT Br J Dermatol

V 180

D 2019

P 272-L 281

DOI 10.1111/BJD. 17203

<original_ref>Mazereeuw-Hautier J., Vahlquist A., Traupe H., Bygum A., Amaro C., Aldwin M., Management of congenital ichthyoses: European guidelines of care, part one, Br J Dermatol, 180, 2019, 272- 281, 10.1111/BJD. 17203</original_ref>

</BIB>

<BIB>

6

S Mazereeuw-Hautier F J.

S Hernández-Martín F A.

S O'Toole F E.A.

S Bygum F A.

S Amaro F C.

S Aldwin F M. <ET-AL>

AT Management of congenital ichthyoses: European guidelines of care, part two

JT Br J Dermatol

V 180

D 2019

P 484-L 495

DOI 10.1111/BJD. 16882

<original_ref>Mazereeuw-Hautier J., Hernández-Martín A., O'Toole E.A., Bygum A., Amaro C., Aldwin M., Management of congenital ichthyoses: European guidelines of care, part two, Br J Dermatol, 180, 2019, 484- 495, 10.1111/BJD. 16882</original_ref>

</BIB>

<BIB>

7

S Patel F N.

S Spencer F L.A.

S English F J.C.

S Zirwas F M.J.

AT Acquired ichthyosis

JT J Am Acad Dermatol

V 55

D 2006

P 647-L 656

DOI 10.1016/J.JAAD. 2006.04.047

<original_ref>Patel N., Spencer L.A., English J.C., Zirwas M.J., Acquired ichthyosis, J Am Acad Dermatol, 55, 2006, 647- 656, 10.1016/J.JAAD. 2006.04.047</original_ref>

</BIB>

<BIB>

8

S Oji F V.

S Tadini F G.

S Akiyama F M.

S Blanchet Bardon F C.

S Bodemer F C.

S Bourrat F E.<ET-AL>

AT Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorze 2009

JT J Am Acad Dermatol

V 63

D 2010

P 607-L 641

DOI 10.1016/J.JAAD. 2009.11.020

<original_ref>Oji V., Tadini G., Akiyama M., Blanchet Bardon C., Bodemer C., Bourrat E., Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorze 2009, J Am Acad Dermatol, 63, 2010, 607- 641, 10.1016/J.JAAD. 2009.11.020</original_ref>

</BIB>

<BIB>

9

S Gutiérrez-Cerrajero F C.

S Sprecher F E.

S Paller F A.S.

S Akiyama F M.

S Mazereeuw-Hautier F J.

S Hernández-Martín F A.<ET-AL>

AT Ichthyosis

JT Nat Rev Dis Primers

V 9

D 2023

P 2

DOI 10.1038/s41572-022-00412-3

<original_ref>Gutiérrez-Cerrajero C., Sprecher E., Paller A.S., Akiyama M., Mazereeuw-Hautier J., Hernández-Martín A., Ichthyosis, Nat Rev Dis Primers, 9, 2023, 2, 10.1038/s41572-022-00412-3</original_ref>

</BIB>

<BIB>

10

S Brown F S.J.

S Relton F C.L.

S Liao F H.

S Zhao F Y.

S Sandilands F A.

S McLean F W.H.I.<ET-AL>

AT 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

JT Br J Dermatol

V 161

D 2009

P 884

DOI 10.1111/J. 1365-2133.2009.09339.X

<original_ref>Brown S.J., Relton C.L., Liao H., Zhao Y., Sandilands A., McLean W.H.I., 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, Br J Dermatol, 161, 2009, 884, 10.1111/J. 1365-2133.2009.09339.X</original_ref>

</BIB>

<BIB>

11

S Wells F R.S.

AT Genetic Classification of Ichthyosis

JT Arch Dermatol

V 92

D 1965

P 1

DOI 10.1001/archderm.1965.01600130007001

<original_ref>Wells R.S., Genetic Classification of Ichthyosis, Arch Dermatol, 92, 1965, 1, 10.1001/archderm.1965.01600130007001</original_ref>

</BIB>

<BIB>

12

S Clabbers F J.M.K.

S Bolling F M.C.

S Burms F C.

S Vreeburg F M.

S Lemmink F H.H.

S van den Akker F P.C.<ET-AL>

AT Palmoplantar keratoderma as a clinical feature of pathogenic variants in the filaggrin gene

JT J Eur Acad Dermatol Venereol

V 37

DOI 10.1111/jdv.18699

D 2023

P e486-L e490

<original_ref>Clabbers J.M.K., Bolling M.C., Burms C., Vreeburg M., Lemmink H.H., van den Akker P.C., Palmoplantar keratoderma as a clinical feature of pathogenic variants in the filaggrin gene, J Eur Acad Dermatol Venereol, 37, 10.1111/jdv.18699, 2023, e486- e490</original_ref>

</BIB>

<BIB>

13

S Akiyama F M.

AT FLG mutations in ichthyosis vulgaris and atopic eczema: Spectrum of mutations and population genetics

JT Br J Dermatol

V 162

D 2010

P 472-L 477

DOI 10.1111/J. 1365-2133.2009.09582.X

<original_ref>Akiyama M., FLG mutations in ichthyosis vulgaris and atopic eczema: Spectrum of mutations and population genetics, Br J Dermatol, 162, 2010, 472- 477, 10.1111/J. 1365-2133.2009.09582.X</original_ref>

</BIB>

<BIB>

14

S Sybert F V.P.

S Dale F B.A.

S Holbrook F K.A.

AT Ichthyosis vulgaris: Identification of a defect in synthesis of filaggrin correlated with an absence of keratohyaline granules

JT J Invest Dermatol

V 84

D 1985

P 191-L 194

DOI 10.1111/1523-1747.EP12264813

<original_ref>Sybert V.P., Dale B.A., Holbrook K.A., Ichthyosis vulgaris: Identification of a defect in synthesis of filaggrin correlated with an absence of keratohyaline granules, J Invest Dermatol, 84, 1985, 191- 194, 10.1111/1523-1747.EP12264813</original_ref>

</BIB>

<BIB>

15

S Kirchmeier F P.

S Zimmer F A.

S Bouadjar F B.

S Rösler F B.

S Fischer F J.

AT Whole-exome-sequencing reveals small deletions in CASP14 in patients with autosomal recessive inherited ichthyosis

JT Acta Derm-Venereol

V 97

D 2017

P 102-L 104

DOI 10.2340/00015555-2510/

<original_ref>Kirchmeier P., Zimmer A., Bouadjar B., Rösler B., Fischer J., Whole-exome-sequencing reveals small deletions in CASP14 in patients with autosomal recessive inherited ichthyosis, Acta Derm-Venereol, 97, 2017, 102- 104, 10.2340/00015555-2510/</original_ref>

</BIB>

<BIB>

16

S Boyden F L.M.

S Zhou F J.

S Hu F R.

S Zaki F T.

S Loring F E.

S Scott F J.<ET-AL>

AT Mutations in ASPRV1 Cause Dominantly Inherited Ichthyosis

JT Am J Hum Genet

V 107

D 2020

P 158

DOI 10.1016/J.AJHG. 2020.05.013

<original_ref>Boyden L.M., Zhou J., Hu R., Zaki T., Loring E., Scott J., Mutations in ASPRV1 Cause Dominantly Inherited Ichthyosis, Am J Hum Genet, 107, 2020, 158, 10.1016/J.AJHG. 2020.05.013</original_ref>

</BIB>

<BIB>

17

S De Unamuno F P.

S Martin-Pascual F A.

S Garcia-Perez F A.

AT X-linked ichthyosis

JT Br J Dermatol

V 97

D 1977

P 53-L 58

DOI 10.1111/J. 1365-2133.1977.TB15427.X

<original_ref>De Unamuno P., Martin-Pascual A., Garcia-Perez A., X-linked ichthyosis, Br J Dermatol, 97, 1977, 53- 58, 10.1111/J. 1365-2133.1977.TB15427.X</original_ref>

</BIB>

<BIB>

18

S Mohandas F T.

S Shapiro F L.J.

S Sparkes F R.S.

S Sparkes F M.C.

AT Regional assignment of the steroid sulfatase—X-linked ichthyosis locus: Implications for a noninactivated region on the short arm of human X chromosome

JT Proc Natl Acad Sci

V 76

D 1979

P 5779-L 5783

DOI 10.1073/PNAS.76.11.5779

<original_ref>Mohandas T., Shapiro L.J., Sparkes R.S., Sparkes M.C., Regional assignment of the steroid sulfatase—X-linked ichthyosis locus: Implications for a noninactivated region on the short arm of human X chromosome, Proc Natl Acad Sci, 76, 1979, 5779- 5783, 10.1073/PNAS.76.11.5779</original_ref>

</BIB>

<BIB>

19

S Nagtzaam F I.F.

S Stegmann F A.P.A.

S Steijlen F P.M.

S Herbergs F J.

S van Lent-Albrechts F J.A.

S van Geel F M.<ET-AL>

AT Clinically manifest X-linked recessive ichthyosis in a female due to a homozygous interstitial 1 6-Mb deletion of Xp22.31

JT Br J Dermatol

V 166

D 2012

P 905-L 907

DOI 10.1111/j.1365-2133.2011.10685.x

<original_ref>Nagtzaam I.F., Stegmann A.P.A., Steijlen P.M., Herbergs J., van Lent-Albrechts J.A., van Geel M., Clinically manifest X-linked recessive ichthyosis in a female due to a homozygous interstitial 1 6-Mb deletion of Xp22.31, Br J Dermatol, 166, 2012, 905- 907, 10.1111/j.1365-2133.2011.10685.x</original_ref>

</BIB>

<BIB>

20

S Hernández-Martín F A.

S González-Sarmiento F R.

S de Unamuno F P.

AT X-linked ichthyosis: An update

JT Br J Dermatol

V 141

D 1999

P 617-L 627

DOI 10.1046/j.1365-2133.1999.03098.x

<original_ref>Hernández-Martín A., González-Sarmiento R., de Unamuno P., X-linked ichthyosis: An update, Br J Dermatol, 141, 1999, 617- 627, 10.1046/j.1365-2133.1999.03098.x</original_ref>

</BIB>

<BIB>

21

S Rodrigo-Nicolás F B.

S Bueno-Martínez F E.

S Martín-Santiago F A.

S Cañueto F J.

S Vicente F A.

S Torrelo F A.<ET-AL>

AT Evidence of the high prevalence of neurological disorders in nonsyndromic X-linked recessive ichthyosis: A retrospective case series

JT Br J Dermatol

V 179

D 2018

P 933-L 939

DOI 10.1111/bjd.16826

<original_ref>Rodrigo-Nicolás B., Bueno-Martínez E., Martín-Santiago A., Cañueto J., Vicente A., Torrelo A., Evidence of the high prevalence of neurological disorders in nonsyndromic X-linked recessive ichthyosis: A retrospective case series, Br J Dermatol, 179, 2018, 933- 939, 10.1111/bjd.16826</original_ref>

</BIB>

<BIB>

22

S Wang F X.

S Tan F L.

S Shen F N.

S Lu F Y.

S Zhang F Y.

AT Exacerbation of ichthyosis vulgaris phenotype by co-inheritance of STS and FLG mutations in a Chinese family with ichthyosis: A case report

JT BMC Med Genet

V 19

D 2018

P 120

DOI 10.1186/s12881-018-0642-5

<original_ref>Wang X., Tan L., Shen N., Lu Y., Zhang Y., Exacerbation of ichthyosis vulgaris phenotype by co-inheritance of STS and FLG mutations in a Chinese family with ichthyosis: A case report, BMC Med Genet, 19, 2018, 120, 10.1186/s12881-018-0642-5</original_ref>

</BIB>

<BIB>

23

S Hernández-Martín F A.

S Garcia-Doval F I.

S Aranegui F B.

S de Unamuno F P.

S Rodríguez-Pazos F L.

S González-Enseñat F M.A.<ET-AL>

AT Prevalence of autosomal recessive congenital ichthyosis: A population-based study using the capture-recapture method in Spain

JT J Am Acad Dermatol

V 67

D 2012

P 240-L 244

DOI 10.1016/J.JAAD. 2011.07.033

<original_ref>Hernández-Martín A., Garcia-Doval I., Aranegui B., de Unamuno P., Rodríguez-Pazos L., González-Enseñat M.A., Prevalence of autosomal recessive congenital ichthyosis: A population-based study using the capture-recapture method in Spain, J Am Acad Dermatol, 67, 2012, 240-244, 10.1016/J.JAAD. 2011.07.033</original_ref>

</BIB>

<BIB>

24

S Dreyfus F I.

S Chouquet F C.

S Ezzedine F K.

S Henner F S.

S Chiavérini F C.

S Maza F A.<ET-AL>

AT Prevalence of inherited ichthyosis in France: A study using capture-recapture method

JT Orphanet J Rare Dis

V 9

D 2014

P 1

DOI 10.1186/1750-1172-9-1

<original_ref>Dreyfus I., Chouquet C., Ezzedine K., Henner S., Chiavérini C., Maza A., Prevalence of inherited ichthyosis in France: A study using capture-recapture method, Orphanet J Rare Dis, 9, 2014, 1, 10.1186/1750-1172-9-1</original_ref>

</BIB>

<BIB>

25

S Kurosawa F M.

S Uehara F R.

S Takagi F A.

S Aoyama F Y.

S Iwatsuki F K.

S Amagai F M.<ET-AL>

AT Results of a nationwide epidemiologic survey of autosomal recessive congenital ichthyosis and ichthyosis syndromes in Japan

JT J Am Acad Dermatol

V 81

D 2019

P 1086.e1-L 1092.e1

DOI 10.1016/J.JAAD. 2018.07.056

<original_ref>Kurosawa M., Uehara R., Takagi A., Aoyama Y., Iwatsuki K., Amagai M., Results of a nationwide epidemiologic survey of autosomal recessive congenital ichthyosis and ichthyosis syndromes in Japan, J Am Acad Dermatol, 81, 2019, 1086.e1- 1092.e1, 10.1016/J.JAAD. 2018.07.056</original_ref>

</BIB>

<BIB>

26

S Challamel F C.

S Hernandez-Martin F A.

S Tchitchiama F C.

S Jonca F N.

S Rossel F S.V.J.

S Gostyński F A.<ET-AL>

AT Patients with autosomal recessive congenital ichthyosis present a distinctive pattern of alopecia

JT J Eur Acad Dermatol Venereol

V 37

DOI 10.1111/jdv.19246

D 2023

P e1274-L e1276

<original_ref>Challamel C., Hernandez-Martin A., Tchitchiama C., Jonca N., Rossel S.V.J., Gostyński A., Patients with autosomal recessive congenital ichthyosis present a distinctive pattern of alopecia, J Eur Acad Dermatol Venereol, 37, 10.1111/jdv.19246, 2023, e1274-e1276</original_ref>

</BIB>

<BIB>

27

S Kelsell F D.P.

S Norgett F E.E.

S Unsworth F H.

S Teh F M.T.

S Cullup F T.

S Mein F C.A.<ET-AL>

S Dopping-Hepenstal F P.J.

AT Mutations in ABCA12 Underlie the Severe Congenital Skin Disease Harlequin Ichthyosis

JT Am J Hum Genet

V 76

D 2005

P 794-L 803

DOI 10.1086/429844

<original_ref>Kelsell D.P., Norgett E.E., Unsworth H., Teh M.T., Cullup T., Mein C.A., Dopping-Hepenstal P.J., Mutations in ABCA12 Underlie the Severe Congenital Skin Disease Harlequin Ichthyosis, Am J Hum Genet, 76, 2005, 794- 803, 10.1086/429844</original_ref>

</BIB>

<BIB>

28

S Rajpopat F S.

S Moss F C.

S Mellerio F J.

S Vahlquist F A.

S Gånemo F A.

S Hellstrom-Pigg F M. <ET-AL>

AT Harlequin ichthyosis: A review of clinical and molecular findings in 45 cases

JT Arch Dermatol

V 147

D 2011

P 681-L 686

DOI 10.1001/ARCHDERMATOL. 2011.9

<original_ref>Rajpopat S., Moss C., Mellerio J., Vahlquist A., Gånemo A., Hellstrom-Pigg M., Harlequin ichthyosis: A review of clinical and molecular findings in 45 cases, Arch Dermatol, 147, 2011, 681- 686, 10.1001/ARCHDERMATOL. 2011.9</original_ref>

</BIB>

<BIB>

29

S Harting F M.

S Brunetti-Pierri F N.

S Chan F C.S.

S Kirby F J.

S Dishop F M.K.

S Richard F G.<ET-AL>

AT Self-Healing Collodion Membrane and Mild Nonbullous Congenital Ichthyosiform Erythroderma Due to 2 Novel Mutations in the ALOX12B Gene

JT Arch Dermatol

V 144

D 2008

P 351-L 356

DOI 10.1001/ARCHDERM.144.3.351

<original_ref>Harting M., Brunetti-Pierri N., Chan C.S., Kirby J., Dishop M.K., Richard G., Self-Healing Collodion Membrane and Mild Nonbullous Congenital Ichthyosiform Erythroderma Due to 2 Novel Mutations in the ALOX12B Gene, Arch Dermatol, 144, 2008, 351- 356, 10.1001/ARCHDERM.144.3.351</original_ref>

</BIB>

<BIB>

30

S Vahlquist F A.

S Bygum F A.

S Gånemo F A.

S Virtanen F M.

S Hellström-Pigg F M.

S Strauss F G.<ET-AL>

AT Genotypic and clinical spectrum of self-improving collodion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients

JT J Invest Dermatol

V 130

D 2010

P 438-L 443

DOI 10.1038/JID. 2009.346

<original_ref>Vahlquist A., Bygum A., Gånemo A., Virtanen M., Hellström-Pigg M., Strauss G., Genotypic and clinical spectrum of self-improving collodion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients, J Invest Dermatol, 130, 2010, 438- 443, 10.1038/JID. 2009.346</original_ref>

</BIB>

<BIB>

31

S Noguera-Morel F L.

S Feito-Rodríguez F M.

S Maldonado-Cid F P.

S García-Miñáur F S.

S Kamsteeg F E.J.

S González-Sarmiento F R.<ET-AL>

AT Two cases of autosomal recessive congenital ichthyosis due to CYP4F22 mutations: Expanding the genotype of self-healing collodion baby

JT Pediatr Dermatol

V 33

D 2016

P e48-L e51

DOI 10.1111/PDE. 12740

<original_ref>Noguera-Morel L., Feito-Rodríguez M., Maldonado-Cid P., García-Miñáur S., Kamsteeg E.J., González-Sarmiento R., Two cases of autosomal recessive congenital ichthyosis due to CYP4F22 mutations: Expanding the genotype of self-healing collodion baby, Pediatr Dermatol, 33, 2016, e48- e51, 10.1111/PDE. 12740</original_ref>

</BIB>

<BIB>

32

S Raghunath F M.

S Hennies F H.C.

S Ahvazi F B.

S Vogel F M.

S Reis F A.

S Steinert F P.M.<ET-AL>

AT Self-healing collodion baby: A dynamic phenotype explained by a particular transglutaminase-1 mutation

JT J Invest Dermatol

V 120

D 2003

P 224-L 228

DOI 10.1046/J. 1523-1747.2003.12032.X

<original_ref>Raghunath M., Hennies H.C., Ahvazi B., Vogel M., Reis A., Steinert P.M., Self-healing collodion baby: A dynamic phenotype explained by a particular transglutaminase-1 mutation, J Invest Dermatol, 120, 2003, 224- 228, 10.1046/J. 1523-1747.2003.12032.X</original_ref>

</BIB>

<BIB>

33

S Mazereeuw-Hautier F J.

S Aufenvenne F K.

S Deraison F C.

S Ahvazi F B.

S Oji F V.

S Traupe F H.<ET-AL>

AT Acral self-healing collodion baby: Report of a new clinical phenotype caused by a novel TGM1 mutation

JT Br J Dermatol

V 161

D 2009

P 456-L 463

DOI 10.1111/J. 1365-2133.2009.09277.X

<original_ref>Mazereeuw-Hautier J., Aufenvenne K., Deraison C., Ahvazi B., Oji V., Traupe H., Acral self-healing collodion baby: Report of a new clinical phenotype caused by a novel TGM1 mutation, Br J Dermatol, 161, 2009, 456- 463, 10.1111/J. 1365-2133.2009.09277.X</original_ref>

</BIB>

<BIB>

34

S Jacyk F W.K.

AT Bathing-suit ichthyosis. A peculiar phenotype of lamellar ichthyosis in South African blacks

JT Eur J Dermatol

V 15

D 2005

P 433-L 436

<original_ref>Jacyk W.K. Bathing-suit ichthyosis. A peculiar phenotype of lamellar ichthyosis in South African blacks. Eur J Dermatol, 15, 2005, 433-436</original_ref>

</BIB>

<BIB>

35

S Oji F V.

S Hautier F J.M.

S Ahvazi F B.

S Hausser F I.

S Aufenvenne F K.

S Walker F T.<ET-AL>

AT Bathing suit ichthyosis is caused by transglutaminase-1 deficiency: Evidence for a temperature-sensitive phenotype

JT Hum Mol Genet

V 15

D 2006

P 3083-L 3097

DOI 10.1093/hmg/ddl249

<original_ref>Oji V., Hautier J.M., Ahvazi B., Hausser I., Aufenvenne K., Walker T., Bathing suit ichthyosis is caused by transglutaminase-1 deficiency: Evidence for a temperature-sensitive phenotype, Hum Mol Genet, 15, 2006, 3083- 3097, 10.1093/hmg/ddl249</original_ref>

</BIB>

<BIB>

36

S Rothnagel F J.A.

S Dominey F A.M.

S Dempsey F L.D.

S Longley F M.A.

S Greenhalgh F D.A.

S Gagne F T.A.<ET-AL>

AT Mutations in the Rod Domains of Keratins 1 and 10 in Epidermolytic Hyperkeratosis

JT Science

V 257

D 1992

P 1128-L 1130

DOI 10.1126/SCIENCE.257.5073.1128

<original_ref>Rothnagel J.A., Dominey A.M., Dempsey L.D., Longley M.A., Greenhalgh D.A., Gagne T.A., Mutations in the Rod Domains of Keratins 1 and 10 in Epidermolytic Hyperkeratosis, Science, 257, 1992, 1128- 1130, 10.1126/SCIENCE.257.5073.1128</original_ref>

</BIB>

<BIB>

37

S Müller F F.B.

S Huber F M.

S Kinaciyan F T.

S Hausser F I.

S Schaffrath F C.

S Krieg F T.<ET-AL>

AT A human keratin 10 knockout causes recessive epidermolytic hyperkeratosis

JT Hum Mol Genet

V 15

D 2006

P 1133-L 1141

DOI 10.1093/HMG/DDL028

<original_ref>Müller F.B., Huber M., Kinaciyan T., Hausser I., Schaffrath C., Krieg T., A human keratin 10 knockout causes recessive epidermolytic hyperkeratosis, Hum Mol Genet, 15, 2006, 1133- 1141, 10.1093/HMG/DDL028</original_ref>

</BIB>

<BIB>

38

S Reolid F A.

S Carrasco F L.

S Noguera-Morel F L.

S Torrelo F A.

S Colmenero F I.

S Ortiz-Cabrera F N.V.<ET-AL>

AT Annular epidermolytic ichthyosis: An exceptional mild subtype of epidermolytic ichthyosis without genotype and phenotype correlation

JT JAAD Case Rep

V 6

D 2020

P 46-L 50

DOI 10.1016/j.jdcr.2019.10.026

<original_ref>Reolid A., Carrasco L., Noguera-Morel L., Torrelo A., Colmenero I., Ortiz-Cabrera N.V., Annular epidermolytic ichthyosis: An exceptional mild subtype of epidermolytic ichthyosis without genotype and phenotype correlation, JAAD Case Rep, 6, 2020, 46- 50, 10.1016/j.jdcr.2019.10.026</original_ref>

</BIB>

<BIB>

39

S Sybert F V.P.

S Francis F J.S.

S Corden F L.D.

S Smith F L.T.

S Weaver F M.

S Stephens F K.<ET-AL>

AT Cyclic ichthyosis with epidermolytic hyperkeratosis: A phenotype conferred by mutations in the 2B domain of keratin K1

JT Am J Hum Genet

V 64

D 1999

P 732

DOI 10.1086/302278

<original_ref>Sybert V.P., Francis J.S., Corden L.D., Smith L.T., Weaver M., Stephens K., Cyclic ichthyosis with epidermolytic hyperkeratosis: A phenotype conferred by mutations in the 2B domain of keratin K1, Am J Hum Genet, 64, 1999, 732, 10.1086/302278</original_ref>

</BIB>

<BIB>

40

S Joh F G.Y.

S Traupe F H.

S Metze F D.

S Nashan F D.

S Huber F M.

S Hohl F D.<ET-AL>

AT A Novel Dinucleotide Mutation in Keratin 10 in the Annular Epidermolytic Ichthyosis Variant of Bullous Congenital Ichthyosiform Erythroderma

JT J Invest Dermatol

V 108

D 1997

P 357-L 361

DOI 10.1111/1523-1747.EP12286491

<original_ref>Joh G.Y., Traupe H., Metze D., Nashan D., Huber M., Hohl D., A Novel Dinucleotide Mutation in Keratin 10 in the Annular Epidermolytic Ichthyosis Variant of Bullous Congenital Ichthyosiform Erythroderma, J Invest Dermatol, 108, 1997, 357- 361, 10.1111/1523-1747.EP12286491</original_ref>

</BIB>

<BIB>

41

S Rothnagel F J.A.

S Traupe F H.

S Wojcik F S.

S Huber F M.

S Hohl F D.

S Pittelkow F M.R.<ET-AL>

AT Mutations in the rod domain of keratin 2e in patients with ichthyosis bullosa of Siemens

JT Nat Genet

V 7

D 1994

P 485-L 490

DOI 10.1038/ng0894-485

<original_ref>Rothnagel J.A., Traupe H., Wojcik S., Huber M., Hohl D., Pittelkow M.R., Mutations in the rod domain of keratin 2e in patients with ichthyosis bullosa of Siemens, Nat Genet, 7, 1994, 485- 490, 10.1038/ng0894-485</original_ref>

</BIB>

<BIB>

42

S Tsubota F A.

S Akiyama F M.

S Sakai F K.

S Goto F M.

S Nomura F Y.

S Ando F S.<ET-AL>

AT Keratin 1 Gene Mutation Detected in Epidermal Nevus with Epidermolytic Hyperkeratosis

JT J Invest Dermatol

V 127

D 2007

P 1371-L 1374

DOI 10.1038/SJ.JID. 5700712

<original_ref>Tsubota A., Akiyama M., Sakai K., Goto M., Nomura Y., Ando S., Keratin 1 Gene Mutation Detected in Epidermal Nevus with Epidermolytic Hyperkeratosis, J Invest Dermatol, 127, 2007, 1371- 1374, 10.1038/SJ.JID. 5700712</original_ref>

</BIB>

<BIB>

43

S Paller F A.S.

S Syder F A.J.

S Chan F Y.-M.

S Yu F Q.-C.

S Hutton F E.

S Tadini F G.<ET-AL>

AT Genetic and Clinical Mosaicism in a Type of Epidermal Nevus

JT N Engl J Med

V 331

D 1994

P 1408-L 1415

DOI 10.1056/NEJM199411243312103

<original_ref>Paller A.S., Syder A.J., Chan Y.-M., Yu Q.-C., Hutton E., Tadini G., Genetic and Clinical Mosaicism in a Type of Epidermal Nevus, N Engl J Med, 331, 1994, 1408- 1415, 10.1056/NEJM199411243312103</original_ref>

</BIB>

<BIB>

44

S Diociaiuti F A.

S Castiglia F D.

S Corbeddu F M.

S Rotunno F R.

S Rossi F S.

S Pisaneschi F E.<ET-AL>

AT First Case of KRT2 Epidermolytic Nevus and Novel Clinical and Genetic Findings in 26 Italian Patients with Keratinopathic Ichthyoses

JT Int J Mol Sci

V 21

D 2020

P 7707

DOI 10.3390/IJMS21207707

<original_ref>Diociaiuti A., Castiglia D., Corbeddu M., Rotunno R., Rossi S., Pisaneschi E., First Case of KRT2 Epidermolytic Nevus and Novel Clinical and Genetic Findings in 26 Italian Patients with Keratinopathic Ichthyoses, Int J Mol Sci, 21, 2020, 7707, 10.3390/IJMS21207707</original_ref>

</BIB>

<BIB>

45

S Guerra F L.

S Diociaiuti F A.

S El Hachem F M.

S Castiglia F D.

S Zambruno F G.

AT Ichthyosis with confetti: Clinics, molecular genetics and management Rare skin diseases

JT Orphanet J Rare Dis

V 10

D 2015

P 1-L 16

DOI 10.1186/S13023-015-0336-4/TABLES/2

<original_ref>Guerra L., Diociaiuti A., El Hachem M., Castiglia D., Zambruno G., Ichthyosis with confetti: Clinics, molecular genetics and management Rare skin diseases, Orphanet J Rare Dis, 10, 2015, 1- 16, 10.1186/S13023-015-0336-4/TABLES/2</original_ref>

</BIB>

<BIB>

46

S Choate F K.A.

S Lu F Y.

S Zhou F J.

S Choi F M.

S Elias F P.M.

S Farhi F A.<ET-AL>

AT Mitotic Recombination in Patients with Ichthyosis Causes Reversion of Dominant Mutations in KRT10

JT Science

V 330

D 2010

P 94-L 97

DOI 10.1126/SCIENCE. 1192280

<original_ref>Choate K.A., Lu Y., Zhou J., Choi M., Elias P.M., Farhi A., Mitotic Recombination in Patients with Ichthyosis Causes Reversion of Dominant Mutations in KRT10, Science, 330, 2010, 94- 97, 10.1126/SCIENCE. 1192280</original_ref>

</BIB>

<BIB>

47

S Choate F K.A.

S Lu F Y.

S Zhou F J.

S Elias F P.M.

S Zaidi F S.

S Paller F A.S.<ET-AL>

AT Frequent somatic reversion of KRT1 mutations in ichthyosis with confetti

JT J Clin Invest

V 125

D 2015

P 1703-L 1707

DOI 10.1172/JCI64415

<original_ref>Choate K.A., Lu Y., Zhou J., Elias P.M., Zaidi S., Paller A.S., Frequent somatic reversion of KRT1 mutations in ichthyosis with confetti, J Clin Invest, 125, 2015, 1703- 1707, 10.1172/JCI64415</original_ref>

</BIB>

</BIBL>

Figura 1 Estructura de la epidermis. Las células madre del estrato basal se diferencian hasta dar lugar al estrato córneo, compuesto de los corneocitos repletos de proteínas estructurales, anclados mediante uniones intercelulares y embebidos en una matriz lipídica extracelular. Fuente: modificado de «Ichthyosis», C. Gutiérrez-Cerrajero et al.[9]. gr1.

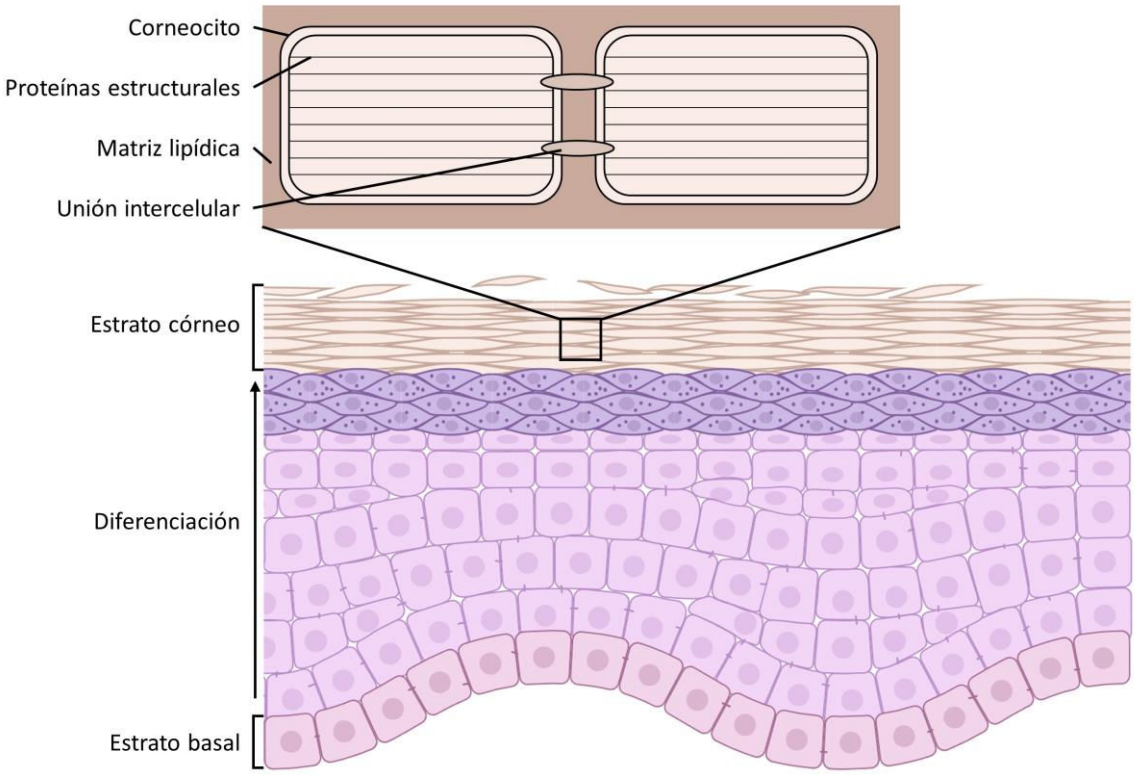


Figura 2 Ictiosis vulgar. Hiperlinearidad palmar *(palmas de filagrina)* en un paciente con una variante patogénica en *FLG*. gr2.

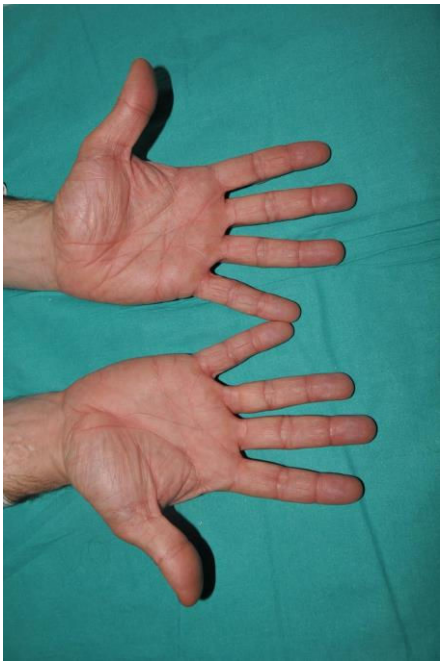


Figura 3 Ictiosis recesiva ligada al cromosoma X. Típica descamación poligonal de tonalidad oscura típica en la extremidad inferior. gr3.

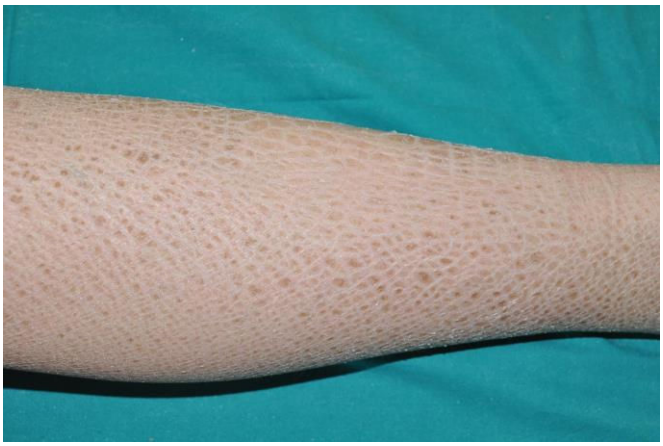


Figura 4 Ruta de síntesis de ceramidas en la epidermis. Estas reacciones constan de la unión de una base esfingoide (azul) y ácido graso (verde) para formar acil-ceramida que puede liberarse como lípido libre (amarillo) o unido a proteínas (naranja). Mutaciones en los genes representados causan ictiosis no sindrómicas (negro) o sindrómicas (rojo). Fuente: modificado de «Ichthyosis», C. Gutiérrez-Cerrajero et al.[9]. gr4.

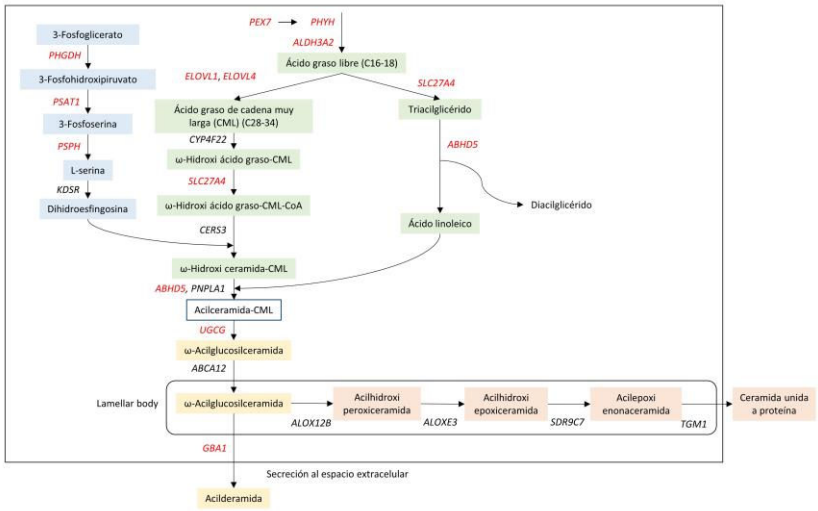


Figura 5 Ictiosis congénita autosómica recesiva. Descamación laminar en un paciente con variante en *TGM1* de fototipo oscuro. gr5.

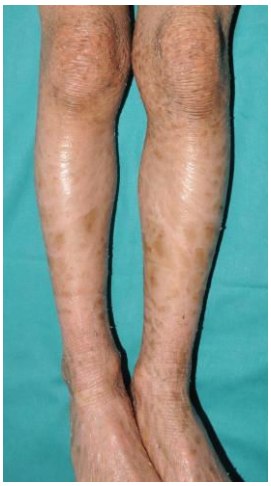


Figura 6 Ictiosis congénita autosómica recesiva. Afectación plantar en un paciente con variante en *TGM1.* La superficie está engrosada, es lisa, brillante y ocasionalmente se fisura. gr6.

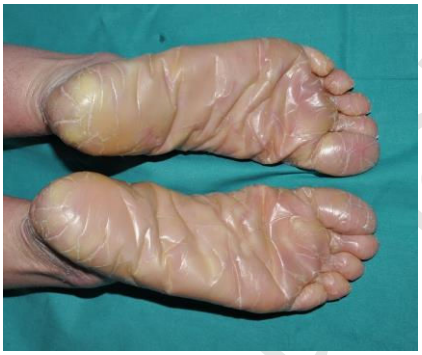


Figura 7 Ictiosis congénita autosómica recesiva. Se aprecia una descamación fina y moderada eritrodermia en un paciente con variante en *ABCA12*, demostrando la variabilidad fenotípica de esta variante genética. gr7.

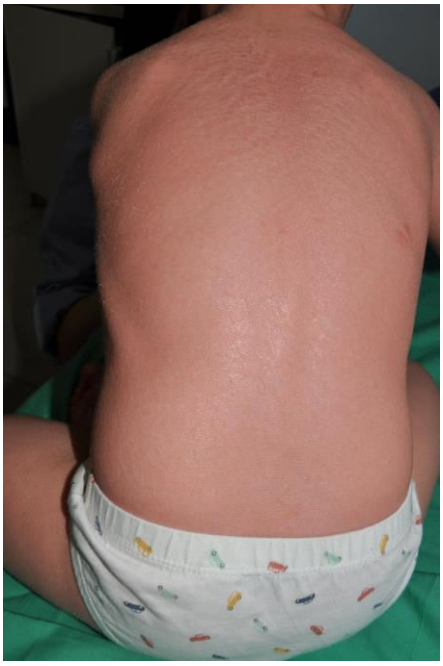


Figura 8 Ictiosis congénita autosómica recesiva. Paciente con variante patogénica en *TGM1*. Seudoleuconiquia. Obsérvese cómo la pérdida de elasticidad de la piel de las manos provoca el vaciamiento de la vascularización del lecho ungueal cuando el paciente intenta estirar los dedos. gr8.

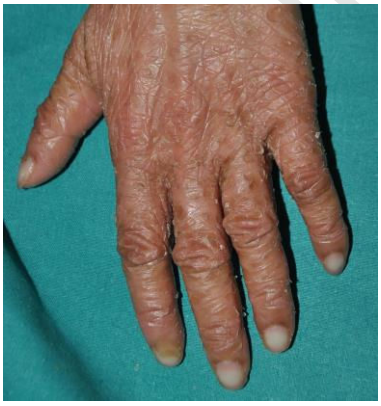


Figura 9 ARCI. Afectación palmar en un paciente con variante en el gen *ALOX12B*. Obsérvese el aspecto engrosado, brillante y descamativo de la palma sin la tonalidad amarillenta que se ve en otras queratodermias palmares. gr9.

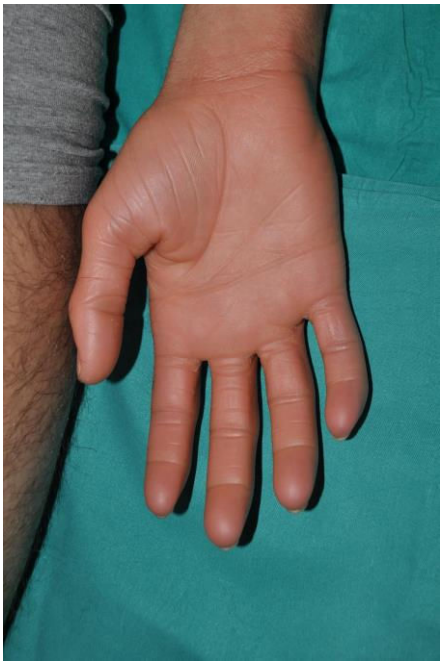


Figura 10 ARCI. Paciente con ictiosis arlequín debido a una variante patogénica en el gen *ABCA12* que presenta deformidad grave de pabellón auricular y alopecia cicatricial en cuero cabelludo. gr10.

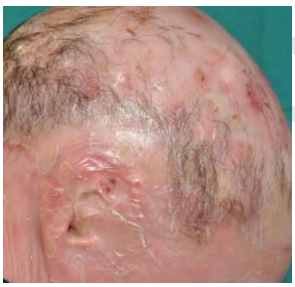


Figura 11 ARCI. Engrosamiento de la piel del dorso de las manos en un paciente con ictiosis automejorativa por variante en *TGM1.* El tronco y el resto de las extremidades superiores tienen un aspecto prácticamente normal. gr11.

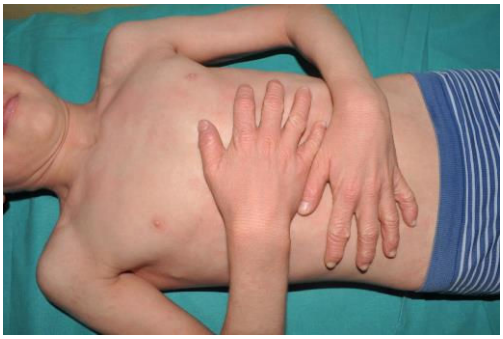


Figura 12 Ictiosis queratinopática epidermolítica por variante patogénica en gen *KRT10.* Se observa una afectación generalizada con extensas áreas de engrosamiento en las extremidades superiores e inferiores y áreas de fragilidad cutánea en región pretibial y lateral de los pies. La afectación se detiene en el borde palmoplantar y respeta palmas y plantas. gr12.

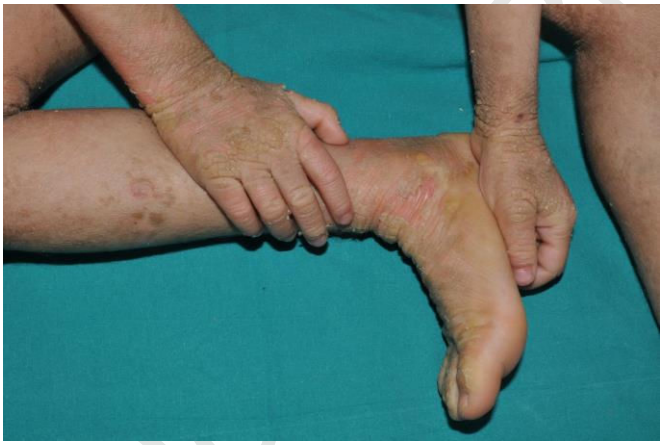


Figura 13 Ictiosis queratinopática epidermolítica por variante patogénica en el gen *KRT1*. Se observa engrosamiento palmar difuso y afectación de la extremidad inferior, con evidentes áreas de fragilidad cutánea. gr13.

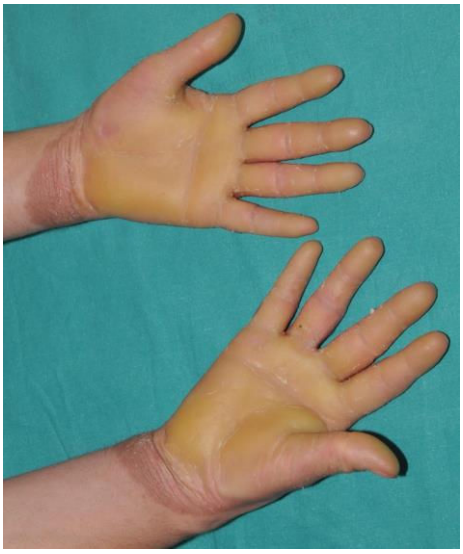


Figura 14 Ictiosis queratinopática epidermolítica anular por variante en gen *KRT10*. Se observa una lesión anular con descamación periférica superficial típica de determinadas variantes de *KRT10* que resultan en esta forma clínica peculiar. gr14.

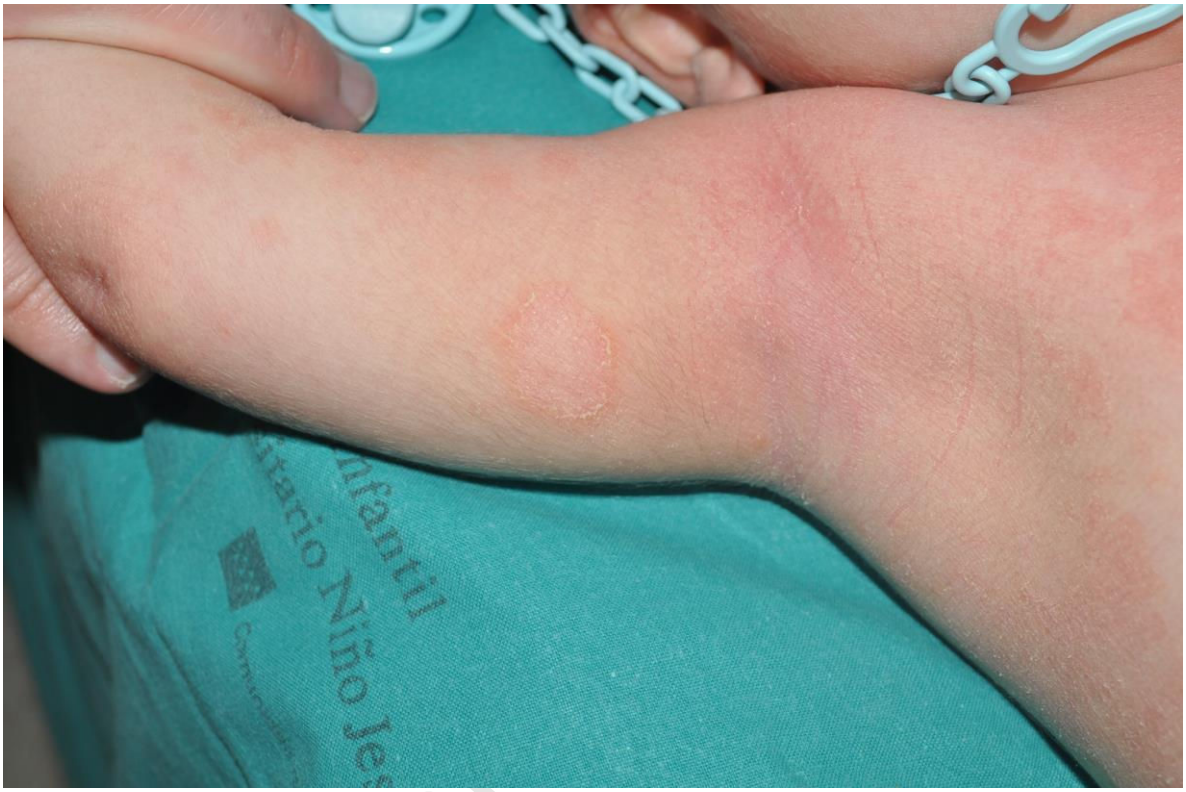


Figura 15 Ictiosis queratinopática epidermolítica superficial por variante en *KRT2* donde se aprecia el desprendimiento parcheado superficial de la epidermis («desconchado»). gr15.

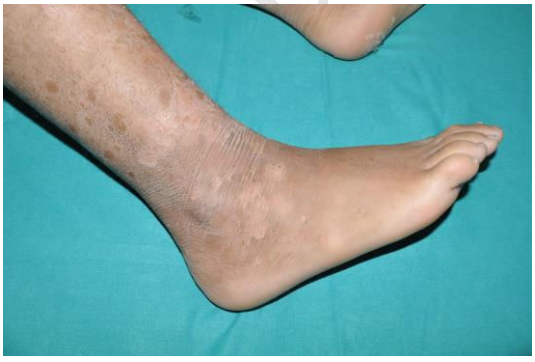


Figura 16 Ictiosis queratinopática no epidermolítica con mosaicismo reverso por variante en *KRT10.* Obsérvense las lesiones lenticulares con aspecto de piel normal en la parte anterior del tronco. gr16.

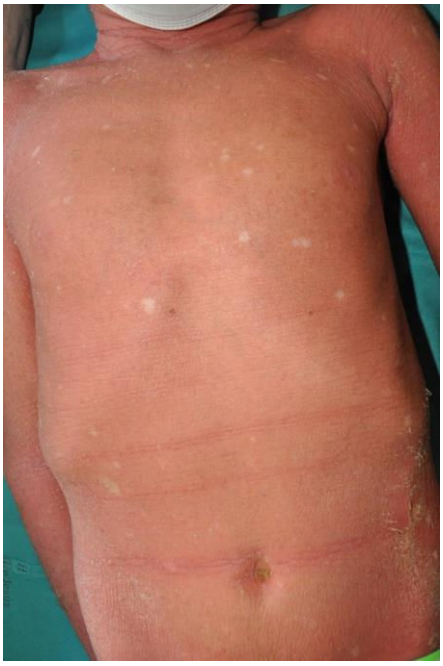


Figura 17 Síndrome de la exfoliación cutánea por variante patogénica en *CDSN*. El paciente presenta eritema difuso con áreas parcheadas de exfoliación superficial. gr17.

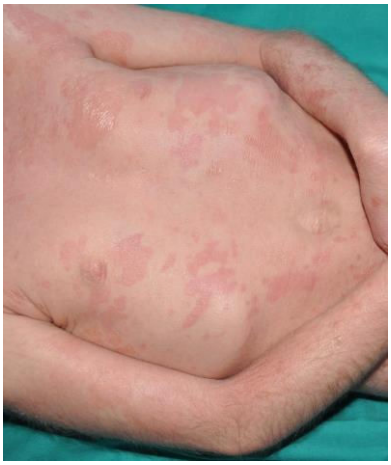


Figura 18 Queratodermia por loricrina. Afectación plantar difusa en un individuo afectado en la que se aprecian pequeñas depresiones de aspecto cribiforme. gr18

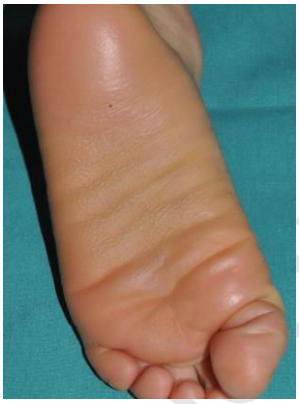


Tabla 1 Función de los principales genes involucrados en la aparición de las ictiosis congénitas

Gen (código MIM)	Función
Proteínas estructurales	
Queratinas	
▒*KRT1* (139350)	Contribuye al citoesqueleto de filamentos intermedios en las células epidérmicas suprabasales.
▒*KRT2* (600194)	Contribuye al citoesqueleto de filamentos intermedios en las células epidérmicas suprabasales más superficiales.
▒*KRT10* (148080)	Contribuye al citoesqueleto de filamentos intermedios en las células epidérmicas suprabasales, menos importante en la piel palmoplantar.
Filagrina	
▒*ASPRV1* (611765)	Proteasa involucrada en el procesamiento de filagrina, debido a su fenotipo, probablemente tenga más dianas.

▒*CASP14* (605848)	Proteasa involucrada en el procesamiento de filagrina.
▒*FLG* (135940)	Proteína que agrega los filamentos intermedios de queratina a través del fomento de la formación de puentes disulfuro y la separación de fases líquido-líquido, forma parte de la envoltura cornificada y una vez proteolizada contribuye a la formación de los factores hidratantes naturales epidérmicos.
▒*POMP* (613386)	Chaperona molecular responsable de fomentar la formación de proteasomas y, por tanto, la maduración de proteínas críticas para la diferenciación epidérmica, como la filagrina.
Envoltura cornificada	
▒*LORICRIN* (152445)	Proteína precursora de la envoltura cornificada.
▒*TGM5* (603805)	Enzima que entrecruza las proteínas precursoras de la y a la envoltura cornificada.
Metabolismo lipídico	

Ceramidas	
ABCA12 (607800)	Enzima involucrada en la carga de ceramidas a los cuerpos lamelares.
ABHD5 (604780)	Funciona como una aciltransferasa y como coactivador de la lipasa de triglicéridos en adipocitos.
ALDH3A2 (609523)	Enzima involucrada en la síntesis de ácidos grasos, que según algunos estudios se utilizan como precursores de ceramidas.
ALOX12B (603741)	Enzima involucrada en el entrecruzamiento de las ceramidas a la envoltura cornificada para formar la envoltura lipídica del corneocito.
ALOXE3 (607206)	Enzima involucrada en el entrecruzamiento de las ceramidas a la envoltura cornificada para formar la envoltura lipídica del corneocito.
CERS3 (61	Sintetiza ceramida a partir de ácidos grasos de cadena muy larga modificados y dihidroesfingosina.

5276)	
CYP4F22 (611495)	ω-hidroxilación de ácidos grasos de cadena muy larga para la síntesis de acilceramida.
ELOVL1 (611813)	Elongasa de ácidos grasos involucrada en la síntesis de ácidos grasos de cadena muy larga, que son precursores de las ceramidas.
ELOVL4 (605512)	Elongasa de ácidos grasos involucrada en la síntesis de ácidos grasos de cadena muy larga, que son precursores de las ceramidas.
GBA1 (606463)	Cataliza la rotura de la glucosilceramida a ceramida y glucosa.
KDSR (136440)	Sintetiza dihidroesfingosina, precursor de las ceramidas, a partir de serina.
LIPN (613924)	Papel mal definido en la síntesis de ceramidas.
NIPAL4	Papel mal definido en la síntesis de ceramidas.

(609383)	
PEX7 (601757)	Participa en la importación de proteínas al peroxisoma (incluyendo la fitanoil-CoA hidroxilasa).
PHGDH (606879)	Enzima utilizada en la síntesis de serina, que se utiliza como precursor de ceramidas.
PHYH (602026)	Enzima involucrada en la síntesis de ácidos grasos en el peroxisoma, que son precursores de ceramidas.
PNPLA1 (612121)	Cataliza la ω-O-esterificación de ácido linoleico para formar acilceramidas.
PSAT1 (610936)	Enzima utilizada en la síntesis de serina, que se utiliza como precursor de ceramidas.
PSPH (172480)	Enzima utilizada en la síntesis de serina, que se utiliza como precursor de ceramidas.
SDR	Enzima involucrada en el entrecruzamiento de ceramida a la envoltura cornificada para formar la envoltura lipídica del corneocito.

9C7 (609769)	
▒*SLC27A4* (604194)	Añade coenzima A a ácidos grasos de cadena muy larga para la síntesis de ceramidas.
▒*TGM1* (190195)	Enzima con funciones poco estudiadas en el entrecruzamiento de las ceramidas a la envoltura cornificada para formar la envoltura lipídica del corneocito.
▒*UGCG* (602874)	Glicosila acil-ceramidas.
Colesterol	
▒*EBP* (300205)	Enzima involucrada en la síntesis de colesterol.
▒*MBTPS2* (300294)	Metaloproteasa de membrana involucrada en la activación de factores de transcripción relacionados con la transcripción de enzimas de la ruta biosintética del colesterol.
▒*NSDHL* (30	Enzima involucrada en la síntesis de colesterol.

0275)	
▒*SREBF1* (184756)	Factor de transcripción involucrado en la transcripción de enzimas de la ruta biosintética del colesterol.
▒*STS* (300747)	Sintetiza colesterol a partir de colesterol sulfato.
▒*SULT2B1* (604125)	Responsable de la sulfonación de colesterol, que regula la diferenciación epidérmica.
▒*SUMF1* (607939)	Responsable de la modificación de diferentes sulfatasas.
Cuerpos lamelares	
▒*SNAP29* (604202)	Media eventos de fusión de cuerpos lamelares.
▒*VIPAS39* (61	Media eventos de fusión de cuerpos lamelares.

3401)	
▒*VPS33B* (608552)	Media eventos de fusión de cuerpos lamelares.
Dolicol	
▒*DOLK* (610746)	Fosfata dolicol.
▒*MPDU1* (604041)	Añade manosa a dolicoles para la O-glicosilación y N-manosilación de proteínas.
▒*PIGL* (605947)	Involucrada en la síntesis de anclajes de glicosilfosfatidilinositol.
▒*SRD5A3* (611715)	Involucrada en la síntesis de dolicol.
Uniones intercelulares	

Uniones ocluyentes	
▒*CLDN1* (603718)	Proteína de las uniones ocluyentes, controla la permeabilidad paracelular.
▒*CLDN10* (617579)	Proteína de las uniones ocluyentes, controla la permeabilidad paracelular.
Uniones gap	
▒*GJA1* (121014)	Proteína de las uniones gap, controla la comunicación intercelular.
▒*GJB2* (220290)	Proteína de las uniones gap, controla la comunicación intercelular.
▒*GJB3* (603324)	Proteína de las uniones gap, controla la comunicación intercelular.
▒*GJB4* (605425)	Proteína de las uniones gap, controla la comunicación intercelular.

▒*GJB6* (604418)	Proteína de las uniones gap, controla la comunicación intercelular.
Desmosomas	
▒*CDSN* (602593)	Componente de los corneodesmosomas en el estrato córneo, aumenta su resistencia mecánica.
▒*DSG1* (125670)	Proteína desmosómica, asegura la adhesión intercelular.
▒*DSP* (125647)	Proteína desmosómica, asegura la adhesión intercelular.
▒*FLG2* (616284)	Asegura la adhesión intercelular en las capas superiores de la epidermis de forma dependiente de corneodesmosina.
Proteasas e inhibidores	
▒*SPINK5* (60	Inhibidor de serina proteasas, impide la degradación de uniones intercelulares.

5010)	
▒*CAST* (114090)	Inhibidor de cisteína proteasas, impide la degradación de uniones intercelulares.
▒*CSTA* (184600)	Inhibidor de cisteína proteasas, impide la degradación de uniones intercelulares.
▒*SERPINB8* (601697)	Inhibidor de serina proteasas, impide la degradación de uniones intercelulares.
▒*ST14* (606797)	Activador epitelial de membrana de otras proteasas. También tiene funciones en el procesamiento de la profilagrina y crecimiento del folículo piloso.
Transcripción/traducción	
▒*AARS1* (601065)	Sintetasa de alanil ARN de transferencia.
▒*ERCC2* (12	Componente del complejo TFIIH involucrado en reparación por escisión de nucleótidos y transcripción de genes tipo 2.

6340)	
ERCC3 (133510)	Componente del complejo TFIIH involucrado en reparación por escisión de nucleótidos y transcripción de genes tipo 2.
GTF2E2 (189964)	Componente del complejo TFIIE involucrado en la transcripción de genes tipo 2.
GTF2H5 (608780)	Componente del complejo TFIIH involucrado en reparación por escisión de nucleótidos y transcripción de genes tipo 2.
MARS1 (156560)	Sintetasa de metionil ARN de transferencia.
RNF113A (300951)	Proteína de dedo RING involucrada en el procesamiento de los pre-ARN mensajero.
TARS1 (187790)	Sintetasa de treonil ARN de transferencia.

Canales de calcio	
TRPM4 (606936)	Canal iónico activado por calcio, asociado a regulación de la proliferación.
Vesículas recubiertas de clatrina	
AP1B1 (600157)	Parte del complejo adaptador de las vesículas recubiertas de clatrina.
AP1S1 (603531)	Parte del complejo adaptador de las vesículas recubiertas de clatrina.
Otros	
MPLKIP (609188)	Interacciona con quinasas dependientes de ciclina y polo quinasas, mantiene la integridad del ciclo celular.

MIM: código del gen en la base de datos OMIM.

Tabla 2 Clasificación de las ictiosis no sindrómicas

Ictiosis no sindrómicas
Ictiosis vulgar (IV) (ORPHA: –)
Ictiosis recesiva ligada al X (IRLX) (ORPHA: 461)
Ictiosis congénita autosómica recesiva (ORPHA: 281097)
▪Ictiosis laminar o lamelar (ORPHA: 313)
▪Eritrodermia ictiosiforme congénita (ORPHA: 79394)
▪Ictiosis arlequín (ORPHA: 457)
▪Bebé colodión automejorativo (ORPHA: 281122)
▪Bebé colodión automejorativo acral (ORPHA: 281127)
▪Ictiosis en traje de baño (ORPHA: 100976)
Ictiosis queratinopáticas (ORPHA: 281103)
▪Ictiosis epidermolítica autosómica dominante (ORPHA: 312)
▪Ictiosis epidermolítica autosómica recesiva (ORPHA: 512103)
▪Ictiosis epidermolítica anular (ORPHA: 281139)
▪Ictiosis Curth-Macklin (ORPHA: 79503)
▪Ictiosis con confeti (ORPHA: 281190)
▪Ictiosis epidermolítica superficial (ORPHA: 455)
▪Nevo epidermolítico (EN, ORPHA: 497737)
Síndromes de exfoliación cutánea (ORPHA: 817)
▪Síndrome de descamación cutánea generalizada (ORPHA: 263543)
▪Síndrome de descamación cutánea acral (ORPHA: 263534)
▪Síndrome PLACK (ORPHA: 44138)
Eritroqueratodermias (ORPHA: 79355)
▪Queratodermia por loricrina (ORPHA: 79395)
▪Síndrome KLICK (ORPHA: 281201)

KLICK: *keratosis linearis, ichthyosis congenita, and sclerosing keratoderma* (queratosis linear, ictiosis congénita y queratoderma esclerosante); 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, queilitis y almohadillas en los nudillos).

Tabla 3 Formas infrecuentes de las ictiosis no sindrómicas

Grupo	Genes causales	Características principales
Síndromes de descamación cutánea (PSS, ORPHA: 817)		Caracterizados por descamación en la capa superior de la epidermis[1]. Se subdividen dependiendo de las áreas afectadas
Síndrome de descamación cutánea generalizada (PSS generalizado, ORPHA: 263543)	*CDSN*[2] (AR, MIM: 270300)*, FLG2*[1] (AR, MIM: 618084)	La descamación afecta a la superficie cutánea entera[1] e incluye 2 subtipos: – El subtipo A (no inflamatorio, ORPHA: 263548) causado por *FLG2*. – El subtipo B (inflamatorio, ORPHA: 263553) causado por *CDSN*.
Síndrome de descamación cutánea acral (PSS acral, ORPHA: 263534)	*CSTA*[3] (AR, MIM: 607936)*, TGM5*[4] (AR, MIM: 609796)	La descamación afecta primariamente a las superficies plantares y dorsales de manos y pies[1].
Ictiosis exfoliativa (ORPHA: 289586)	*CSTA*[5] (AR, MIM: 607936)*, SERPINB8*[6] (AR, MIM: 617115)	Caracterizada por descamación de la piel y piel seca y escamosa generalizada[5]. No se clasifica típicamente como PSS, pero la ictiosis exfoliativa

		comparte síntomas y alteraciones moleculares subyacentes con PSS acral[5].
▓Síndrome de descamación cutánea - leuconiquia - queratosis punctata acral - queilitis - almohadillas de nudillo (PLACK, ORPHA: 444138)	*CAST*[7] (AR, MIM: 616295)	Caracterizado por descamación cutánea generalizada con leuconiquia (descoloración blanca de las uñas), queratosis punctata acral (parches queratósicos en las extremidades), queilitis y almohadillas en los nudillos.
Otros		
▓Queratodermia loricrina (LK, ORPHA: 79395)	*LORICRIN*[8] (AD, MIM: 604117)	También conocida como queratodermia hereditaria mutilante con ictiosis, enfermedad en camisa o síndrome de Vohwinkel con ictiosis. Se caracteriza por ictiosis generalizada, con hiperqueratosis palmoplantar en pana y a menudo bandas constrictoras alrededor de los meñiques[8].
▓Eritroqueratodermia variable progresiva (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)	Un término que engloba a pacientes con hallazgos clínicos similares: eritema migratorio y lesiones hiperqueratósicas, que cambian de tamaño con el tiempo[15] (a veces llamado eritroqueratodermia

		variable [EKV]) y/o placas fijas marrones a rojas hiperqueratóticas[11] (a veces llamada eritroqueratodermia simétrica progresiva [PSEK]). Los individuos y familias pueden mostrar tanto placas fijas como migratorias causadas por mutaciones en diferentes genes, algunos de los cuales codifican proteínas sin aparente relación funcional. Las características de EKVP a veces se han descrito en algunos pacientes con mutaciones en *NIPAL4*[16] o *ABCA12*[17].
▓Síndrome de queratosis linear - ictiosis congénita - queratodermia esclerosante (KLICK, ORPHA: 281201)	*POMP*[18] (AR, MIM: 601952)	Caracterizado por ictiosis congénita, pápulas discretas en los aspectos flexurales de las articulaciones, queratodermia palmoplantar, bandas constrictoras alrededor de los dedos y deformidades flexurales[18].

AD: autosómico dominante; AR: autosómico recesivo.

1. Alfares A, Al-Khenaizan S, Al Mutairi F, Fuad C, Mutairi A, Abdullah K. Peeling skin syndrome associated with novel variant in FLG2 gene. Am J Med Genet A. 2017;173;3201-3204. https://doi.org/10.1002/AJMG.A.38468.

22. Oji V, Eckl KM, Aufenvenne K, Nätebus M, Tarinski T, Ackermann K, et al. Loss of Corneodesmosin Leads to Severe Skin Barrier Defect, Pruritus, and Atopy: Unraveling the Peeling Skin Disease. Am J Hum Genet. 2010;87;274-281. https://doi.org/10.1016/J.AJHG.2010.07.005.

3. Muttardi K, Nitoiu D, Kelsell DP, O'Toole EA, Batta K. Acral peeling skin syndrome associated with a novel CSTA gene mutation. Clin Exp Dermatol. 2016;41;394–398. https://doi.org/10.1111/CED.12777.

4. Cassidy AJ, van Steensel MAM, Steijlen PM, van Geel M, van der Velden J, Morley SM, et al. A homozygous missense mutation in TGM5 abolishes epidermal transglutaminase 5 activity and causes acral peeling skin syndrome. Am J Hum Genet. 2005;77;909-917. https://doi.org/10.1086/497707.

5. Blaydon DC, Nitoiu D, Eckl KM, Cabral RM, Bland P, Hausser I, et al. Mutations in CSTA, encoding Cystatin A, underlie exfoliative ichthyosis and reveal a role for this protease inhibitor in cell-cell adhesion. Am J Hum Genet. 2011;89;564-571. https://doi.org/10.1016/J.AJHG.2011.09.001.

6. Pigors M, Sarig O, Heinz L, Plagnol V, Fischer J, Mohamad J, et al. Loss-of-Function Mutations in SERPINB8 Linked to Exfoliative Ichthyosis with Impaired Mechanical Stability of Intercellular Adhesions. Am J Hum Genet. 2016;99;430-436. https://doi.org/10.1016/J.AJHG.2016.06.004.

7. Lin Z, Zhao J, Nitoiu D, Scott CA, Plagnol V, Smith FJD, et al. Loss-of-function mutations in CAST cause peeling skin, leukonychia, acral punctate keratoses, cheilitis, and knuckle pads. Am J Hum Genet. 2015;96;440-447. https://doi.org/10.1016/J.AJHG.2014.12.026.

8. 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;70-77. https://doi.org/10.1038/ng0596-70.

9. Boyden LM, Craiglow BG, Zhou J, Hu R, Loring EC, Morel KD, et al. Dominant De Novo Mutations in GJA1 Cause Erythrokeratodermia Variabilis et Progressiva, without Features of Oculodentodigital Dysplasia. J Invest Dermatol. 2015;135;1540-1547. https://doi.org/10.1038/JID.2014.485.

10. 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;366-369. https://doi.org/10.1038/3840.

11. 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;1296-1301. https://doi.org/10.1016/S0002-9297(07)62957-7.

12. Boyden LM, Vincent NG, Zhou J, Hu R, Craiglow BG, Bayliss SJ, et al. Mutations in KDSR Cause Recessive Progressive Symmetric Erythrokeratoderma. Am J Hum Genet. 2017;100;978-984. https://doi.org/10.1016/J.AJHG.2017.05.003.

13. Duchatelet S, Boyden LM, Ishida-Yamamoto A, Zhou J, Guibbal L, Hu R, et al. Mutations in PERP Cause Dominant and Recessive Keratoderma. J Invest Dermatol. 2019;139;380-390. https://doi.org/10.1016/J.JID.2018.08.026.

14. Wang H, Xu Z, Lee BH, Vu S, Hu L, Lee M, et al. Gain-of-Function Mutations in TRPM4 Activation Gate Cause Progressive Symmetric Erythrokeratodermia. J Invest Dermatol. 2019;139;1089-1097. https://doi.org/10.1016/J.JID.2018.10.044/ATTACHMENT/4A5430A4-C020-471F-B7C0-96992C1474D1/MMC1.PDF.

15. Van Steensel MAM, Oranje AP, van der Schroeff JG, Wagner A, van Geel M. The missense mutation G12D in connexin30.3 can cause both erythrokeratodermia variabilis of Mendes da Costa and progressive symmetric erythrokeratodermia of Gottron. Am J Med Genet A. 2009;149A;657-661. https://doi.org/10.1002/AJMG.A.32744.

16. Boyden LM, Craiglow BG, Hu RH, Zhou J, Browning J, Eichenfield L, et al. Phenotypic spectrum of autosomal recessive congenital ichthyosis due to PNPLA1 mutation. Br J Dermatol. 2017;177;319-322. https://doi.org/10.1111/BJD.15570.

17. Sun Q, Burgren NM, Cheraghlou S, Paller AS, Larralde M, Bercovitch L, et al. The Genomic and Phenotypic Landscape of Ichthyosis: An Analysis of 1000 Kindreds. JAMA Dermatol. 2022;158;16-25. https://doi.org/10.1001/JAMADERMATOL.2021.4242.

18. 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;596-603. https://doi.org/10.1016/J.AJHG.2010.02.018.