Ichthyosis

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Abstract

The ichthyoses are a large, heterogeneous group of skin cornification disorders. They can be inherited or acquired, and result in defective keratinocyte differentiation and abnormal epidermal barrier formation. The resultant skin barrier dysfunction leads to increased transepidermal water loss and inflammation. Disordered cornification is clinically characterized by skin scaling with different degrees of thickening, desquamation (peeling), and erythema (redness). Regardless of the type of ichthyosis, many patients suffer from itching, recurrent infections, sweating impairment (hypohidrosis) with heat intolerance, and diverse ocular, hearing and nutritional complications that should be monitored periodically. The characteristic clinical features are considered to be a homeostatic attempt to repair the skin barrier, but heterogeneous clinical presentation and imperfect phenotype–genotype correlation hinders diagnosis. An accurate molecular diagnosis is, however, crucial for predicting prognosis and providing appropriate genetic counseling. Most ichthyoses severely affect patient quality of life and, in severe forms, may cause considerable disability and even death. So far, treatment only provides symptomatic relief. It is life-long, expensive, time-consuming, and often provides disappointing results. A better understanding of the molecular mechanisms underlying these conditions is essential for designing pathogenesis-driven and patient-tailored innovative therapeutic solutions.

Introduction

Ichthyosis is a broad term used to group dermatological disorders characterized by generalized scaly, erythematous skin, accompanied by epidermal barrier function disruptions[1,2]. Disruption of this barrier, localized to the upper epidermis (the outermost layer of the skin)[1], interferes with its functions in protecting the patient from chemical and biological injuries, restricting liquid and solute absorption, and preventing desiccation by limiting water loss to the environment[3].

At the cellular level, the epidermis is mostly comprised of keratinocytes[4]. Generated by division of basal stem cells in the innermost layer of the epidermis, keratinocytes migrate towards the skin surface as they differentiate, transitioning through different phenotypes that give rise to the distinct epidermal layers (FIG. 1)[5,6]. These phenotypical changes lead to reorganization of the keratinocyte cytoskeleton, secretion of lipids into the extracellular space, establishment of intercellular junctions and, ultimately, to the terminal differentiation of keratinocytes into corneocytes[7,8]. This differentiation culminates in the formation of the stratum corneum, a layered structure formed by a lipidic extracellular matrix composed of ceramides, cholesterol and fatty acids, an inner ceramide-rich lipidic envelope (the corneocyte lipid envelope) cross-linked to the cornified envelope (a protein layer that gradually replaces the cell membrane of terminally differentiating keratinocytes[9]), and the protein-rich corneocytes[10]. Together, these changes lay the groundwork for epidermal barrier formation[8], and their disruption leads to the ichthyotic condition.

Ichthyoses can be either acquired or inherited. Acquired forms can be caused by different underlying factors, such as malignancies, autoimmune diseases, nutritional disorders or medication[11] (BOX 1). By contrast, inherited ichthyoses follow patterns of Mendelian inheritance and each form is associated with a mutation in a specific gene that encodes a protein involved in synthesis or metabolism of proteins or lipids that are important in keratinocyte terminal differentiation, leading to the observed phenotypic, histological and molecular abnormalities[12]. These phenotypic abnormalities manifest as scales of variable thickness often accompanied by erythema (redness)[12] and psychological issues due to the visibility of affected skin and the associated stigma[13,14]. In severe cases, the thickened skin is taut, leading to exposure of the inner surface of eyelids and lips (ectropium and eclabium, respectively) and fissures that increase the risk of infection[12]. Excess skin is desquamated (peeling) and can block sweat glands, tear ducts, and the ear canal, leading to difficulty sweating (hypohidrosis) with heat intolerance, dry eyes (xerophtalmia), and potentially irreversible loss of hearing[12–14]. At the same time, barrier disruption increases transepidermal water loss with a concomitant caloric drain leading to failure to thrive[13–15]. Affectation of the nails (onychodystrophy) is also common[12]. In some forms of ichthyosis (called syndromic ichthyosis) the causal gene has functions outside the skin,

leading to diverse extracutaneous manifestations in the hair, genitourinary system, gastrointestinal tract, and nervous system[12].

The study of defective genes not only enables appropriate genetic counseling and prenatal diagnosis for families at risk of disease[16] but has also been instrumental in the delineation of fundamental aspects of skin biology, making ichthyoses a key set of disorders for understanding the epidermal barrier.

In this Primer, we discuss those diseases that fall under the definition of ichthyosis, including their epidemiology, their underlying genetic causes and their relationship to the clinical phenotype. We also discuss disease classification and diagnosis, management, effects on patients' quality of life, and the development of new approaches to the management of these conditions.

Epidemiology

Inherited ichthyoses

Several factors make it difficult to estimate the prevalence of ichthyosis. First, ichthyoses form a heterogeneous group of diseases and each of them has a different prevalence rate, so an overall estimate would bias data towards the most common forms. Second, there are >50 different ichthyoses, most of which are considered rare (<1 patient per 2,000 people[17]); hence, accurate and thorough epidemiological reports are scarce. Furthermore, most of the available data have been collected in specific populations and it is unclear to what extent they are generalizable.

Ichthyosis vulgaris, the most common form of inherited ichthyosis, has variable estimates of prevalence across studies. Its prevalence was as high as 10 in 792 a study of English schoolchildren[18]. By contrast, a prevalence of 1 in 5,025 (n = 497,460) was reported in a West Russian cohort[19] and a prevalence of 1 in 17,372 was estimated based on hospital records of the Jewish population in Israel[20].

Ichthyosis vulgaris is the most common form of ichthyosis in Asia as well. The combined carrier rate of ten ichthyosis vulgaris-causative null mutations in the filaggrin gene (*FLG*) was reported to be 11.1% in Japan[21]. Interestingly, the prevalence of different *FLG* mutations differs greatly between Asian and European populations. In Europe, two extremely prevalent founder mutations (p.R501X and c.2282del4) account for 80% of the *FLG* mutation spectrum[22], whereas in Asian populations >30 low prevalence *FLG* mutations have been found, varying greatly among different Asian ethnic groups, including Chinese, Japanese, Taiwanese, Korean, Malay and Indian populations[22–25].

The second most common form of inherited ichthyosis is recessive X-linked ichthyosis (RXLI), which almost exclusively affects males[26]. Its prevalence was 1 in 1,500 males (n=777,088) in a US cohort[27], 1

in 5,034 males (n=75,653) in a South Italian cohort[28] and 1 in 6,190 males in an English cohort[29]. A prevalence of 1 in 4,152 males was estimated based on hospital records of a Spanish province[30], 1 in 5,250 males was estimated based on hospital records of the Jewish population in Israel[20] and 1 in 9,855 was estimated based on hospital records of a Japanese province[31]. No racial differences in disease prevalence were found among patients in the US study[27].

The remaining ichthyoses are extremely rare (with prevalences under 1 in 100,000). A combined prevalence for all remaining ichthyoses was estimated at 6.7 in 100,000 based on health insurance records in the USA[32], 1.62 in 100,000 based on hospital records in Spain[33], 1.3 in 100,000 based on hospital records in France[34], and 0.17 in 100,000 in Japan[35]. Table 1 shows the prevalences of several rare forms of ichthyosis.

In Saudi Arabia, 6.7 in 1,000 patients who visited one large dermatology center were affected by some form of ichthyosis (half of which were classified as ichthyosis vulgaris)[36]. The molecular epidemiology of ichthyoses might differ in the Middle East as well: in a cohort of 62 patients with autosomal recessive congenital ichthyosis (ARCI), *CYP4F22* and *ABCA12* were the most commonly affected genes, whereas *TGM1* and *NIPAL4* are the most frequent causal genes in Western countries[37]. However, in a cohort of 19 patients with ARCI from Saudi Arabia and Pakistan, *TGM1* and *NIPAL4* mutations were the most abundant[38]. In a series of Iranian patients with ichthyosis vulgaris, no mutations in *FLG* were identified[39]. Further complicating interpretation of these data, one study demonstrated wide variability in pathogenic variant allele frequency in various Middle Eastern subgroups[40]. Some variants were highly associated with specific ethnic backgrounds, which may facilitate molecular diagnostics[40,41]

Patients with inherited ichthyosis, especially those with severe ichthyosis, have various associated conditions and complications, whose prevalence is not well known[13,14]. Pruritus (itchy skin), a characteristic feature of several specific subtypes of inherited ichthyosis, including Netherton syndrome, is one of the most frequent and important complications[13,14]. Recurrent cutaneous bacterial and fungal infections are commonly observed, especially in Netherton syndrome and keratitis-ichthyosis-deafness syndrome (KID) [13,14,42,43]. Heat intolerance due to hypohidrosis is also frequently observed both in severe and mild forms of inherited ichthyosis[44]

Acquired ichthyoses

Acquired ichthyosis is a rare condition. Data regarding its relative prevalence are unreliable due to the varying definitions of acquired ichthyosis in different studies and the fact that it is often confused

with xerosis (dry skin)[45]. Its prevalence seems to be etiology-specific: it affects ~30% of individuals with AIDS[46], ~22% of patients with diabetes mellitus[47], and up to 50% of HTLV-1-positive individuals[48]. It is extremely rare among patients with cancer; however, when it is observed, it is mostly in patients with Hodgkin's lymphoma[49].

Mechanisms/pathophysiology

Cutaneous mechanisms

All ichthyoses are characterized by disruptions of the epidermal barrier, a unique structure established by the differentiating keratinocytes. This structure is organized as a set of concentric layers formed by the terminally differentiated corneocytes at its center and the extracellular space surrounding them, in what is sometimes called the bricks and mortar model[10] (FIG. 1)[50]. According to this model, the filaggrin-rich and keratin-rich corneocyte cytoplasm and loricrin-rich cornified envelope resembles the protein bricks that lend the barrier its mechanical resilience[10]. The lipids, which are covalently bound to the cornified envelope to form the corneocyte lipid envelope and the intercellular lamellar lipids, form the mortar that seals the barrier, preventing solute and liquid diffusion across it[10].

Most of the genes associated with inherited ichthyoses encode proteins that are involved in the synthesis or metabolism of other proteins and lipids that form the epidermal barrier (Supplementary Table 1). When these genes are mutated, the normal epithelial function is disrupted. Thus, ichthyoses can be classified not only phenotypically but also based on gene variant[51].

Some of these encoded proteins are involved in maintaining the intracellular structural protein network that confers keratinocytes and corneocytes their mechanical resilience[52]. Keratins are a family of >54 proteins with very well regulated expression patterns, which are specific to the tissue and differentiation stage[52]. Keratins 1, 2 and 10 (encoded by *KRT1*, *KRT2* and *KRT10*) are the main components of the keratinocyte intermediate filament cytoskeleton[53,54]. Filaggrin (encoded by *FLG*[55]) is initially translated as a preprotein[56] and then processed by proteases caspase 14 (encoded by *CASP14*[57]), matriptase (encoded by *ST14*[58]), and aspartic peptidase (*ASPRV1*[59]) to aggregate the keratin filaments. Filaggrin is eventually degraded by the proteasome (assembled by chaperones such as the protein encoded by *POMP*[60]) into amino acids that act as moisturizing factors for maintaining skin hydration[56]. Loricrin (encoded by *LORICRIN*) is the major component of the cornified envelope[9]. Crosslinking enzymes like transglutaminases 1 and 5 (encoded by *TGM1* and *TGM5*) link both the various proteins of the cornified envelope and the keratin intermediate filaments with the cornified envelope[61].

Other genes are involved in the biosynthesis, metabolism, and transport of the lipids which establish the impermeability of the skin barrier (FIG. 2). Ceramides, which are composed of a sphingosine molecule and one or two long-chain fatty acids[62], are crosslinked to the cornified envelope, forming the corneocyte lipid envelope, and are also a component of the lamellar lipids of the extracellular space[63]. The protein encoded by *ALDH3A2* oxidizes fatty aldehydes and alcohols to fatty acids[64]. The proteins encoded by *ELOVL1*[65] and *ELOVL4*[66] are enzymes involved in ultra-long-chain (ULC) fatty acid synthesis[67]. The product of *CYP4F22*[68,69] catalyzes ω-hydroxylation of ULC-fatty acids. *SLC27A4*[70,71] encodes the acyl-CoA synthetase which synthesizes ω-hydroxy-ULC-fatty acid-CoA[70]; *PHYH*[72,73] and *PEX7*[74] encode proteins with poorly-defined functions in peroxisomal fatty acid synthesis[67,75]. Furthermore, the enzymes encoded by *PHGDH*, *PSAT1* and *PSPH* catalyze de novo serine biosynthesis[76–78], which is used for dihydrosphingosine biosynthesis by 3-ketodihydrosphingosine (KDS) reductase (encoded by *KDSR*)[79]. Then, ω-hydroxy-ULC-ceramide is formed from ω-hydroxy-ULC-fatty acid-CoA and dihydrosphingosine by the product of *CERS3*[80–82]. The function of protein products from, *NIPAL4*[83,84] and *LIPN*[85] are not yet completely clear. *ABHD5*[86] encodes an accessory protein responsible for recruiting a transacylase encoded by *PNPLA1*[87,88], which uses linoleic acid to catalyze the conversion of ω-hydroxy-ULC-ceramides to ULC-acylceramides[67]. ULC-acylceramides are glycosylated into ULC-acyl-glucosylceramides by ceramide glucosyltransferase (encoded by *UGCG*)[89], and transported into specialized secretory vesicles, called lamellar bodies, by a special transporter encoded by *ABCA12*[90]. At this stage, glucocerebrosidase (encoded by *GBA1*[91]) cleaves the link to the glucosidic residue, enabling their secretion as free lipids[92]. Alternatively, *ALOX12B*[93], *ALOXE3*[93], and *SDR9C7*[94] encode a number of enzymes that esterify the ULC-acyl-glucosylceramides before their crosslinking to the cornified envelope proteins to form the corneocyte lipid envelope[92], a poorly-understood process that might involve *TGM1*[95–98].

Cholesterol is another lipid component of the epidermal barrier found in the extracellular space[63] (FIG. 3). *MBTPS2* encodes a zinc metalloprotease that activates signal proteins involved in cholesterol and dolichol synthesis[99]. *SREBF1* encodes a transcription factor that regulates proteins involved in cholesterol and dolichol synthesis[100]. *NSDHL* and *EBP* encode enzymes involved in cholesterol synthesis[101,102]. *SULT2B1*[103] encodes a cholesterol sulfotransferase, which sulfonates cholesterol to cholesterol sulfate and has been shown to inhibit transglutaminase 1-catalyzed ceramide crosslinking[104] and protease-mediated degradation of intercellular junctions[51]. *STS*[105] encodes a sulfatase that converts cholesterol sulfate to cholesterol and is activated by sulfatase modifying factor (encoded by *SUMF1*)[106,107]. These lipids are secreted into the extracellular space by lamellar bodies. Unsurprisingly, mutations in genes whose products are involved in lamellar body fusion events

(*SNAP29*[108], *VIPAS39*[109] and *VPS33B*[110]), which are critical to lamellar body function, also result in forms of ichthyosis.

Other lipids function as intermediates in the post-translational modification of proteins. Dolichols, a group of unsaturated and long-chain lipids, are necessary for protein N-glycosylation and O-mannosylation, as well as for the formation of glycosylphosphatidylinositol (GPI) anchors[111]. Dolichols share the beginning of their biosynthetic pathway with cholesterol and diverge with the synthesis of polyprenol instead of squalene[111]. *SRD5A3*[112], *DOLK*[113] and *MPDU1*[114] encode a series of enzymes that sequentially catalyze the steps that lead to the formation of dolichol phosphate mannose, which is then used as a mannose donor in N-glycosylation, O-mannosylation and GPI anchor synthesis. N-acetylglucosaminyl-phosphatidylinositol de-N-acetylase (encoded by *PIGL*)[115] is also required for GPI anchor synthesis.

Intercellular junctions connect keratinocytes and corneocytes (FIG 1), ensuring intercellular adhesion, facilitating intercellular communication and restricting extracellular solute diffusion[116]. Claudins encoded by *CLDN1*[117] and *CLDN10*[118] are components of tight junctions, controlling paracellular permeability in the stratum granulosum[118]. *GJA1*[119], *GJB2*[120], *GJB3*[121], *GJB4*[122], and *GJB6*[123] encode connexins 43, 26, 31, 30.3 and 30, which form gap junctions that enable intercellular communication[123]. Desmoglein 1 and desmoplakin (encoded by *DSG1* and *DSP*) are components of desmosomes and mediate intercellular adhesion[124,125]. Corneodesmosin (encoded by *CDSN*[126]) is present only in corneodesmosomes, the highly-specialized junctions connecting corneocytes, and the p53 apoptosis effector related to PMP-22 (encoded by *PERP*) is both a component in desmosomes and an apoptosis mediator[127]. Junctions are degraded by proteases as part of the desquamation process. *ST14* encodes a serine protease, which has been associated with the degradation of corneodesmosomes, as well as filaggrin[128]. *SERPINB8*[129] and *SPINK5*[130,131] encode serine protease inhibitors, and *CAST*[132] and *CSTA*[133] encode cysteine protease inhibitors. Filaggrin 2 (encoded by *FLG2*[134]) is necessary to prevent corneodesmosin degradation and, thereby, maintain intercellular adhesion in the upper epidermal layers[135].

Finally, gene mutations in individuals with ichthyosis affect gene transcription and translation. *ERCC2*[136], *ERCC3*[137] and *GTF2H5*[138] encode different elements of the TFIIH protein complex, which regulates DNA polymerase II binding to DNA and thus is associated with both nucleotide excision DNA repair and regulation of gene transcription[138]. *GTF2E2* encodes a part of the TFIIE complex that recruits TFIIH[139] and also regulates DNA polymerase II binding to *RNF113A*[140] encodes a ring finger protein involved in pre-mRNA splicing[141] and, additionally, acts as an E3 ubiquitin ligase[142]. *AARS1*[143], *MARS1*[143] and *TARS1*[144] encode, respectively, alanyl-, methyonyl- and threonyl-tRNA synthetases involved in

translation. This group of genes are widely expressed and play roles in pathways crucial to all tissues. Given that some of them can cause other diseases as well as ichthyosis[145–147], the phenotype might be mutation-specific, but their exact mechanism in skin is unknown

AP1B1 and *AP1S1* encode components of the AP1 adaptor complex of clathrin-coated vesicles[148,149]. *TRPM4* encodes a protein which has been associated with the regulation of proliferation[150] and M-phase-specific PLK1-interacting protein (encoded by *MPLKIP*)[151] is believed to interact with cyclin-dependent kinase 1 and polo-like kinase 1, maintaining cell cycle integrity[152].

Defects in these genes lead to the scaly skin phenotype that characterizes ichthyosis primarily through two mechanisms[51]: altered cell-to-cell adhesion and desquamation (of relevance mainly to ichthyoses caused by genes involved in intercellular junctions and their proteases)[51]; and keratinocyte hyperproliferation, corneocyte accumulation and enhanced lipid biosynthesis as a physiological response aimed at mitigating the consequences of defective epidermal barrier function[153]. These two mechanisms can explain the development of most forms of ichthyosis, and the wide range of ichthyosis-causing genetic defects account for their heterogeneity and complicate the interpretations of genotype-phenotype correlations.

Extracutaneous mechanisms

The phenotypic heterogeneity is exacerbated in syndromic forms that present certain extracutaneous manifestations, depending on the affected genes. Cholesterol metabolism is important in the retina (where it has been linked to rod function)[154] and embryonal development[155]; consequently, defects in its synthesis lead to epithelial disturbance that causes ulcers, increased vascularization, progressive corneal scarring and photophobia[99], as well as defects in skeletal structure and organ formation[101,102]. Ceramides are another lipid family with functions outside the epidermis, where they act as sphingomyelin precursors[156]. Thus, most genes whose products are involved in ceramide synthesis cause neurologic symptoms such as seizures[66], spastic paraplegia[65], neuropathy[73], and intellectual disability[66]. Some of these genes encode proteins involved in especially sensitive steps in this process, such as L-serine synthesis[77] and ceramide secretion[91], and their mutations lead to fetal death[91]. Some gene products use lipids, especially dolichol, as mediators in glycosylation and GPI anchor synthesis. Mutations in these genes lead to disorders of glycosylation characterized by excessive muscle tone (hypertonia)[114] or defective muscle tone (hypotonia)[113] and intellectual disability[112].

Junctions and their proteases can also have extracutaneous functions and, thus, lead to syndromic forms of ichthyosis. Desmosomes are integral in maintaining cardiac muscle integrity[157] and, therefore, their mutation can lead to cardiomiopathy[158]. Tight junctions control paracellular

permeability in secretory ducts, leading to inflammation and scarring of the bile ducts (sclerosing cholangitis)[117], dry mouth (xerostomia)[118], dry eyes (xerophtalmia)[118], and renal electrolyte loss[118]. All of the above mentioned genes, as well as those coding for proteases and their inhibitors, are involved in hair follicle integrity[159], with their defects leading to sparse hair (hypotrichosis)[117,124,128,130]. Gap junctions form networks enabling sound transduction in the cochlea[160] and their alteration leads to sensorineural deafness[120]. Clathrin-coated vesicles mediate endocytosis in most tissues, including in the cochlea[161] and in neuronal myelination[162], so mutations in their adaptor complex lead to sensorineural deafness[148] and peripheral neuropathy[148]. Genes involved in transcription and translation are crucial in a variety of tissues, with mutations that lead to fragile hair and nails, photosensitivity, progressive neuropathy, and accelerated aging[143].

Additionally, most patients with ichthyosis show a hyperactive inflammatory response characterized by a Th17 immunophenotype[163,164], likely in response to the barrier impairment and altered cutaneous microbiome. These microbial alterations are characterized by notable increases in *Staphylococcus aureus* and, in response, *Staphylococcus capitis* and corynebacteria, but reductions in cutibacteria and Malassezia species, which are lipid-dependent colonizers that cannot survive in a dry skin milieu[165]. Th17/IL-23 driven inflammation, however, likely has a pathogenic role in some forms of ichthyosis, given responses to biologics that target this pathway.

Diagnosis, screening and prevention

Classification

The wide range of genes with ichthyosis-causing variants and the well-known clinical heterogeneity characterizing these conditions render their diagnosis challenging (FIG. 4). Although the presence of generalized skin scaling, typically congenital or appearing shortly after birth[85], is clearly indicative of ichthyosis, narrowing down the specific subtype is difficult, given the many genes associated with the ichthyoses, and often requires in-depth phenotypic characterization and genetic testing[51]. An accurate diagnosis is, however, crucial for predicting prognosis, optimizing treatments and follow-up appointments, and family planning through genetic counseling and prenatal diagnosis.

Genetic variants, together with the clinical characteristics of each disease subtype, can be used to group the inherited ichthyoses. The currently accepted clinical classification was generated at the 2009 “First Ichthyosis Consensus” Sorèze international conference[1]. This classification has been adjusted in this Primer to add the genetic discoveries of the recent years, as well as disease subtypes that are not as well characterized.

All patients with ichthyosis show variable involvement and degrees of scaling, thickening of the skin and erythema, which may be different in individuals with the same genotype and even vary in the course of their own disease. Of note, phenotypes on darker skin may have slightly different findings. Desquamation in patients with dark phototypes is slightly darker than the rest of the skin. Although this may also be the case in Caucasian patients with X-linked ichthyosis and lamellar ichthyosis (two typical forms of ichthyosis showing retention hyperkeratosis), it is more pronounced in patients of African origin than in those with lighter phototypes. Also, erythema can be harder to observe in a darker background. The broadest groups into which ichthyoses can be classified are non-syndromic, if the phenotypic expression of the underlying genetic defect exclusively affects the skin, and syndromic, if it affects both the skin and other organs[1].

Non-syndromic ichthyoses can be further subdivided into common ichthyosis (ichthyosis vulgaris and recessive X-linked ichthyosis, RXLI), autosomal recessive congenital ichthyosis (ARCI), and keratinopathic ichthyoses. Common ichthyoses have a markedly higher incidence than the rest of the ichthyoses and are usually milder; despite being congenital, desquamation frequently develops weeks to months after birth in these patients[55]. ARCI patients are often born as collodion babies, encased in a shiny, tight, translucent membrane[166] before developing generalized scaling with pronounced underlying erythema (congenital ichthyosiform erythroderma, CIE)[167] or large polygonal scales (lamellar ichthyosis)[90]. Harlequin ichthyosis is a particularly severe, sometimes lethal form of ARCI (overall survival rate ranging from 56% to 81.3%)[168,169]. Keratinopathic ichthyoses are characterized by extensive blistering and erosions at birth (epidermolytic ichthyosis) that heal and give way to a diffuse thickening of the skin (hyperkeratosis) and a variable degree of skin fragility (tendency to erode easily with minor trauma) throughout life[53].

Syndromic ichthyoses are grouped according to their mode of inheritance. X-linked syndromes affect genes in the X chromosome, mainly affecting the retina and skeletal structures due to defects in cholesterol synthesis[170]. Autosomal syndromes are divided further into those with hair abnormalities, such as Netherton syndrome (which is also associated with allergic conditions)[130] and trichothiodystrophy[136]; those with neurologic symptoms, such as Refsum disease[72] and Sjögren-Larsson syndrome[64]; and those with a variety of systemic findings such as ocular or liver function anomalies[115].

While the original Sorèze primarily clinical classification divides the ichthyoses according to the manifestations with which patients present in clinical practice, Supplementary Tables 2 & 3 summarize a proposed classification of non-syndromic and syndromic ichthyoses, respectively. Table 2 provides another alternative classification focusing on the molecular mechanisms underlying each disease may

also be of equal clinical relevance as it may guide targeted treatment choices. Although the molecular characterization is undoubtedly useful, genetic testing is not widely available and it does not allow for a definite diagnosis in all cases, failing to detect the molecular basis in some 15-20% of patients worldwide[37,44,171–173]. Indeed, the clinical and molecular classifications are complementary and allow establishing associations between phenotypes and genotypes, helping both clinicians and patients with diagnosis and development of future precision therapies

Diagnostic work-up

Inherited ichthyoses

The generalized cutaneous barrier impairment in patients with inherited ichthyoses is present since birth or early in life, making it easy to diagnose the condition clinically. However, the imperfect correlation between phenotype and genotype precludes a straightforward diagnosis in many cases. Nevertheless, collodion babies most often have ARCI, which is extremely unusual in Netherton syndrome or RXLI[1]. Similarly, the lamellar ichthyosis phenotype of ARCI is most often caused by mutations in *TGM1*[171] and epidermolytic ichthyoses caused by mutations in *KRT10* lack keratoderma (thickening) of the palms and soles, unlike those caused by *KRT1* mutations[1].

If inherited ichthyosis is suspected, it is necessary to obtain a detailed family history of the disease, including potential parental consanguinity, and to perform a thorough physical examination beyond the cutaneous evaluation (FIG. 5). Special attention should be paid to the presence of blisters and erosions (breakdowns of the outer layer of the epidermis that leave a denuded surface), hair and dental anomalies, and signs of systemic involvement, such as developmental delay, liver dysfunction, sensorineural deafness or pulmonary involvement, as well as potential complications (for example, hypernatremic dehydration, failure to thrive or recurrent sepsis) that may even lead to death. All these findings are important not only to guide clinical diagnosis but also to detect early treatment complications.

Laboratory assessment, including blood cell count, hepatic and renal function, blood electrolyte levels, serum immunoglobulins levels, and a blood smear may be helpful to exclude syndromic forms of ichthyosis with associated anomalies[174]. For example, Netherton syndrome and desmosomal disorders have an associated risk of hypernatremic dehydration in babies[14,124], Chanarin-Dorfman syndrome shows lipid droplets within the granulocytes and monocytes in the peripheral blood smear (the so-called Jordan´s anomaly)[175], and arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome diagnosis can be supported by the plasmatic metabolic disturbances[176]. In addition, immunoglobulin serum levels can be useful in the differential diagnosis with hereditary

immunodeficiencies, which may also show cutaneous redness and desquamation. Referral to other specialists must be considered depending on the findings[174].

Biopsy for routine histology, immunohistochemistry or, rarely, electron microscopy may be helpful, since they can be used for differential diagnosis and can reveal hypogranulosis (ichthyosis vulgaris), epidermolytic changes or binucleated keratinocytes (epidermolytic ichthyosis), retained nuclei with granular inclusions (loricrin keratoderma), acantholysis (desmosomal disorders), and many other diagnostically useful findings[177] (FIG. 6). Negative immunostaining for LEKTI (encoded by *SPINK5*) can confirm a diagnosis of Netherton syndrome[178] and is of special importance if genetic testing is unavailable[177]. Microscopic examination of the hair by light microscopy is an inexpensive, non-invasive investigation that provides extremely useful information in ichthyosis associated with specific hair shaft anomalies, such as trichorrhexis invaginata in Netherton syndrome and 'tiger tail' appearance under polarized light in trichothiodystrophy[179]. Although the clinical diagnosis of ichthyosis can be made easily, genotype-phenotype correlation is often difficult to establish. Genetic testing by next generation sequencing is now widely available in developed countries to confirm the diagnosis but fails to detect a genetic abnormality in 15–20% of patients with ichthyosis phenotype[37,44,171–173]. This can be due to either undetectable or unknown pathogenic variants, with the latter usually showing unique phenotypic features that enable further genetic discovery in ichthyosis.

Acquired ichthyoses

There are no clinical or pathological features that are pathognomonic for acquired ichthyosis, which is therefore a diagnosis usually posed by exclusion. Late onset, the existence of an inciting factor and the absence of family history and of personal or familial atopic diathesis, all support the diagnosis of acquired ichthyosis. Clinically and histopathologically, many cases have been reported to resemble ichthyosis vulgaris, but exceptions have been described[45].

Screening

Inherited ichthyoses respond to known hereditary patterns, enabling genetic counseling, in which information is provided to affected families (patients and relatives) on the molecular mechanisms that cause their specific disease and the possibility of transmission to descendants. However, the risk perception of having an affected child varies greatly depending on each type of ichthyosis, and a pregnancy may not be considered high-risk by couples who already have a mildly affected child. By contrast, patients with severe forms or with an important quality of life impairment may request genetic counseling to avoid risk in future pregnancies[180]. Regional, cultural and socioeconomic particularities may also play a role in genetic counselling access. Although genetic counselling outcomes have not been systematically studied in ichthyosis, there are some anecdotal reports of

interrupted pregnancies in cases of harlequin ichthyosis, the most severe form of ichthyosis[181,182], and of RXLI[183]. Formerly prenatal diagnosis of harlequin ichthyosis was performed by ultrastructural investigations of fetal skin biopsies[184],but it is nowadays DNA-based.

Prenatal diagnosis requires obtaining embryonic tissue or, in some cases, can be performed using imaging techniques, such as ultrasonography[185]. This can help with prognosis of neonatal complications associated with some forms of ichthyosis and let parents decide whether to terminate the pregnancy[185]. Decreased levels of unconjugated estriol and the copy-number variation on maternal serological screening (that detects deletions in the maternal sex chromosomes) are closely related to the higher risk of XLI in male fetuses and can be used, in addition to other molecular techniques, for prenatal diagnosis[183,186]. Nevertheless, the method of choice for prenatal diagnosis is molecular genetic testing for pathogenic variants known in the family. Preimplantation diagnosis can be used by at-risk couples to choose non-affected embryos before in vitro fertilization, though in many countries it is not considered appropriate for ichthyosis[187].

Management

Ichthyosis are genetic, non-curable diseases for which available therapy is needed throughout life and only offers symptomatic relief. Topical therapy involves using greasy products, is time-consuming and often has suboptimal results, reducing compliance. Systemic therapy with oral retinoids can provide further improvement, particularly in forms of ichthyosis with pronounced skin thickening, but may also increase skin fragility and have potential adverse effects. Other treatment strategies, including targeted therapy with biologics to tackle inflammation or those focused on enzyme replacement and substitution therapies with the defective gene products, are promising alternatives that still need to be validated. Management of systemic findings specific to syndromic forms as well as ocular, auditory and nutritional issues common to all types of ichthyosis should be tailored to each patient[16]. Most patients require daily life-long therapy, so treatment must be not only effective but also well tolerated and safe. However, evidence levels for the long-term treatment safety profile in ichthyoses are low[188]. Furthermore, care guidelines are based mainly on expert recommendations, patient and caregiver experience, and exchanges with patient organizations[13,14].

Topical treatment

Topical treatment is a fundamental pillar in all types of ichthyosis. Its objective is to restore the epidermal barrier function and facilitate peeling of thickened skin to improve skin appearance and relieve symptoms, such as tightness and itching[189]. Given that efficacy and tolerance are subgroup-

specific and individual-specific, treatment choice depends on personal preferences, physician experience and availability.

Emollients

Emollients moisturize the skin barrier and prevent transepidermal water loss by sealing the stratum corneum. They provide different degrees of hydration, lubrication and occlusion depending upon their formulation and water-to-lipid content. Petrolatum and paraffin are safe and inexpensive lubricating agents, but their occlusive effect can interfere with sweating and be cosmetically intolerable, so patients often prefer less greasy emollient creams, such as glycerol, urea (<5%), propylenglycol (<20%) or dexpanthenol[13]. The frequency of application of moisturizers depends on the severity of the ichthyosis and the patient's habits, with most people needing topical therapy at least twice a day[13].

Keratolytics

Keratolytics (such as alpha-hydroxy and beta-hydroxy acids and urea) reduce scaling and skin thickness by diminishing the stratum corneum through proteolytic cleavage of keratins or promoting cell-to-cell disruption[190]. The age of the patient, as well as type, severity, extent and location of lesions, guides selection of the keratolytic agent. Application frequency is variable and can be reduced according to clinical response. Adverse effects are usually mild and include itching, burning, and irritation[13]. Systemic toxicity from skin absorption of salicylic and lactic acid is a rare but worrisome event[191]. Specifically, salicylic acid can cause life-threatening toxic effects, called salycilism, which is characterized by nausea, vomiting, fever, tachypnea, irritability, comatose state, and death. Although newborns are particularly at risk, it may also happen in children beyond infancy and in adult patients, even at low concentrations.[192] Hence, its use other than for localized areas is contraindicated in children <2 years of age and is better avoided in older children[13]. In adults, systemic absorption of topical salicylate is rare but can occur and it should be used with caution, especially when it is applied to more than 20% of the body surface or in patients with abnormal hepatic or renal function[193].

Retinoids

Retinoids are synthetic derivatives of vitamin A that decrease skin thickness, normalize keratinocyte proliferation and differentiation, and can decrease inflammation[189]. They are available for topical use in some jurisdictions (for example, in the USA) through repurposing of acne medications (especially tazarotene, trifaroten, adapalene and tretinoin for body and scalp use)[194,195]. Thus, they can only be prescribed off-label after adequate informed consent. For patients with recessive X-linked ichthyosis and mild-to-moderate lamellar ichthyosis, topical tazarotene may be sufficient for an excellent clinical result[196]. In a unilaterally-treated-areas trial, 8 of the 12 patients with different types of ichthyosis who were treated with 0.05% tazarotene gel showed good to excellent reduction in

roughness and scaling within 1–3 weeks of starting therapy, and for up to 2 months. The main adverse effect was dose-related local irritation [196]. In another study, daily use of tazarotene for one month in up to 20% of the body surface was not associated with systemic absorption[197]. Topical tazarotene has been helpful as an adjunctive agent for treating contractures and other tight skin of neonates with harlequin ichthyosis and severely affected collodion babies, and is the treatment of choice for treating ectropion (exposure of the inside surface of the eyelids)[194]. Unfortunately, tazarotene is not available worldwide (that is., Spain, France, Japan,Israel, Brasil, Chile, Bulgaria, Switzerland, Austria, and The Netherlands). Adapalene, another topical retinoid marketed for acne, has been efficacious in one 14-year-old patient with epidermolytic ichthyosis[195]. Additional topical retinoids specifically aimed at ichthyosis patients are in development[198]. Although they would be an excellent alternative for patients in whom oral retinoids are contraindicated or not well accepted (that is, those willing to become pregnant and patients fearing oral retinoid adverse effects), their use is limited not only by their efficacy but also by the secondary skin irritation and potential absorption if applied on large areas.

Daily baths and mechanical exfoliation

Bathing softens the stratum corneum, helping to mechanically remove scales and reduce subjective discomfort but is time-consuming. Patients need to bathe at least once daily for 30–60 minutes, but some prefer showers (which are also acceptable as long as they enable mechanical exfoliation)[2]. Scales can be removed by gently rubbing with the hand or by using sponges, emery boards, microfiber cloths or pumice stone. Careful use of scissors for partially adherent large scales and sharp debridement with scalpels of thickened palms and soles may also be needed. Salts, oils, or baking soda can be added to provide additional hydration and promote exfoliation[199] Highly diluted sodium hypochlorite (bleach) has also been added to reduce odor due to microbial colonization in some patients[13].

Hair care

Scalp scaling is a common and difficult problem, varying from fine, unattached scales to thick, adherent scales and even crusts and erosions that may eventually lead to alopecia[200,201]. Mechanical removal of scales with brushes and combs (including nit combs) is recommended to avoid accumulation of crusts and potential microbial superinfection[13]. Keratolytics and emollients may also be helpful[2], but should be used sparingly, given the increased absorption through the scalp[202]. Brushing and scalp care should be particularly gentle in patients with ichthyosis that causes brittle hair, such as Netherton syndrome and trichothiodystrophy.

Systemic treatment

Some patients with moderate-to-severe involvement or seeking to reduce the burden of skin care benefit from systemic treatment with oral retinoids. Different oral retinoids are available for

treatment of ichthyosis. Acitretin, alitretinoin, and isotretinoin are most widely used[13]. In Japan, etretinate is the only oral retinoid approved on the market[203]. Retinoid acid metabolism blocking agents (RAMBAs), another class of retinoids, seemed efficacious in some clinical studies[204,205], but did not progress to market [204,205]. Oral retinoid therapy markedly benefits most ichthyosis patients, particularly those suffering from lamellar forms of ARCI, due to greater scaling. Patients with epidermolytic ichthyosis and Netherton syndrome may respond poorly to oral retinoids, with increased skin fragility and exacerbated tendency towards blistering and erythema. Some conditions, such as erythrokeratodermia variabilis et progressiva[206], are particularly responsive to oral retinoid therapy, though the cause is not known.

Unfortunately, there are no clinical trials that evaluate the best agent, efficacy, minimum age of initiation, optimal dose or long-term adverse effects[188]. In general, daily acitretin can adequately control the disease and reduced dosing for maintenance therapy is often sufficient. Some patients may benefit from discontinuous therapy[13]. For further information on this topic, the European clinical guidelines[13,14] and the North American consensus recommendations for its use in children and adolescents[207] can be consulted.

Oral retinoids have been associated with numerous potential adverse effects. Despite lacking controlled trials[188], many decades of treatment experience with oral retinoids exist, and their adverse effects are well-known[208,209]. They vary in frequency and severity and are usually dose-dependent. Common acute reversible adverse effects include cheilitis (inflammation of the lips), nasal dryness, xerosis (dry skin), hair loss, conjunctival irritation, and lipid and liver anomalies[207–209]. Chronic toxic effects primarily affect the skeletal system and consist of diffuse skeletal hyperostosis, that is, spurs and calcifications along the spine (usually anterior spinal ligament) and at tendon and ligament attachments around joints in adult patients, especially those undergoing long-term treatment[210]. In children, premature closure of the epiphysis has been reported, but only at very high cumulative dosages[207]. Oral retinoids are teratogenic, mandating thorough counselling and adequate contraception in individuals who can become pregnant. Effects on sperm or teratogenic potential has not been reported. Oral retinoids are lipophilic drugs that are slowly eliminated from the body; in particular, acitretin has the potential to persist in the body for a long time (especially with alcohol consumption)[211]; thus, pregnancy should be avoided during treatment and for at least 3 years after discontinuation[13]. Isotretinoin and alitretinoin have a shorter teratogenicity half-life than acitretin, with a one-month wash-out period required before pregnancy and are good therapeutic alternatives for those considering pregnancy[212,213]. Patients who receive oral retinoids need periodic laboratory tests, at a minimum liver enzymes and fasting lipid profile, and pregnancy testing in those of childbearing age[13,207]. The optimal periodicity of skeletal radiographic surveys in children is not well

established and should be tailored according to each patient[207]. The relationship between use of systemic retinoids and development of psychiatric symptoms is controversial and has not been examined in ichthyosis patients under therapy. Ichthyoses are chronic disorders, which in itself can contribute to psychiatric symptoms. It is wise, though, to monitor the development of such symptoms in these patients, particularly in those with depression, anxiety or other affective disorders and even provide co-management with a mental health provider[207].

Pathogenesis-based therapies

The cutaneous immunological profile in inherited ichthyosis has been described with polarization towards the Th17/IL-23 immunophenotype in all of the most common orphan forms of ichthyosis[163]. In addition, the same polarization to the Th17/IL23 pathway has been demonstrated by flow cytometry in blood cells, suggesting systemic immune activation[214]. As a result, biological drugs for psoriasis that block Th17/IL23 signaling have been repurposed as a therapeutic alternative[215]. The demonstrated value of ustekinumab for erythrokeratodermia with cardiomyopathy (EKC) syndrome, resulting from *DSP* variants and deficiency of functional desmoplakin, has led to dramatic improvement in the erythema, scaling, and pruritus of the disorder, as well as reversal of the cardiomyopathy[216,217]. Similarly, use of secukinumab[218] or ustekinumab[219] has been described in many patients with severe dermatitis-multiple allergies-metabolic wasting (SAM) syndrome, resulting from *DSG* variants and deficiency of functional desmoglein 1, to reverse the failure to thrive and recurrent infections, as well as improve the skin phenotype[218]. Although these biologics also improve scaling, the Th17/IL-23 polarization correlates best with skin erythema; thus, not surprisingly, biologics targeting Th17/IL-23 are most effective for erythrodermic forms, Netherton syndrome and forms of CIE (especially NIPAL4 and harlequin ichthyosis[220]), with dramatic anecdotal results shown in many affected individuals. However, a double-blind, randomized, placebo-controlled trial of secukinumab demonstrated responses in some, but not all, with Netherton syndrome and CIE, limited response in EI, and no responses for LI[221].

In general, Th2 signaling pathways are not activated in the ichthyoses; however, a subset of patients with the ichthyosis linearis circumflexa form of Netherton syndrome have shown increases in IL-4$^+$ or IL-13$^+$ memory CD4$^+$ T cells and Th2 cytokines[222], perhaps explaining the response of some patients with ichthyosis to dupilumab[223], which inhibits the IL-4 receptor and, therefore, IL-4/IL-13 signaling of type 2 immunity.

Special aspects of treatment

Regardless of the type of ichthyosis, many patients suffer from itching, recurrent infections, sweating impairment (hypohidrosis) with heat intolerance, and various ocular, auditory, and nutritional complications that should be periodically monitored. Evidence-based recommendations about the ideal timeframe for monitoring are lacking, so timing of visits should be tailored on an individual basis.

Pruritus

Pruritus is present in up to 93% of patients with ichthyosis and considerably affects patients' daily life[224]. Weather changes, a hot environment, and stressful situations exacerbate itch and its effects, including scratching, insomnia, moodiness, and loss of concentration. Although not formally assessed in clinical trials[188], antihistamines and antidepressants are of little value[14].The specific pathophysiology of pruritus in ichthyosis has not been systematically studied but might be related to skin inflammation[163]. Interestingly, therapy with several biologics, such as dupilumab[224,225], ustekinumab[216,226] and secukinumab[218], was efficacious in was efficacious in managing pruritus in different types of ichthyosis, but these findings remain to be validated in controlled trials.

Hypohidrosis

Hypohidrosis is a major problem, even in patients with mild disease. Sweating impairment increases patients' risk of heat stroke, so it is necessary to limit physical activity, particularly in warm weather. Patients should stay in a cool environment using air conditioning, fans, or other cooling devices. Sun exposure can improve some types of ichthyosis (IV and RXLI) but can worsen others. Although UV can lower inflammation, as observed in common chronic inflammatory disorders such as atopic dermatitis or psoriasis, it may also negatively affect the epidermal barrier[227]. Heat, heat-induced sweating and heat intolerance are poorly tolerated and sun protection creams difficult to apply, so the net effect of sun exposure may vary from case to case.

Ocular complications

Ocular complications are common in all types of ichthyosis. Desquamation and tightness of the eyelids, conjunctivitis and eyelash anomalies can eventually lead to corneal damage[228]. The primary goal of eye care with frequent prophylactic ocular lubrication is to maintain the integrity of the ocular surface, particularly at night when ectropion prevents the eyelids from fully closing, leading to ocular exposure. Topical tazarotene [194] and hyaluronic acid injections[229] have been successfully used to treat ectropion in ichthyosis patients. Surgical management of eyelid ectropion is often disappointing, and recurrences are common[230].

Auditory complications

Excessive desquamation within the external auditory canal promotes plugging of the ears and predisposes patients to conductive hearing loss and recurrent infections of the external and middle ear that may lead to permanent eardrum damage[231]. Hearing loss may have implications early on in communication, auditory processing, language development, educational progress and achievement, and psychosocial and cognitive development[232]. Thus, early intervention and regular follow-up by an otolaryngologist is needed. Ear pruritus and pain are also important complaints of ichthyosis in all age groups. The causes vary from mere desquamation of the external ear canal to different degrees of otitis (middle ear infection) and should be managed on an individualized basis.

Nutritional problems and growth

The impaired epidermal barrier and skin inflammation increase caloric need, and growth retardation is commonly associated with children suffering from congenital forms of ichthyosis[14]. A prospective observational study in 50 children with ichthyosis emphasized the risk of malnutrition in this age group, particularly in the most severely affected and younger patients[233]. Rickets have been described in many patients and incidental observations suggest that high doses of vitamin D may improve clinical presentation, though these data remain to be validated[234]. Regular monitoring of clinical, biochemical, hormonal, and nutritional parameters is recommended to provide adequate vitamin D and micronutrient supplementation according to the degree of deficiency.

Recurrent skin infections

Impaired epidermal barrier promotes bacterial, viral and fungal colonization and infection. Despite the lack of systematic microbiome studies in this group of patients, microbial colonization is often recognized by a characteristic (and often unpleasant) smell in patients with a prominent thickening of the skin (hyperkeratosis) similar to epidermolytic ichthyosis. Although the exact incidence of infections in ichthyosis patients is unknown, some forms such as epidermolytic ichthyosis, Netherton syndrome, and keratitis-ichthyosis-deafness syndrome are particularly prone to recurrent infections that can be easily overlooked in the context of an ichthyotic skin[14]. In cases of suspicion, microbiological culture and antibiogram should be routinely performed to provide adequate topical or systemic therapy. Recurrent episodes of sepsis are particularly common in babies with Netherton syndrome or desmosomal disorders due their severe skin barrier impairment, putting these patients at risk of death.

Quality of life

Quality of life (QoL) varies greatly due to the heterogeneity of ichthyosis subtypes, with severe phenotypes correlating with decreased QoL[42,43]. Further analysis using the Dermatology Life Quality Index (DLQI) questionnaire on six areas of patients' lives ("symptoms and feelings", "daily activities", "leisure", "work", "personal relationships" and "treatment") in France found DLQI scores of >10 (a severe or very severe effect) in 31% of patients[235]. This QoL decrease is associated with patient disease burden due to heat intolerance, pruritus, recurrent skin infections and mobility-limiting palmoplantar keratoderma, which is invariably present in patients with KRT1 pathogenic variants[173]. The factors that most affect QoL are cutaneous pain, pruritus, and scaling, in that order[235]. In addition, multivariate analysis revealed that females scored higher on average in their DLQI scores[235]. Although gender differences have not been studied in depth, women may suffer a greater decrease in QoL due to exigent societal beauty standards[236]. A cross-sectional questionnaire survey of ichthyosis patients revealed that 93% had pruritus, and itching was often or always present in 63%[224]. Pruritus is, therefore, one of the most important concerns for ichthyosis patients, and was most severe in patients with Netherton syndrome[224].

Additionally, in a French national survey on the disease burden of ichthyosis, patients and parents of affected children reported a major effect on their domestic life due to time spent on additional housework, such as vacuuming, changing bed sheets, and skin care[237], especially for those with severe forms[237]. The patients also reported financial burdens, with substantial out-of-pocket expenses, mainly due to the cost of emollients[237]. Younger patients reported a feeling of rejection from classmates at school, and adult patients reported workplace discrimination that had affected their career decisions[237]. Furthermore, more than one-third of patients reported considerable restrictions on sports and leisure, especially swimming pool activities[237].

A final, but important effect of ichthyosis on QoL is psychological. Patients reported that the disease affects both their self-image and interpersonal relationships, largely due to the high visibility of the affected skin[238]. Specifically, patients reported various reactions from others, including staring, tactlessness and inquisitiveness. Concerning intimate relations, patients were afraid of reactions of repulsion and the disease burden posed an obstacle to the continuation of relationships[238]. Regarding self-image, patients reported various negative feelings, such as sadness, discouragement, loneliness and anger[238], which can lead to an increased risk of anxiety and depression[239]. Thus, ideally, psychological support should be provided not only by a psychologist, but also by other healthcare providers including dermatologists and specialist nurses, throughout life, for children, adults and family members[13,14]. During the neonatal and infantile periods, close parent-child physical contact is

important[13,14]. For the psychological management, family therapy, patient or family group interviews, and educational intervention such as 'ichthyosis school' (self-management programs focused on providing patients with the knowledge and skills to solve problems they may encounter) are helpful[13,14]. Patients and their family members should be given sufficient information about the activities of national patient support groups, which exist in many countries[13,14]. Testimonials from patients and caregivers are provided in Box 2 and Box3.

Outlook

In the short term of ichthyosis management, there is a critical need for multidisciplinary teams to provide adequate care. Ophthalmologists, ear, nose and throat specialists, and nutritionists are particularly important in children with both syndromic and non-syndromic ichthyoses. Patients with extracutaneous manifestations need specialists according to the organs involved (neurologists, gastroenterologists, nutritionists in those with diseases affecting lipid metabolism, such as neutral lipid storage disease with ichthyosis, as well as those that need diet supplementation). Certain neurometabolic disorders, such as X-linked ichthyosis, commonly present with attention deficit disorder and hyperactivity, requiring psychologists[240]. Finally, some studies have shown that physiotherapy decreases symptom severity and improves overall quality of life[241].

Long term management involves the development of new, curative treatments for ichthyosis patients. The past decades have witnessed dramatic advances in our understanding of the pathobiology and clinical manifestations of ichthyoses, with exciting implications for the development of innovative approaches to the treatment of these conditions. However, outstanding questions remain.

Despite great progress made thanks to the advent of new technologies (such as exome sequencing) in the deciphering of the molecular etiology of inherited ichthyoses, the genetic basis remains elusive in some patients[171,242–249]. It is likely that atypical cases may result from complex interactions with modifier traits that alter the phenotypic manifestations. These effects may aggravate[250] (as shown with the combination of mutations in both *STS* (recessive X-linked ichthyosis) and *FLG* (ichthyosis vulgaris))[250] or attenuate[251] (combination of variants in *ALOX3E*, leading to mild CIE suppressing the effect of the *TGM5* variant/acral peeling skin syndrome)[251] the observed phenotype. Novel technologies and bioinformatics tools may be needed to identify other genetic defects causing disorders of cornification, which may occasionally be localized in non-coding regions of the genome[252] or result from epigenetic changes[253].

In addition, understanding the mechanism of disease is leading to pathogenesis-based therapy, both curative and pharmacologic gene therapy, and therapies targeting pathways that lead to the increased scaling and inflammation related to the primary barrier impairment[215]. Replacement therapy, which has the aim of supplying exogenous proteins or lipids to correct the metabolic deficiencies in some ichthyoses, is being assessed to replenish transglutaminase 1 in lamellar ichthyosis[254]. Lipid replacement therapy with topically applied cholesterol in disorders of cholesterol biosynthesis (forms of porokeratosis, congenital hemidysplasia with ichthyosis and limb defects/CHILD syndrome) did not repair the defect. However, the topically applied combination of a statin and cholesterol (typically 2% lovastatin/2% cholesterol) to both replenish cholesterol and block the accumulation of toxic metabolites has led to marked improvement in patients with CHILD syndrome[255,256] and porokeratoses[257]. Lipid replacement therapy is also being considered for the many forms of CIE that alter ceramide biosynthesis.

Treatment strategies targeting the underlying genetic mutations that cause ichthyoses are still few and experimental. To date, a few somatic gene therapy approaches, aimed at correcting the causal genetic defect in the skin, have been tested in clinical trials[258] These clinical trials include one based on topical delivery of an inactivated herpes simplex virus 1 transduced with copies of *TGM1* for treatment of lamellar ichthyosis[259], and another using autologous epidermal sheets produced from genetically modified keratinocytes for treatment of Netherton syndrome[260]. A number of other treatments are in in vitro and in vivo stages: retroviral systems for transglutaminase 1 (ARCI) and steroid sulfatase (X-linked ichthyosis) expression[258], non-viral systems for *ABCA12* (ARCI) and *ALDH3A2* (Sjögren-Larsson syndrome) delivery[258], nucleases for mutant *KRT1* and *KRT10* (keratinopathic ichthyoses) mRNA degradation[258], and gene therapy aimed at correcting *TGM1* (ARCI) defects in the embryo using modified CRPISPR/Cas9 prime editing**.** Additional targeted therapies include transglutaminase 1 enzyme replacement therapy for treating ARCI[261,262] and corneodesmosin protein replacement therapy for treating peeling skin syndrome[263].

Also in development are inhibitors of downstream effects of the genetic changes, patterned after the topical blockade of cholesterol biosynthesis with statins and replenishment of cholesterol as a way to treat disorders of cornification that result from deficiency of enzymes of cholesterol synthesis, as occurs in CHILD syndrome[256] and porokeratosis[257]. Specifically, several companies are developing new therapeutics to inhibit the increase in kallikreins that are implicated in the features of Netherton syndrome[264,265] and efforts are ongoing to supplement the deficient esterified omega-hydroxy ceramides of CIE[266]. Additionally, retinoic acid metabolism blocking agents, which inhibit endogenous CYP450-mediated retinoid degradation, are being developed as an alternative to oral retinoids[205,267]. These new developments in the understanding of ichthyosis highlight the crucial importance of a close

and bilateral dialogue between molecular genetics and clinical practice for accurate diagnosis, prevention and treatment of inherited ichthyoses. The ever-expanding knowledge of the molecular causes will likely be most beneficial in the management of this disease. Some new therapies are being tested, but the next challenge will be to use our knowledge of ichthyosis and the constant improvement of genome editing technology to develop therapeutics targeted at the underlying molecular defects and curative treatments that go beyond managing symptoms.

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Highlighted references

"Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorze 2009"[1].
This publication delivers a general overview of the disease and the first classification of the many forms of ichthyosis that remains the basis upon which all proposed classifications are built.

"Anatomy and Physiology of the Skin"[4].
This publication describes an overview of the skin structure

"Epidermal structure and differentiation"[8].
This paper provides an in depth view of keratinocyte differentiation and its critical role in epidermal formation.

"Prevalence of inherited ichthyosis in France: a study using capture-recapture method"[34].
This paper presents an in-depth epidemiological studies on the rare forms of ichthyosis.

"Bricks and mortar of the epidermal barrier"[10].
This publication describes th brick and mortar molecular model of the stratum corneum.

"Cellular and Metabolic Basis for the Ichthyotic Phenotype in NIPAL4 (Ichthyin)–Deficient Canines"[67].
This paper presents research into the metabolic causes of ichthyosis, its supplementary figures provide a clear overview of the ceramide pathway that became the basis for FIG. 2.

"From glycosylation disorders to dolichol biosynthesis defects: a new class of metabolic diseases"[111].
This paper presents an overview of the disorders of glycosylation, the dolichol pathway and its connection to cholesterol synthesis, which became the basis for FIG. 3.

"Proposal for a 6-step approach for differential diagnosis of neonatal erythroderma"[174].
This publication provides a diagnostic approach to ichthyosis in newborns.

"Current Strategies for the Gene Therapy of Autosomal Recessive Congenital Ichthyosis and Other Types of Inherited Ichthyosis"[258].
This review discusses the treatment of ichthyosis with an emphasis on novel gene therapy studies.

"Factors Associated with Impaired Quality of Life in Adult Patients Suffering from Ichthyosis"[235].
This publication reports statistical analysis of the factors affecting quality of life in ichthyosis patients.

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Competing interests

The authors declare the following competing interests:

- Carlos Gutiérrez-Cerrajero, Eli Sprecher, Masashi Akiyama, and Rogelio González-Sarmiento have no competing interests.

- Amy Paller: AbbVie, AnaptysBio, Eli Lilly, Incyte, Janssen, Krystal Biotech, Regeneron Pharmaceuticals Inc., UCB – investigator; AbbVie, Acrotech, Almirall, Amgen, Amryt Pharma, Arcutis Biotherapeutics, Arena Pharmaceuticals, Azitra, BioCryst, BiomX, BMS, BridgeBio, Castle Creek Biosciences, Catawba Research, Eli Lilly, Exicure, Gilead, Incyte, Janssen, Johnson & Johnson, Kamari Pharma, LEO Pharma, Novartis, OM Pharma, Pfizer, Pierre Fabre, RAPT Therapeutics, Regeneron Pharmaceuticals Inc., Sanofi, Seanergy, UCB – consultant with honorarium; AbbVie, Abeona Therapeutics, Bausch Health, Galderma, Novan – data and safety monitoring board

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Author contributions

Introduction (AH-M, CG-C, RG-S); Epidemiology (AH-M, CG-C, ES, RG-S); Mechanisms/pathophysiology (CG-C, ES, MA, RG-S); Diagnosis/screening/prevention (AH-M, CG-C, ES, AP, RG-S); Management (AH-M, ES, AP, MA, JM-H); Quality of life (AH-M, CG-C, ES, AP); Outlook (AH-M, CG-C, RG-S); Overview of the Primer (A-M).

Tables

Table 1. Incidence of the rare forms of ichthyosis

Disease	Incidence (per million)		
	Spain	France	Japan
Non-syndromic ichthyoses			
Lamellar ichthyosis (LI)	4.47[33]	4.50[34]	0.23[35]
Congenital ichthyosiform erythroderma (CIE)	2.18[33]	1.90[34]	0.75[35]
Harlequin ichthyosis (HI)	0.05[33]	NA	0.12[35]
Bathing suit ichthyosis (BSI)	0.10[33]	0.46[34]	NA
Self-healing collodion baby (SHCB)	0.30[33]	0.11[34]	NA
Acral self-healing collodion baby (acral SHCB)	0.05[33]	NA	NA
Keratinopathic ichthyoses	NA	1.1[34]	0.43[268]
Erythrokeratodermia variabilis et progressiva (EKVP)	NA	0.46[34]	NA
Peeling skin syndrome (PSS)	NA	0.11[34]	NA
Keratosis linearis-ichthyosis congenita-sclerosing keratoderma syndrome (KLICK)	NA	0.23[34]	NA
Syndromic ichthyoses			
Total	NA	1.9[34]	0.67[35]
Syndromic recessive x-linked ichthyosis (syndromic RXLI)	NA	0.11[34]	NA
Chondrodysplasia punctata type 2 (CDPX2)	NA	0.23[34]	NA
Netherton syndrome (NS)	NA	0.80[34]	NA
Trichothiodystrophy (TTD)	NA	0.23[34]	NA
Sjögren-Larsson syndrome (SLS)	NA	0.11[34]	NA
Keratitis-ichthyosis-deafness syndrome (KID)	NA	0.34[34]	NA
Neutral lipid storage disease with ichthyosis (NLSDI)	NA	0.11[34]	NA

NA, not available.

1497 **Table 2. Molecular classification of the ichthyoses**

Affected component	Disease	Genes
Intracellular protein network		
Keratins	**Autosomal dominant epidermolytic ichthyosis (EI, ORPHA: 312)**	*KRT1*[53] (AD, MIM: 113800), *KRT10*[53] (AD, MIM: 113800)
	Autosomal recessive epidermolytic ichthyosis (AREI, ORPHA: 512103)	*KRT10*[269] (AR, MIM: 113800))
	Superficial epidermolytic ichthyosis (SEI, ORPHA: 455)	*KRT2*[54] (AD, MIM: 146800)
	Annular epidermolytic ichthyosis (AEI, ORPHA: 281139)	*KRT1*[270] (AD, MIM: 607602), *KRT10*[271] (AD, MIM: 607602)
	Epidermolytic nevus (EN, ORPHA: 497737)	*KRT1*[272] (M, MIM: -), *KRT10*[273] (M, MIM: -), *KRT2*[274] (M, MIM: -)
	Ichthyosis Curth-Macklin (ICM, ORPHA: 79503)	*KRT1*[275] (AD, MIM: 146590)
	Ichthyosis with confetti (IWC, ORPHA: 281190)	*KRT1*[276] (AD, MIM: 609165), *KRT10*[277] (AD, MIM: 609165)
Filaggrin	**Ichthyosis vulgaris (IV, ORPHA: -)**	*FLG*[55] (SD, MIM: 146700), *CASP14*[57] (AR, MIM: 617320), *ASPRV1*[59] (AD, MIM: 146750)
	Keratosis linearis-ichthyosis congenita-sclerosing keratoderma syndrome (KLICK, ORPHA: 281201)	*POMP*[60] (AR, MIM: 601952)
Cornified envelope	**Loricrin keratoderma (LK, ORPHA: 79395)**	*LORICRIN*[9] (AD, MIM: 604117)
Lipid metabolism		
Ceramides	**Lamellar ichthyosis (LI, ORPHA: 313)**	*ABCA12*[90] (AR, MIM: 601277), *ALOX12B*[278] (AR, MIM: 242100), *ALOXE3*[279] (AR, MIM: 606545), *CYP4F22*[68] (AR, MIM: 604777), *LIPN*[85] (AR, MIM: 613943), *NIPAL4*[83] (AR, MIM: 612281), *SDR9C7*[94] (AR, MIM: 617574), *SULT2B1*[103] (AR, MIM: 617571), *TGM1*[95] (AR, MIM: 242300)
	Congenital non-bullous ichthyosiform erythroderma (CIE, ORPHA: 79394)	*ABCA12*[167] (AR, MIM: 601277), *ALOX12B*[93] (AR, MIM: 242100), *ALOXE3*[93] (AR, MIM: 606545), *CERS3*[82] (AR, MIM: 615023), *CYP4F22*[44] (AR, MIM: 604777), *NIPAL4*[83] (AR, MIM: 612281), *PNPLA1*[87] (AR, MIM: 615024), *TGM1*[280] (AR, MIM: 242300)
	Harlequin ichthyosis (HI, ORPHA: 457)	*ABCA12*[281] (AR, MIM: 242500)
	Self-healing collodion baby (SHCB, ORPHA: 281122)	*ALOX12B*[282] (AR, MIM: 242100), *ALOXE3*[283] (AR, MIM: 606545), *CYP4F22*[284] (AR, MIM: 604777), *TGM1*[285] (AR, MIM: 242300)
	Acral self-healing collodion baby (ASHCB, ORPHA: 281127)	*TGM1*[286] (AR, MIM: 242300)
	Bathing suit ichthyosis (BSI, ORPHA: 100976)	*TGM1*[287] (AR, MIM: 242300)
	Sjögren-Larsson syndrome (SLS, ORPHA: 816)	*ALDH3A2*[64] (AR, MIM: 270200)
	Refsum disease (ORPHA: 773)	*PEX7*[74] (AR, MIM: 308100), *PHYH*[72,73] (AR, MIM: 266500)
	Ichthyotic keratoderma-spastic paraplegia-hypomyelination-dysmorphic facies (ORPHA: -)	*ELOVL1*[65] (AD, MIM: 618527)
	Congenital ichthyosis-intellectual disability-spastic quadriplegia syndrome (ORPHA: 352333)	*ELOVL4*[66] (AR, MIM: 614457)
	Fetal Gaucher disease (FGD, ORPHA: 85212)	*GBA1*[91] (AR, MIM: 608013)
	Neu-Laxova syndrome (NLS, ORPHA: 2671)	*PHGDH*[77] (AR, MIM: 256520), *PSAT1*[78] (AR, MIM: 616038), *PSPH*[76] (AR, MIM: -)
	Deficiency of UDP-glucose ceramide glycosyltransferase (ORPHA: -)	*UGCG*[89] (AR, MIM: -)
	Neutral lipid storage disease with ichthyosis (NLSDI, ORPHA: 98907)	*ABHD5*[86] (AR, MIM: 275630)

	Ichthyosis-prematurity syndrome (IPS, ORPHA: 88621)	*SLC27A4*[70] (AR, MIM: 608649)
	Ichthyosis-short stature-brachydactyly-microspherophakia syndrome (ORPHA: 363992)	*CERS3*[82] + *ADAMTS17*[82] (HD, MIM: -)
	Palmoplantar and perianal keratoderma/harlequin ichthyosis-like ichthyosis with thrombocytopenia (ORPHA: -)	*KDSR*[288] (MIM: -)
Cholesterol	**Recessive X-linked ichthyosis (RXLI, ORPHA: 461)**	*STS*[105] (AR, MIM: 308100)
	Syndromic recessive X-linked ichthyosis (Syndromic RXLI, ORPHA: 281090 and ORPHA: 1643[289]**)**	*STS*[170] (HD, MIM: 308100) + contiguous genes
	Ichthyosis follicularis-alopecia-photophobia syndrome (IFAP, ORPHA: 2273)	*MBTPS2*[99] (XR, MIM: 308205), *SREBF1*[100] (XD, MIM: 619016)
	Chondrodysplasia punctata type 2 (CDPX2, ORPHA: 35173)	*EBP*[102] (XD, MIM: 302960)
	Male EBP disorder with neurological defects (MEND, ORPHA: 401973)	*EBP*[290] (XR, MIM: 300960)
	Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD, ORPHA: 139)	*NSDHL*[101] (XD, MIM: 308050)
	Multiple sulfatase deficiency (MSD, ORPHA: 585)	*SUMF1*[106] (AR, MIM: 272200)
Lamellar bodies	**Autosomal recessive keratoderma-ichthyosis-deafness (ARKID, ORPHA: -)**	*VPS33B*[291] (AR, -)
	Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma syndrome (CEDNIK, ORPHA: 66631)	*SNAP29*[108] (AR, MIM: 609528
	Arthrogryposis-renal dysfunction-cholestasis syndrome (ARC, ORPHA: 2697)	*VIPAS39*[109] (AR, MIM: 613404), *VPS33B*[110] (AR, MIM: 208085)
Dolichol	**Congenital disorder of glycosylation type 1F (CDG-1F, ORPHA: 79323)**	*MPDU1*[114] (AR, MIM: 609180)
	Congenital disorder of glycosylation type 1M (CDG-1M, ORPHA: 91131)	*DOLK*[113] (AR, MIM: 610768)
	Congenital disorder of glycosylation type 1Q (CDG-1Q, ORPHA: 324737)	*SRD5A3*[112] (AR, MIM: 612379)
	Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation, and ear anomalies syndrome (CHIME, ORPHA: 3474)	*PIGL*[115] (AR, MIM: 280000)
Intercellular junctions		
Tight junctions	**Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis (ILVASC, ORPHA: 59303)**	*CLDN1*[117] (AR, MIM: 607626)
	Hypohidrosis-electrolyte imbalance-lacrimal gland dysfunction-ichthyosis-xerostomia syndrome (HELIX, ORPHA: 528105)	*CLDN10*[118] (AR, MIM: 617671)
Desmosomes	**Severe dermatitis-multiple allergies-metabolic wasting syndrome (SAM, ORPHA: 369992)**	*DSG1*[124] (AR, MIM: 615508), *DSP*[125] (AD, MIM: -)
	Erythrokeratodermia-cardiomyopathy syndrome (EKC, ORPHA: 476096)	*DSP* (AD[158] or AR[292], MIM: 605676)
	Generalized peeling skin syndrome (generalized PSS, ORPHA: 263543)	*CDSN*[126] (AR, MIM: 270300), *FLG2*[134] (AR, MIM: 618084)
Proteases	**Netherton syndrome (NS, ORPHA: 634)**	*SPINK5*[130] (AR, MIM: 256500)

	Peeling skin-leukonychia-acral punctate keratoses-cheilitis-knuckle pads syndrome (PLACK, ORPHA: 289586)	*CAST*[132] (AR, MIM: 616295)
	Exfoliative ichthyosis (ORPHA: 289586)	*CSTA*[133] (AR, MIM: 607936), *SERPINB8*[129] (AR, MIM: 617115)
Others		
	Trichothiodystrophy (TTD, ORPHA: 33364)	DNA damage repair, transcription, and translation: *AARS1*[143] (AR, MIM: 619691), *ERCC2*[136] (AR, MIM: 601675), *ERCC3*[137] (AR, MIM: 616390), *GTF2E2*[139] (AR, MIM: 616943), *GTF2H5*[138] (AR, MIM: 616395), *MAARS1*[143] (AR, MIM: 619692), *MPLKIP*[151] (AR, MIM: 234050), *RNF113A*[140] (XR, MIM: 300953), *TARS1*[144] (AR, MIM: 618546)
	Mental disability-enteropathy-deafness-peripheral neuropathy-ichthyosis-keratodermia syndrome (MEDNIK, ORPHA: 171851)	Clathrin-coated vesicle adaptor complex: *AP1S1*[148] (AR, MIM: 609313)
	Keratitis-ichthyosis-deafness- autosomal recessive syndrome (KIDAR, ORPHA: -)	Clathrin-coated vesicle adaptor complex: *AP1B1*[149] (AR, MIM: 242150)
Multiple functions		
	Ichthyosis-hypotrichosis syndrome (IHS, ORPHA: 91132)	Filaggrin maturation and corneodesmosome degradation: *ST14*[128] (AR, MIM: 602400)
	Acral peeling skin syndrome (acral PSS, ORPHA: 263534)	Protease inhibitor: *CSTA*[293] (AR, MIM: 607936) Cornified envelope cross-linking: *TGM5*[61] (AR, MIM: 609796)
	Erythrokeratoderma variabilis et progressiva (EKVP, ORPHA: 308166)	Gap junctions: *GJA1*[119] (AD, MIM: 617525), *GJB3*[121] (AD or AR, MIM: 133200), *GJB4*[122] (AD, MIM: 617524) Desmosomes: *PERP*[127] (AR, MIM: 619209) Ceramides: *KDSR*[79] (AR, MIM: 617526) Ca^{2+} channels: *TRPM4*[150] (AD, MIM: 618531)
	Keratitis-ichthyosis-deafness syndrome (KID, ORPHA: 477)	Gap junctions: *GJB2* (AD[120] or M[294], MIM: 148210), *GJB6*[123] (AD, MIM: -) Clathrin-coated vesicle adaptor complex: *AP1B1*[295] (AR, MIM: 242150)

ORPHA, disease code in the ORPHANET database; MIM, phenotype code in the OMIM database; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; XD, X-linked dominant inheritance; XR, X-linked recessive inheritance; HD, homozygous deletion; M, mosaicism.

Figures

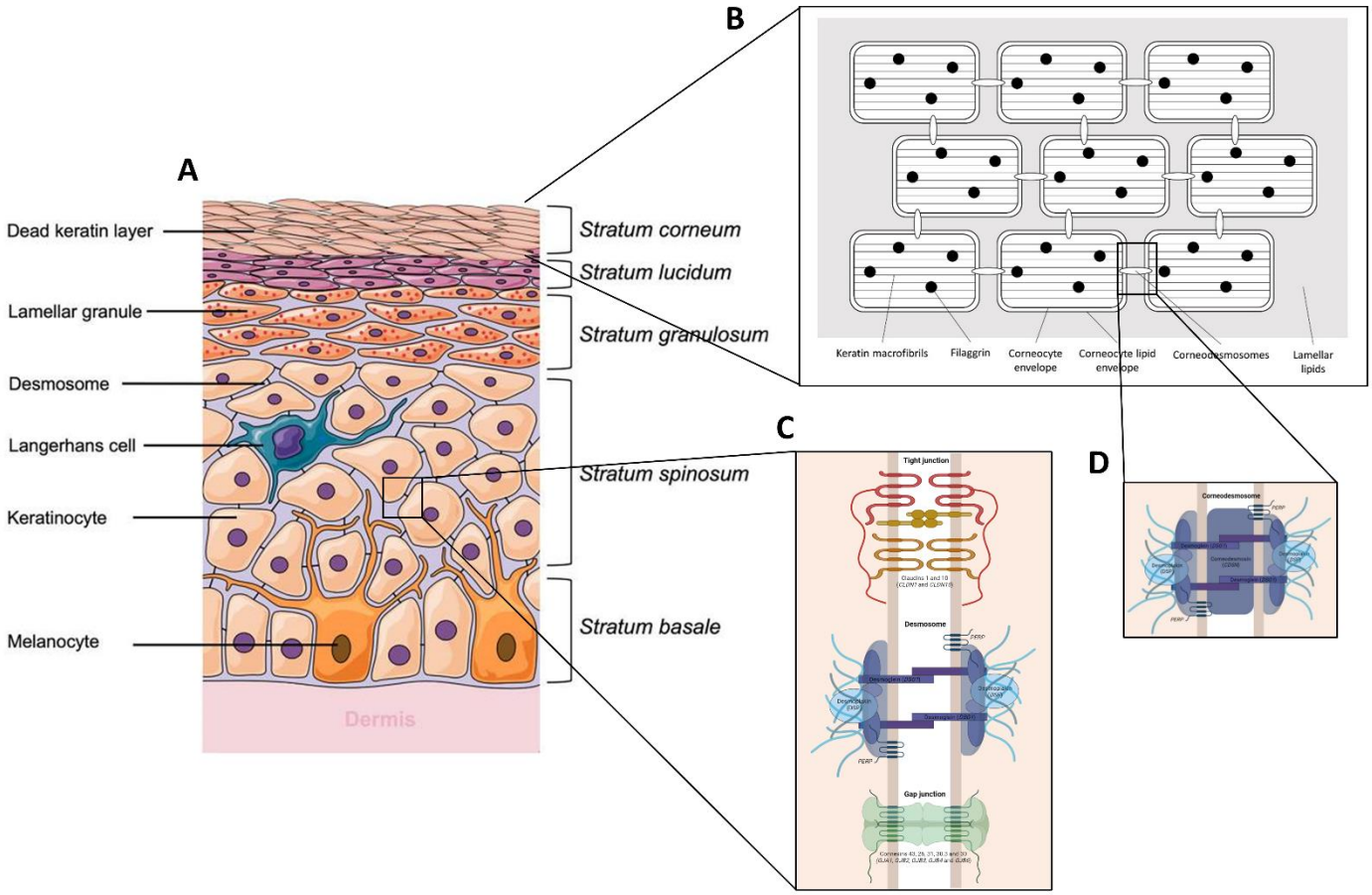
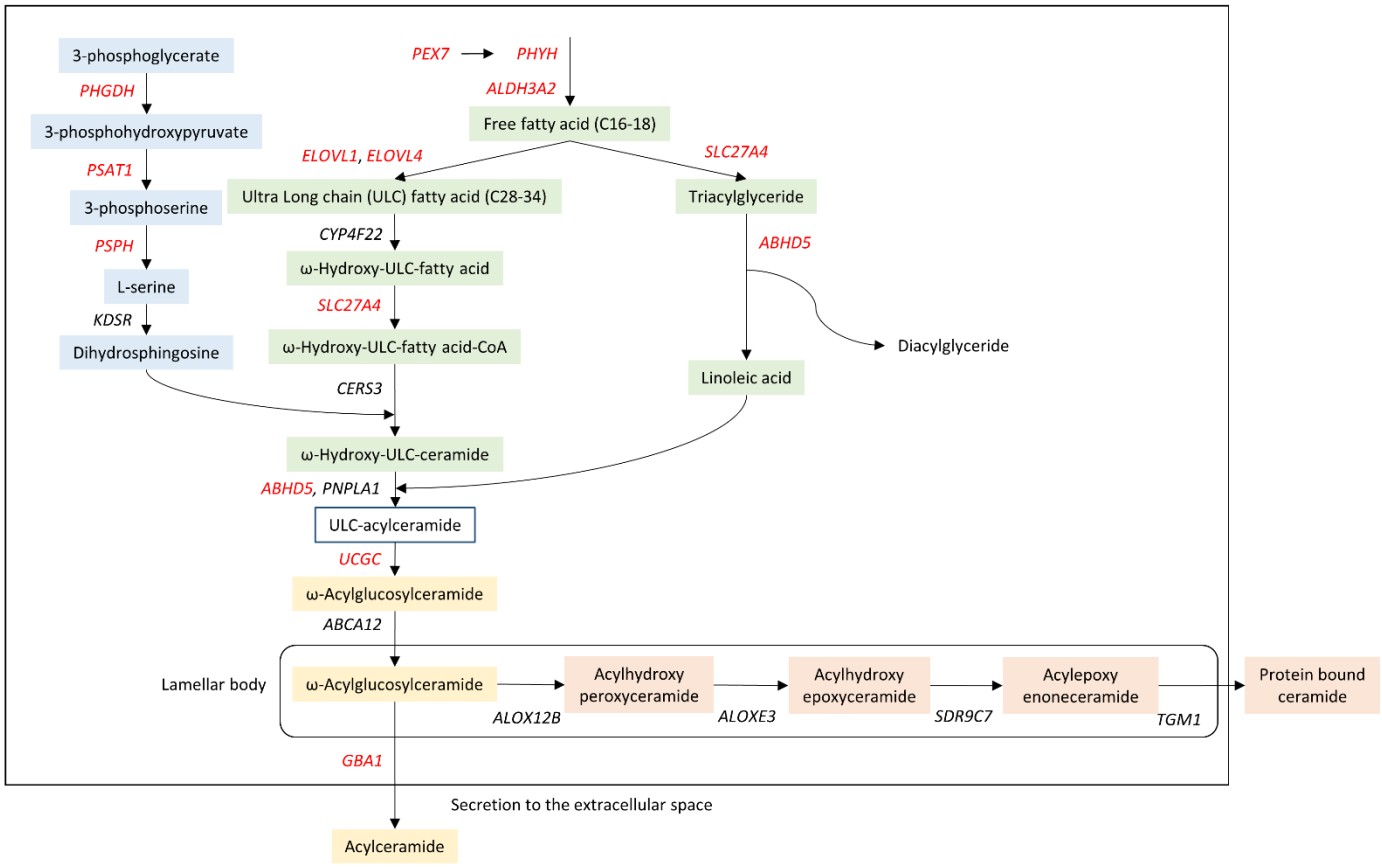


Figure 1. Structure of the epidermis

The epidermis is divided into layers that reflect the stages of keratinocyte differentiation; keratinocytes are the most common cell type found in the epidermis. The stem cells of the stratum basale (called basal cells divide asymmetrically and some of the daughter cells migrate towards the skin surface, passing through the stratum spinosum and stratum granulosum, differentiating along the way. The end product of this process is the stratum corneum, a layer comprising the terminally differentiated and enucleated keratinocytes (called corneocytes) embedded in a lipidic extracellular matrix. Most of these layers are constant throughout the skin but the stratum lucidum is exclusive to areas of thickened skin, such as the ones found in the palms of the hands and soles of the feet. Melanin-producing melanocytes and tissue-resident macrophages (Langerhans cells) contribute to protection from ultraviolet light and infections, respectively. In the stratum corneum, most of the corneocyte cytoplasm is occupied by keratin macrofibrils and filaggrin. These 'bricks' are encased by the cornified envelope, with its covalently-bound lipid layer (the corneocyte lipid envelope). The whole structure is embedded into the intercellular lamellar lipids, the ‘mortar’ of the structure. Desmosomes maintain epithelial cohesion, gap junctions facilitate intercellular communication, and tight junctions restrict extracellular solute diffusion. Corneodesmosomes are specialized desmosomes exclusive to the stratum corneum that confer its increased mechanical resilience. Mutations in the genes annotated lead to specific forms of ichthyosis.



1518

1519 **Figure 2. Ceramide pathway in the epidermis**

1520 Ceramides are important in forming the corneocyte lipid envelope in the upper layer of the epidermis and
1521 as free lipids in the extracellular space. A series of reactions leads from ceramide synthesis from a sphingoid
1522 base (blue) and a fatty acid (green) to ceramide fate as a free (grey) or protein-bound lipid (green). Defects in
1523 the depicted genes lead to ichthyosis (the genes in red cause symptoms outside the skin).

1524

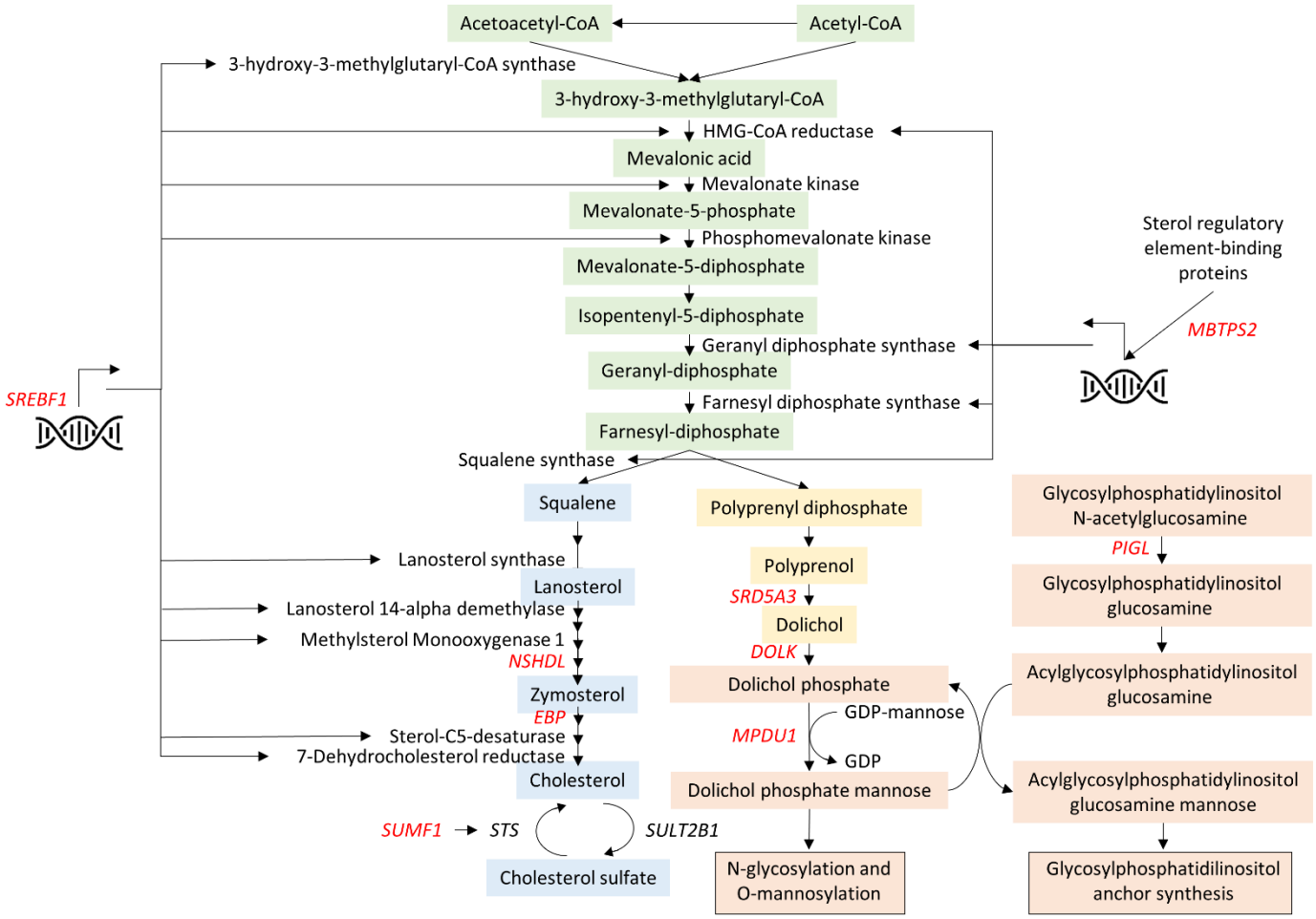


Figure 3. Cholesterol and dolichol synthesis pathways in the epidermis

Cholesterol and dolichol are synthesized from a common precursor (grey) before diverging into cholesterol-specific (green) and dolichol-specific (blue) reactions. Free cholesterol is an important component of the extracellular space in the uppermost layer of the epidermis, whereas cholesterol sulfate inhibits ceramide crosslinking to the corneocyte lipid envelope. Dolichol is necessary for protein N-glycosylation, O-mannosylation and synthesis of glycosylphosphatidylinositol anchors to the plasma membrane (orange). Defects in the depicted genes lead to ichthyosis (the genes in red cause defects outside the skin).

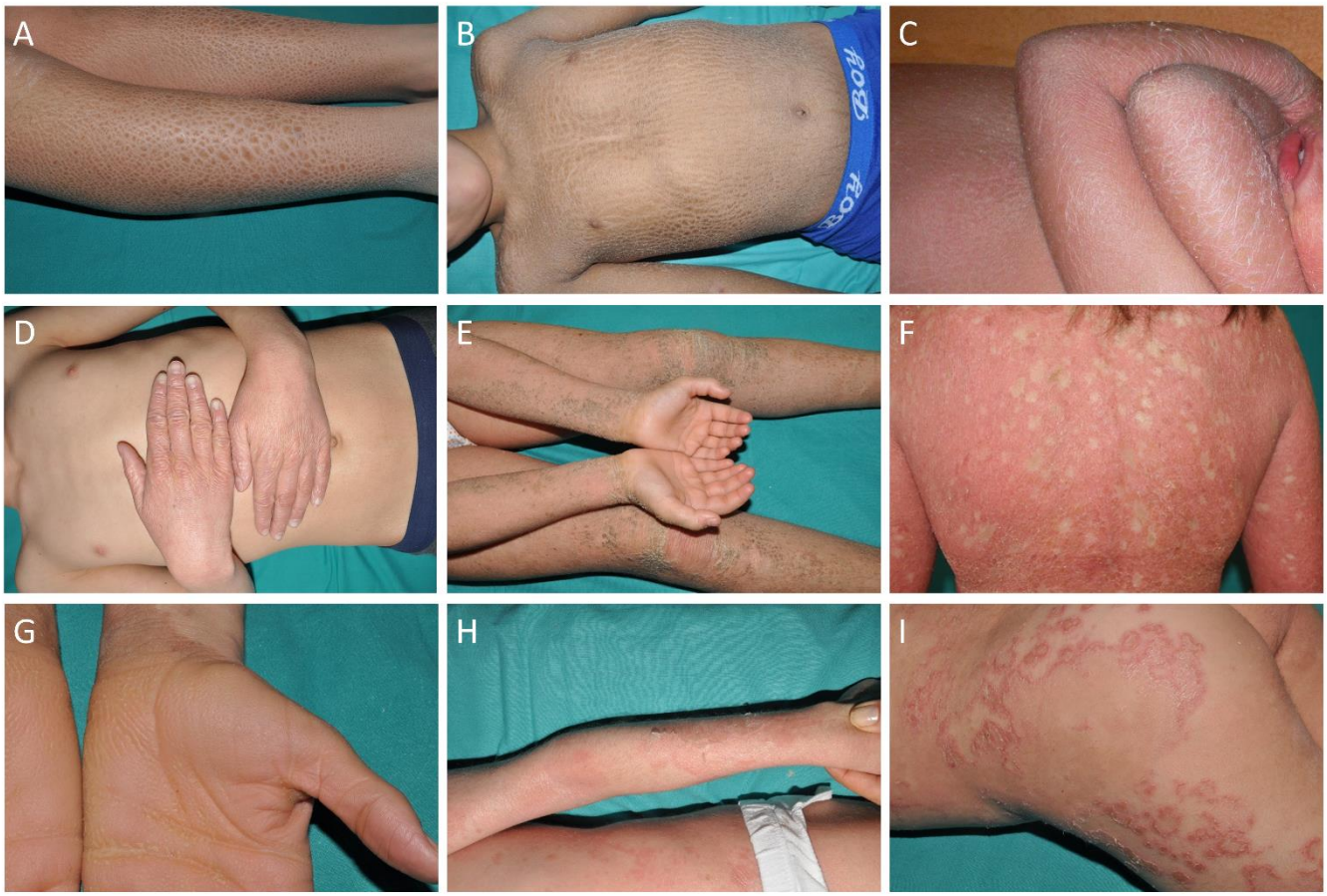
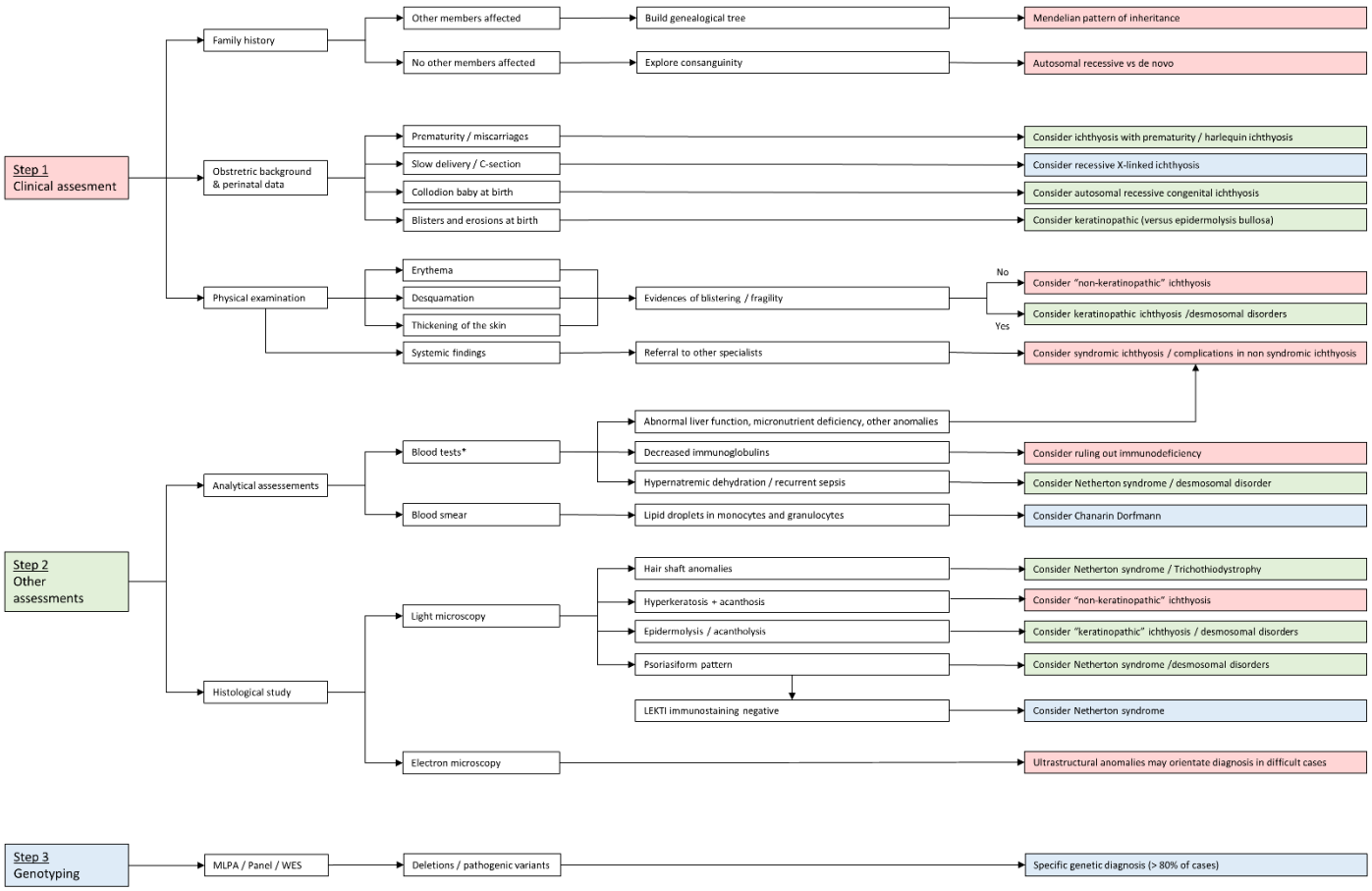


Figure 4. Symptomatic presentation of the ichthyoses

(A) Recessive X-linked ichthyosis presenting with dark polygonal scales on the extensor aspects of the legs. (B) Autosomal recessive congenital ichthyosis (ARCI) (Lamellar ichthyosis) patient of North African origin presenting with a darker brownish tone of the coarse and large (plate-like) scales on the anterior trunk. (C) ARCI (Congenital ichthyosiform erythroderma) presenting with generalized fine scaling on the upper extremities and anterior trunk over a moderate underlying erythema. (D) Self-improving ARCI with thickness on the dorsal hands as the only visible sign of congenital ichthyosis. (E) *KRT10*-related epidermolytic ichthyosis displaying pronounced hyperkeratosis on the upper and lower limbs sparing palms. (F) Ichthyosis with confetti, a severe ichthyosiform displaying erythroderma with patchy areas of normal skin on the upper posterior trunk. (G) Loricrin keratoderma showing diffuse palmar keratoderma with honeycomb pattern. (H) Peeling skin type B presenting with diffuse erythroderma with patchy areas of superficial desquamation on the left upper limb. (I) Netherton syndrome with double-edged scales (ichthyosis linearis circumflexa) on the buttock and thigh.



*Blood tests include: complete blood cell count, electrolytes, liver function test, urine, creatinine, immunoglobulins, immnunophenotype

Figure 5. Decision tree for the diagnosis of ichthyosis

Schematic representation of the workflow used for differential diagnosis of ichthyosis in a patient. The colored boxes represent the information gleaned from the diagnostic tests and clinical characteristics: red boxes are not conclusive (they discard a few diseases or point to a large group of diseases), green boxes are mostly conclusive (they point towards a small group of diseases), and blue boxes point towards a single disease. WES, whole exome sequencing; MLPA, multiplex ligation dependent probe amplification.

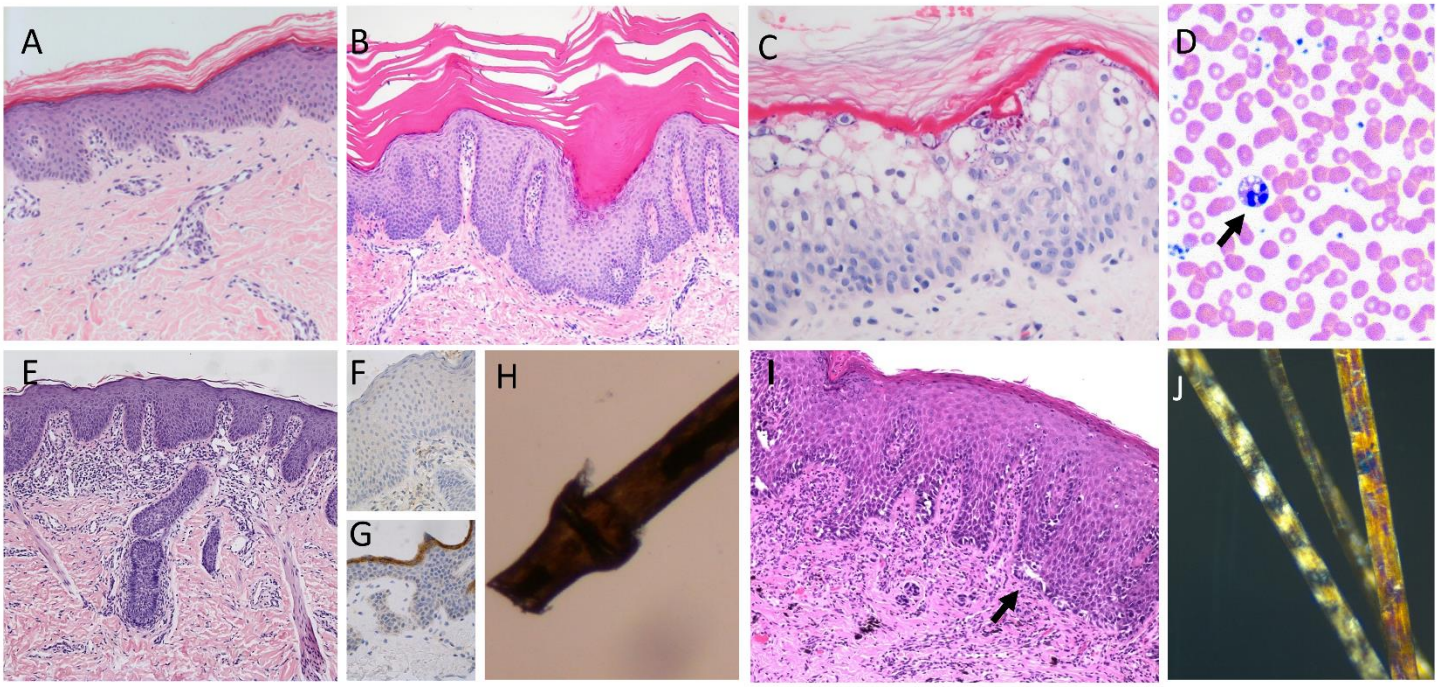


Figure 6. Histological characteristics of the ichthyoses

(A) Autosomal recessive congenital ichthyosis; orthohyperkeratosis (compact thickening of the stratum corneum), acanthosis (thickening of the epidermis) and absent inflammatory infiltrate within the dermis; hematoxylin & eosin (H&E) staining (10x magnification). (B) Harlequin ichthyosis; dense and thick orthohyperkeratosis, irregular acanthosis and dilated blood vessels in the otherwise normal underlying dermis; H&E staining (20x magnification). (C) Epidermolytic ichthyosis; orthokeratotic hyperkeratosis and vacuolated keratinocytes in the upper and mid layers of the epidermis; conspicuous keratohyalin granules (blue dots); H&E staining (40x magnification). (D) Chanarin-Dorfman syndrome; peripheral blood smear showing lipid droplets within granulocytes (Jordan´s anomaly) (black arrow). (E) Netherton syndrome; psoriasiform epidermal hyperplasia with moderate inflammatory infiltrate within the dermis and dilated blood vessels; H&E staining (10x magnification). (F) Netherton syndrome; lack of LEKTI staining in the stratum corneum of a patient (20x magnification). (G) Skin sample from a healthy patient showing normal LEKTI immunostaining on the stratum corneum (10x magnification). (H) Netherton syndrome; trichorrexis invaginata or “bamboo hair”, invagination of the distal hair shaft into the proximal hair shaft on electron microscopy. (I) Desmosomal disorder; erythrokeratodermia with cardiomyopathy due to heterozygous DSP variant; parakeratotic hyperkeratosis, psoriasiform epidermal hyperplasia and widening of the intercellular spaces with clefts in the suprabasal layers of the epidermis (acantholysis) (black arrow); H&E staining (20x magnification). (J) Trichothiodystrophy; alternating dark and light banding pattern under polarized light (“tiger tail” appearance).

(A, I) Courtesy of Dr Isabel Colmenero, Department of Pathology, Hospital Infantil Niño Jesús, Madrid, Spain
(B) Courtesy of Dr Takenori Yoshikawa, Department of Dermatology, Nagoya University Graduate School of Medicine, Japan
(C) Courtesy of Kana Tanahashi Department of Dermatology, Nagoya University Graduate School of Medicine, Japan

(E, F, G) Courtesy of Dr Stephanie Leclerc-Mercier, Department of Dermatopathologie, Hôpital Necker Enfants Malades Paris, France

Boxes

BOX 1. Acquired ichthyosis

Acquired ichthyosis is usually characterized by a late onset and often clinically resembles ichthyosis vulgaris, although a wide variety of manifestations have been observed ranging from mild xerosis up to severe scaling[11]. Acquired ichthyosis can result from different and unrelated causes including neoplasia, infectious diseases and nutritional deficiencies.

Among the cancers most often found in association with ichthyosis, lymphoproliferative disorders including Hodgkin's disease and multiple myeloma, are most common[296,297]. Ichthyosis in the context of lymphomas can occur as a paraneoplastic sign or be a manifestation of cutaneous T cell lymphoma[298]. Acquired ichthyosis can be observed in the presence of solid tumors and even with Kaposi's sarcoma. Successful treatment of the malignancy usually leads to improvement of the ichthyosis, and recurrence can forecast tumor recurrence[299].

Acquired ichthyosis has also been described in association with endocrine conditions, such as renal failure, diabetes, and hyperparathyroidism, as well as inflammatory disorders, such as lupus erythematosus and dermatomyositis[300]. Acquired ichthyosis has been described in a wide range of infectious diseases, such as leprosy, other mycobacterial diseases, and HIV[301].

Finally, nutritional deficiencies most often associated with abnormal lipid metabolism and vitamin levels can also cause acquired ichthyosis [302]. Nutritional deficiencies can result from malabsorption due to gastrointestinal diseases, such as Crohn's disease and celiac disease[303] or be secondary to medication, including cholesterol-lowering agents[304], allopurinol, EGFR and BRAF inhibitors, and acitretin[305].

A special pattern of acquired ichthyosis , known as pityriasis rotunda[306], features a sharply defined, circular patch of ichthyosiform scaling with no inflammatory changes. This subtype is relatively common in the Far East, especially Japan, where it accounts for ~0.2% of all dermatological conditions. In South Africa, it was observed in 16% of a series of patients with hepatocellular carcinoma and in nearly 5% of those with tuberculosis[307].

BOX 2. Patient testimonial

"Living with lamellar ichthyosis is not easy. I wake up to the light hurting my eyes. They are very sensitive because of wounds and scars inside them. While I shower, I try to clean my skin using an exfoliating glove, which is exhausting since I have to scratch my whole body. I often take my electric and abrasive file to carefully fight against the bigger scales on my soles. After the shower I put on creams, which are not reimbursed by the national health system, all over my body. After that I rub my scalp with a special comb; I sometimes hurt myself while doing so. No matter the pain, I have to put on another layer of cream and, finally, fifty minutes later, I have breakfast. I get dressed and before going out I check my clothes, carefully removing visible pieces of skin.

Getting to work is not easy because my eyes do not adjust well and I have to cope with the sun and traffic lights, or even wind and rain some days. At work, I switch on my humidifier and I do my job. To relieve the itch, pain and stiffness, I keep putting on creams every few hours during the whole day.

When I get home, I take another shower and do the routine exfoliation and hydration. After dinner I take my daily drugs and then I lay down, exhausted, on my bed. I fall asleep thinking about all the things I could not do because of my ichthyosis.

And I do this every day, over and over and over and over again"

This testimonial was provided by an anonymous patient with lamellar ichthyosis.

BOX 3. Caregiver testimonial

When our child with ichthyosis was born, we were also born to a new life. We not only began to see the world in a different way, but the world in which we lived suddenly seemed very different to us. We felt like the foundations of our reality were shaking. We were newly born into a situation with a new environment to adapt to (hospitals and health care centers), a new language to learn (the medical language), more baggage to carry (the fears, the guilt, the loneliness, the uncertainty). We advanced along a path that was not only unknown to us, but we did not know anyone who had traveled it before.

Ichthyosis is a disease that greatly impacts the quality of life of our child and our family. It is a very visible disease that causes rejecting stares, difficulty integrating and self-esteem issues. It is a disease that requires extensive care (baths, careful exfoliation, cures, continuous hydration), taking a lot out of our time and budget. It is a disease that does not allow us or our child to simply walk down the street due to the photophobia, propensity to heat stroke, and mobility problems, or even rest at night because of the itching and painful skin cracks.

Life with ichthyosis is tough.

This testimonial was provided by an anonymous caregiver of a patient with ichthyosis

Supplementary Information

Supplementary Table 1 | Genes and proteins involved in ichthyosis pathogenesis

Gene	Name	Function
Structural proteins		
Keratins		
KRT1	Keratin 1	Contributes to the intermediate filament cell cytoskeleton in suprabasal epidermal cells[53,54].
KRT10	Keratin 10	Contributes to the intermediate filament cell cytoskeleton in suprabasal epidermal cells, less important in palmoplantar skin[53,54].
KRT2	Keratin 2	Contributes to the intermediate filament cell cytoskeleton in the uppermost suprabasal epidermal cells[53,54].
Filaggrin		
ASPRV1	Aspartic Peptidase Retroviral Like 1	Protease involved in filaggrin processing, due to phenotype it probably targets additional proteins[59].
CASP14	Caspase 14	Protease involved in filaggrin processing[57].
FLG	Filaggrin	Protein that aggregates keratin intermediate filaments through promotion of disulfide-bond formation and liquid-liquid phase separation, is part of the cornified cell envelope and upon proteolysis contributes to the formation of the epidermal natural moisturizing factor[55].
POMP	Proteasome Maturation Protein	Molecular chaperone responsible for promoting proteasome formation and thereby for the maturation of proteins critical for epidermal differentiation such as filaggrin[60].
Cornified envelope		
LORICRIN	Loricrin Cornified Envelope Precursor Protein	Precursor protein of the CE[9].
TGM5	Transglutaminase 5	Enzyme that crosslinks precursor proteins of and to the CE[61].
Lipid metabolism		
Ceramides		
ABCA12	ATP Binding Cassette Subfamily A Member 12	Enzyme involved in ceramide loading to the lamellar bodies[90].
ABHD5	Abhydrolase Domain Containing 5	Functions as an acyltransferase and as a coactivator of adipocyte triglyceride lipase[86].
ALDH3A2	Aldehyde Dehydrogenase 3 Family Member A2	Enzyme involved in fatty acid synthesis, which some studies suggest are used as ceramide precursors[64].
ALOX12B	Arachidonate 12-Lipoxygenase	Enzyme involved in ceramide crosslinking to the CE to form the CLE[93].
ALOXE3	Arachidonate Lipoxygenase 3	Enzyme involved in ceramide crosslinking to the CE to form the CLE[93].
CERS3	Ceramide Synthase 3	Synthesizes ceramide from modified ULC-fatty acid and dihydrosphingosine[80–82].
CYP4F22	Cytochrome P450 Family 4 Subfamily F Member 22	□-hydroxylation of ULC-fatty acids for acylceramide synthesis[68,69].
ELOVL1	ELOVL Fatty Acid Elongase 1	Fatty acid elongase involved in ULC-fatty acid synthesis, which are ceramide precursors[65].
ELOVL4	ELOVL Fatty Acid Elongase 4	Fatty acid elongase involved in ULC-fatty acid synthesis, which are ceramide precursors[66].
GBA1	Acid beta-glucoderebrosidase	Catalyzes the breakdown of the glycolipid glucosylceramide to ceramide and glucose[91].
KDSR	3-Ketodihydrosphingosine Reductase	Synthesizes ceramide precursor dihydrosphingosine from serine[79].

LIPN	Lipase Family Member N	Unclear role in ceramide synthesis[85].
NIPAL4	NIPA Like Domain Containing 4	Unclear role in ceramide synthesis[83,84].
PEX7	Peroxisomal Biogenesis Factor 7	Plays an essential role in peroxisomal protein import (including phytanoyl-CoA hydroxylase)[74].
PHGDH	Phosphoglycerate Dehydrogenase	Enzyme involved in serine synthesis, which is used as a ceramide precursor[76–78].
PHYH	Phytanoyl-CoA 2-Hydroxylase	Enzyme involved in synthesis of peroxisomal fatty acids, which are used as ceramide precursors[72,73].
PNPLA1	Patatin Like Phospholipase Domain Containing 1	Catalyzes ω-O-esterification with linoleic acid to form acylceramides[87,88].
PSAT1	Phosphoserine Aminotransferase 1	Enzyme involved in serine synthesis, which is used as a ceramide precursor[76–78].
PSPH	Phosphoserine Phosphatase	Enzyme involved in serine synthesis, which is used as a ceramide precursor[76–78].
SDR9C7	Short Chain Dehydrogenase/Reductase Family 9C Member 7	Enzyme involved in ceramide crosslinking to the CE to form the CLE[94].
SLC27A4	Solute Carrier Family 27 Member 4	Adds coenzyme A (CoA) to ULC-fatty acids for ceramide synthesis[70,71].
TGM1	Transglutaminase 1	Enzyme with poorly understood functions in ceramide crosslinking to the CE to form the CLE[95].
UGCG	UDP-Glucose Ceramide Glucosyltransferase	Glycosylates acyl-ceramide[89].
Cholesterol		
EBP	EBP Cholestenol Delta-Isomerase	Enzyme involved in cholesterol synthesis[101,102].
MBTPS2	Membrane Bound Transcription Factor Peptidase, Site 2	Membrane metalloprotease involved in activation of transcription factors involved in cholesterol enzyme transcription[99].
NSDHL	NAD(P) Dependent Steroid Dehydrogenase-Like	Enzyme involved in cholesterol synthesis[101,102].
SREBF1	Sterol Regulatory Element Binding Transcription Factor 1	Transcription factor involved in cholesterol enzyme transcription[100].
STS	Steroid Sulfatase	Synthesizes cholesterol from cholesterol sulfate[105].
SULT2B1	Sulfotransferase Family 2B Member 1	Responsible for cholesterol sulfation, which plays a major role in the regulation of epidermal differentiation[103].
SUMF1	Sulfatase Modifying Factor 1	Responsible for modifying various sulfatases[106,107].
Lamellar bodies		
SNAP29	Synaptosome Associated Protein 29	Mediates lamellar body fusion events[108].
VIPAS39	VPS33B Interacting Protein, Apical-Basolateral Polarity Regulator, Spe-39 Homolog	Mediates lamellar body fusion events[109].
VPS33B	VPS33B Late Endosome And Lysosome Associated	Mediates lamellar body fusion events[110].
Dolichol		
DOLK	Dolichol Kinase	Phosphates dolichol[113].
MPDU1	Mannose-P-Dolichol Utilization Defect 1	Adds mannose to dolichols as preparation for protein O-glycosylation and N-mannosylation[114].
PIGL	Phosphatidylinositol Glycan Anchor Biosynthesis Class L	Involved in GPI anchor synthesis[115].
SRD5A3	Steroid 5 Alpha-Reductase 3	Involved in dolichol synthesis[112].
Intercellular junctions		
Tight junctions		

CLDN1	Claudin 1	Tight junction protein, controls paracellular permeability[117].
CLDN10	Claudin 10	Tight junction protein, controls paracellular permeability[118].
Gap junctions		
GJA1	Gap Junction Protein Alpha 1 (Connexin 43)	Gap junction protein, controls intercellular communication[119].
GJB2	Gap Junction Protein Beta 2 (Connexin 26)	Gap junction protein, controls intercellular communication[120].
GJB3	Gap Junction Protein Beta 3 (Connexin 31)	Gap junction protein, controls intercellular communication[121].
GJB4	Gap Junction Protein Beta 4 (Connexin 30.3)	Gap junction protein, controls intercellular communication[122].
GJB6	Gap Junction Protein Beta 6 (Connexin 30)	Gap junction protein, controls intercellular communication[123].
Desmosomes		
CDSN	Corneodesmosin	Component of corneodesmosomes in the SC, increases mechanical resistance[126].
DSG1	Desmoglein 1	Desmosome protein, ensures intercellular adhesion[124,125].
DSP	Desmoplakin	Desmosome protein, ensures intercellular adhesion[124,125].
FLG2	Filaggrin 2	Ensures cell-cell adhesion in the upper epidermal layers in a corneodesmosin-dependent fashion[134].
PERP	P53 Apoptosis Effector Related To PMP22	Promotes desmosome assembly[127].
Proteases and inhibitors		
SPINK5	Serine Peptidase Inhibitor Kazal Type 5	Serine protease inhibitor, prevents junction degradation[130,131].
CAST	Calpastatin	Cysteine protease inhibitor, prevents junction degradation[132].
CSTA	Cystatin A	Cysteine protease inhibitor, prevents junction degradation[133].
SERPINB8	Serpin Family B Member 8	Serine protease inhibitor, prevents junction degradation[129].
ST14	ST14 Transmembrane Serine Protease Matriptase	Functions as an epithelial membrane activator for other proteases and plays a role in profilaggrin processing and hair follicle growth[128].
Transcription / translation		
AARS1	Alanyl-TRNA Synthetase 1	Alanyl-tRNA synthetase[143].
ERCC2	ERCC Excision Repair 2, TFIIH Core Complex Helicase Subunit	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription[136].
ERCC3	ERCC Excision Repair 3, TFIIH Core Complex Helicase Subunit	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription[137].
GTF2E2	General Transcription Factor IIE Subunit 2	Component of the TFIIE complex involved in type 2 gene transcription[139].
GTF2H5	General Transcription Factor IIH Subunit 5	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription[138].
MARS1	Methionyl-TRNA Synthetase 1	Methionyl-tRNA synthetase[143].
RNF113A	Ring Finger Protein 113A	Ring finger protein involved in pre-mRNA splicing[140].
TARS1	Threonyl-TRNA Synthetase 1	Threonyl-tRNA synthetase[144].
Miscellaneous		
AP1B1	Adaptor Related Protein Complex 1 Subunit Beta 1	Part of clathrin-coated vesicle adaptor complex[148,149].
AP1S1	Adaptor Related Protein Complex 1 Subunit Sigma 1	Part of clathrin-coated vesicle adaptor complex[148,149].

MPLKIP	M-Phase Specific PLK1 Interacting Protein	Interacts with cyclin dependent and polo kinases, maintains cell cycle integrity[151].
TRPM4	Transient Receptor Potential Cation Channel Subfamily M Member 4	Calcium activated-ion channel, associated with proliferation regulation[150].

Supplementary Table 2 | Proposed classification of the non-syndromic ichthyoses

Group	Causal genes	Main characteristics
Common ichthyoses		High prevalence relative to the other ichthyoses.
Ichthyosis vulgaris (IV, ORPHA: -)	*FLG*[55] (SD, MIM: 146700), *CASP14*[57] (AR, MIM: 617320), *ASPRV1*[59] (AD, MIM: 146750)	Characterized by a delayed onset (of up to six months) of light brown scaling of the skin that often spares the antecubital and popliteal regions, as well as the face[2]. Scaling on the legs is most prominent and hyperlinear palms are characteristic. While *FLG* is the most-commonly affected gene, other forms of ichthyosis that affect filaggrin expression are autosomal recessive in inheritance and rare, but mechanistically should be considered with IV. *CASP14* (MIM: 617320) leads to fine white scales and no collodion membrane at birth[57]. *ASPRV1* (MIM: 146750), causes ichthyosis that resembles lamellar ichthyosis (see below), but has hyperlinear palms and no collodion membrane at birth[59].
Recessive X-linked ichthyosis (RXLI, ORPHA: 461)	*STS*[105] (XR, MIM: 308100)	Presents with firmly-attached dark brown or grey polygonal scales that usually spare the antecubital and popliteal regions, as well as the face, soles and palms[2,166]. The scalp and neck are often most severely affected. It affects mostly males, with female carriers showing no clinical phenotype because *STS* localizes to a region of the X-chromosome that escapes X-inactivation[2,166].
Autosomal recessive congenital ichthyosis (ARCI, ORPHA: 281097)		This heterogeneous subgroup often presents at birth[1] as a collodion baby, characterized by encasement in a shiny membrane that peels off within a few weeks after birth[166] and transitions to a more specific ichthyotic phenotype within the subsequent 3-6 months. In most cases, the defective gene products are involved in ceramide metabolism.
Lamellar ichthyosis (LI, ORPHA: 313)	*ABCA12*[90] (AR, MIM: 601277), *ALOX12B*[278] (AR, MIM: 242100), *ALOXE3*[279] (AR, MIM: 606545), *CYP4F22*[68] (AR, MIM: 604777), *LIPN*[85] (AR, MIM: 613943), *NIPAL4*[83] (AR, MIM: 612281), *SDR9C7*[94] (AR, MIM: 617574), *SULT2B1*[103] (AR, MIM: 617571), *TGM1*[95] (AR, MIM: 242300)	Classically present with large polygonal scales with coloration ranging from light brown in fair-skinned patients to dark brown in those with skin of color and involvement of the joint flexures[1].
Congenital ichthyosiform erythroderma (CIE, ORPHA: 79394)	*ABCA12*[167] (AR, MIM: 601277), *ALOX12B*[93] (AR, MIM: 242100), *ALOXE3*[93] (AR, MIM: 606545), *CERS3*[82] (AR, MIM: 615023), *CYP4F22*[44] (AR, MIM: 604777), *NIPAL4*[83] (AR, MIM: 612281), *PNPLA1*[87] (AR, MIM: 615024), *TGM1*[280] (AR, MIM: 242300)	Patients may be born with a less-severe collodion membrane before transitioning to generalized fine white scaling with pronounced erythroderma (red, inflamed skin) and involvement of the joint flexures[1]. While homozygosity mapping identified an additional causative locus at 12p11.2-q13.1 (MIM: 615022)[308], it has later been revealed that *SDR9C7* and *ALOX12B* were the genes responsible for those cases[309].
Harlequin ichthyosis (HI, ORPHA: 457)	*ABCA12*[281] (AR, MIM: 242500)	The most severe form of ARCI. Babies are born with thickened, rigid skin that impairs movement sucking and breathing and present with deep cutaneous fissures (that can resemble the diamond-shaped patterns of a harlequin costume)[166]. They usually display ectropion and eclabium (exposure of the eyelid and lip inner surfaces) and those patients who survive the first weeks of life develop a severe form of CIE[166].

Self-healing collodion baby (SHCB, ORPHA: 281122)	*ALOX12B*[282] (AR, MIM: 242100), *ALOXE3*[283] (AR, MIM: 606545), *CYP4F22*[284] (AR, MIM: 604777), *TGM1*[285] (AR, MIM: 242300)	Also known as self-improving congenital ichthyosis, it is a rare variant in which patients are born with a collodion membrane that peels spontaneously leaving very mild or no scaling[2]. While the mechanism remains unclear, it is possible that this unusual presentation reflects the sensitivity of the gene products to hydrostatic and ambient atmospheric pressure[285].
Acral self-healing collodion baby (ASHCB, ORPHA: 281127)	*TGM1*[286] (AR, MIM: 242300)	A very rare variant similar to the SHCB, but the collodion membrane affects only the extremities[1]
Bathing suit ichthyosis (BSI, ORPHA: 100976)	*TGM1*[287] (AR, MIM: 242300)	Another variant of LI in which patients are born with a collodion membrane that recedes spontaneously on the face and extremities, but persists on the trunk and scalp[2] because of temperature-sensitive pathogenic variants that affect warmer body areas.
Keratinopathic ichthyoses (KPI, ORPHA: 281103)		
Autosomal dominant epidermolytic ichthyosis (EI, ORPHA: 312)	*KRT1*[53] (AD, MIM: 113800), *KRT10*[53] (AD, MIM: 113800)	Also known as epidermolytic ichthyosis. Affected individuals often have blistering at birth, which may be confused with epidermolysis bullosa, but with time develop epidermal thickening and scaling, accentuated in joint areas. The intensity of erythroderma is variable, but can be severe[53]. Given that keratin 1 is a key protein in palmar and plantar skin, whereas keratin 10 is substituted with keratin 9 in these regions, variants in *KRT1* often manifest with particularly severe palmoplantar keratoderma (which is usually mild in those with *KRT10* mutations)[53]
Autosomal recessive epidermolytic ichthyosis (AREI, ORPHA: 512103)	*KRT10*[269] (AR, MIM: 113800)	Shows similar symptoms to EI[269].
Superficial epidermolytic ichthyosis (SEI, ORPHA: 455)	*KRT2*[54] (AD, MIM: 146800)	Formerly called ichthyosis bullosa of Siemens, it has a milder phenotype than EI, without erythroderma at birth. It is characterized by areas of skin peeling, prominent involvement of the flexures and patches of normal skin (called the molting or mauserung phenomenon)[1].
Annular epidermolytic ichthyosis (AEI, ORPHA: 281139)	*KRT1*[270] (AD, MIM: 607602), *KRT10*[271] (AD, MIM: 607602)	Characterized by erythroderma and skin blistering at birth, similar to EI, which then give way to patches of annular erythema and skin thickening that cyclically flare to affect most of the body surface before receding[270].
Ichthyosis Curth-Macklin (ICM, ORPHA: 79503)	*KRT1*[275] (AD, MIM: 146590)	Also known as ichthyosis hystrix of Curth-Macklin, it is characterized by mutilating palmoplantar thickening of the skin leading to auto-amputation (pseudoainhum), accompanied by a histology of spiky hyperkeratosis with bi-nucleated keratinocytes[275].
Epidermolytic nevus (EN, ORPHA: 497737)	*KRT1*[272] (M, MIM: -), *KRT10*[273] (M, MIM: -), *KRT2*[274] (M, MIM: -)	Although they do not blister, epidermal nevi with epidermolytic hyperkeratosis manifest as hyperpigmented keratotic epidermal papules that track curvilinearly along the Blaschko lines with the same epidermolytic histological pattern of EI[1,2]. While epidermal nevi can form a single streak or many, they do not involve most of the integument, thus not fulfilling that criterion for ichthyosis; nonetheless individuals with multiple nevi are more likely to have both somatic and gonadal mosaic involvement and are thus at risk for an offspring with generalized EI[273]
Ichthyosis with confetti (IWC, ORPHA: 281190)	*KRT1*[276] (AD, MIM: 609165), *KRT10*[277] (AD, MIM: 609165)	Sometimes called congenital reticular ichthyosiform erythroderma or ichthyosis variegata, it is characterized by erythroderma and skin thickening, with the appearance of spots of healthy skin that increase in number and size with age[276]. This "confetti" patches of normal skin result from loss of heterozygosity of the disease-causing allele by mitotic recombination[276]. IWC is often mistaken for CIE until the mosaic patches appear.
Others		
Peeling skin syndromes (PSS, ORPHA: 817)		Characterized by desquamation of the upper layer of the epidermis[134] . They are further subdivided depending on the affected areas

Generalized peeling skin syndrome (generalized PSS, ORPHA: 263543)	*CDSN*[126] (AR, MIM: 270300), *FLG2*[134] (AR, MIM: 618084)	Peeling involves the entire surface of the skin[134] and includes two 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*[293] (AR, MIM: 607936), *TGM5*[61] (AR, MIM: 609796)	The shedding affects primarily the plantar and dorsal surfaces of the hands and feet[134].
Exfoliative ichthyosis (ORPHA: 289586)	*CSTA*[133] (AR, MIM: 607936), *SERPINB8*[129] (AR, MIM: 617115)	Characterized by shedding of the skin and generalized dry, scaling skin[133]. It is not typically classified as a PSS, but exfoliative ichthyosis shares signs and underlying molecular basis with acral PSS[133].
Peeling skin-leukonychia-acral punctate keratoses-cheilitis-knuckle pads syndrome (PLACK, ORPHA: 44138)	*CAST*[132] (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*[9] (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[9]
Erythrokeratoderma variabilis et progressiva (EKVP, ORPHA: 308166)	*GJA1*[119] (AD, MIM: 617525), *GJB3*[121] (AD or AR, MIM: 133200), *GJB4*[122] (AD, MIM: 617524), *KDSR*[79] (AR, MIM: 617526), *PERP*[127] (AR, MIM: 619209), *TRPM4*[150] (AD, MIM: 618531)	An umbrella term that includes patients with similar clinical findings: migratory erythema and hyperkeratotic lesions, which change size over time[310] (sometimes called erythrokeratoderma variabilis (EKV)) and/or fixed brown-red hyperkeratotic plaques[122] (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*[311] or *ABCA12*[173] mutations
Keratosis linearis-ichthyosis congenita-sclerosing keratoderma syndrome (KLICK, ORPHA: 281201)	*POMP*[60] (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[60].

ORPHA, disease code in the ORPHANET database; MIM, phenotype code in the OMIM database; AD, autosomal dominant inheritance; SD, autosomal semi-dominant inheritance; AR, autosomal recessive inheritance; XR, X-linked recessive inheritance; M, mosaicism.

Supplementary Table 3 | Proposed classification of the syndromic ichthyoses

Disease	Causal genes	Main characteristics
X-linked ichthyosis syndromes (ORPHA: 281210)		
Syndromic recessive X-linked ichthyosis (Syndromic RXLI, ORPHA: 281090)	*STS*[170] (HD, MIM: 308100) + contiguous genes	Results from X-chromosomal deletions that include *STS*, which is responsible for the ichthyotic phenotype, and contiguous genes[170]. Clinical manifestations will depend on the spectrum of genes deleted along with *STS*[170], but often includes anosmia and delayed development (Kallman syndrome). Xp22.3 microdeletion syndrome (ORPHA: 1643) is another manifestation of syndromic RXLI, since it includes the *STS* locus[289] with other manifestations.
Ichthyosis follicularis-alopecia-photophobia syndrome (IFAP, ORPHA: 2273)	*MBTPS2*[99] (XR, MIM: 308205), *SREBF1*[100] (AD, MIM: 619016)	Characterized by generalized skin thickening and erythema, with follicular-based accentuation, palmoplantar keratoderma, usually total baldness (alopecia) and light sensitivity (photophobia)[99]. It is caused by variants in *MBTPS2*. A phenotypically similar autosomal dominant disorder was shown to be caused by variants in *SREBF1*.
Chondrodysplasia punctata type 2 (CDPX2, ORPHA: 35173)	*EBP*[102] (XD, MIM: 302960)	Also known as chondrodystrophia calcificans congenita, X-linked dominant chondrodysplasia punctata, or Conradi-Hünermann-Happle syndrome. It is characterized by male lethality, ichthyotic changes along the Blaschko lines and in fold areas (ptychotropism), skeletal abnormalities with short stature and shortening of the limbs (chondrodysplasia punctata), and cataracts[102].
Male EBP disorder with neurological defects (MEND, ORPHA:) 401973	*EBP*[290] (XR, MIM: 300960)	Characterized by ichthyosis, neurological symptoms (delayed development and seizures), and craniofacial dysmorphism, with possible involvement of other organs[290].
Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD, ORPHA: 139)	*NSDHL*[101] (XD, MIM: 308050)	Characterized by a largely ipsilateral (affecting strictly half of the body along the sagittal plane) nevus with hypoplasia of the skeletal structures (shortness or absence of limbs) and, in some patients, brain and viscera (lungs, heart, and kidneys)[101].
Autosomal ichthyosis syndromes (with)		
Prominent hair abnormalities (ORPHA: 281222)		
Netherton syndrome (NS, ORPHA: 634)	*SPINK5*[130] (AR, MIM: 256500)	Also known as bamboo hair syndrome, or Comèl-Netherton syndrome. It is characterized by congenital erythroderma and scaling, with frequent prematurity and hypernatremic dehydration in the neonatal period[130]. With advancing age, affected individuals may have a persistent erythroderma, but often have more localized disease with a typical pattern of scaling called ichthyosis linearis circumflexa, in which lesions are surround be a wall of scaling[130]. Most affected individuals have distinct hair shaft defects (trichorrhexis invaginate or bamboo hair), which leads to easy breakage. Patients have a tendency towards atopic disorders (atopic diathesis)[130] and verrucous lesions.
Severe dermatitis-multiple allergies-metabolic wasting syndrome (SAM, ORPHA: 369992)	*DSG1*[124] (AR, MIM: 615508), *DSP*[125] (AD, MIM: -)	Also known as congenital erythroderma-hypotrichosis-recurrent infections-multiple food allergies syndrome, features erythroderma with superficial desquamation and skin thickening and hypotrichosis, accompanied by recurrent infections and multiple food allergies, leading to a failure to thrive and developmental delay[124].
Ichthyosis-hypotrichosis syndrome (IHS, ORPHA: 91132)	*ST14*[128] (AR, MIM: 602400)	Also known as ichthyosis - follicular atrophoderma - hypotrichosis - hypohidrosis syndrome. It is characterized by diffuse congenital ichthyosis, follicular atrophoderma, sparse hair (hypotrichosis) and hypohidrosis[128].
Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis; (ILVASC, ORPHA: 59303)	*CLDN1*[117] (AR, MIM: 607626)	Also known as neonatal ichthyosis-sclerosing cholangitis syndrome. It is associated with ichthyosis, scalp hypotrichosis, scarring alopecia, dental anomalies, ichthyosis, and inflammation of the bile ducts[117].
Trichothiodystrophy (TTD, ORPHA: 33364)	*AARS1*[143] (AR, MIM: 619691), *ERCC2*[136] (AR, MIM: 601675), *ERCC3*[137] (AR, MIM: 616390),	Characterized by sulfur deficiency leading to ichthyosis and brittle hair and nails[143]. Some forms of this disease are photosensitive, with progressive neuropathy and accelerated aging, associated with defects in DNA repair[143]. This subgroup is caused by variants in *ERCC2*, *ERCC3*, and *GTF2H5*.

	GTF2E2[139] (AR, MIM: 616943), *GTF2H5*[138] (AR, MIM: 616395), *MAARS1*[143] (AR, MIM: 619692), *MPLKIP*[151] (AR, MIM: 234050), *RNF113A*[140] (XR, MIM: 300953), *TARS1*[144] (AR, MIM: 618546)	In contrast, the non-photosensitive forms are caused by variants in *AARS1*, *GTF2E2*, *MARS1*, *MPLKIP*, *RNF113A*, and *TARS1.*
Prominent neurologic signs (ORPHA: 281238 and ORPHA: 281241)		
Sjögren-Larsson syndrome (SLS, ORPHA: 816)	*ALDH3A2*[64] (AR, MIM: 270200)	Also known as fatty acid alcohol oxidoreductase deficiency. It is characterized by intellectual disability, spasticity and skin thickening[64].
Refsum disease (ORPHA: 773)	*PEX7*[74] (AR, MIM: 308100), *PHYH*[72,73] (AR, MIM: 266500)	Also known as hereditary motor and sensory neuropathy type 4, heredopathia atactica polyneuritiformis, or phytanic-CoA hydroxylase deficiency. It is characterized by progressive loss of retinal function (retinitis pigmentosa), peripheral neuropathy, lack of sense of smell (anosmia), lack of movement coordination (cerebellar ataxia) and ichthyosis[74].
Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma syndrome (CEDNIK, ORPHA: 66631)	*SNAP29*[108] (AR, MIM: 609528)	Typically leads to early death from aspiration pneumonia[108].
Mental disability-enteropathy-deafness-peripheral neuropathy-ichthyosis-keratoderma syndrome (MEDNIK, ORPHA: 171851)	*AP1S1*[148] (AR, MIM: 609313), *AP1B1*[149] (AR, MIM: 242150)	Caused by recessive pathogenic variants in *AP1S1*. A phenotypically similar, MEDNIK-like syndrome, also known as keratitis-ichthyosis-deafness- autosomal recessive syndrome (KIDAR, ORPHA: -), was shown to be caused by recessive variants in *AP1B1*.
Ichthyotic keratoderma-spastic paraplegia-hypomyelination-dysmorphic facies (ORPHA: -)	*ELOVL1*[65] (AD, MIM: 618527)	Ichthyotic keratoderma, spastic paraplegia - hypomyelination - dysmorphic facies
Congenital ichthyosis-intellectual disability-spastic quadriplegia syndrome (ORPHA: 352333)	*ELOVL4*[66] (AR, MIM: 614457)	Also known as ELOVL4-related neuro-ichthyosis, this disease also features seizures.
Arthrogryposis-renal dysfunction-cholestasis syndrome (ARC, ORPHA: 2697)	*VIPAS39*[109] (AR, MIM: 613404), *VPS33B*[110] (AR, MIM: 208085)	Characterized by neurogenic arthrogryposis, renal tubular dysfunction, bile production defects (cholestasis), ichthyosis and death within the first year of life[110]. This disease is allelic to autosomal recessive-keratoderma-ichthyosis-deafness (ARKID, ORPHA: -), also caused by recessive pathogenic variants in *VPS33B*[291].
Fetal Gaucher disease (FGD, ORPHA: 85212)	*GBA1*[91] (AR, MIM: 608013)	Also called type II or perinatal lethal Gaucher disease. It is characterized by decreased fetal movement, joint contractures (arthrogryposis), facial dysmorphism, sometimes thrombocytopenia, ichthyosis and death *in utero* or shortly after birth[91]. These neonates and infants experience progressive neurologic deterioration.
Multiple sulfatase deficiency (MSD, ORPHA: 585)	*SUMF1*[106] (AR, MIM: 272200)	Also known as Austin type juvenile sulfatidosis. It is characterized by ichthyosis that resembles RXLI, developmental delay, the neurological and skeletal abnormalities of storage disorders, and early death due to respiratory complications[312].
Neu-Laxova syndrome (NLS, ORPHA: 2671)	*PHGDH*[77] (AR, MIM: 256520), *PSAT1*[78] (AR, MIM: 616038), *PSPH*[76] (AR, MIM: -)	Characterized by collodion membrane, severe malformations, microcephaly, and intra uterine growth retardation that lead to death *in utero* or shortly after birth[76].
Disorders of glycosylation		
Deficiency of UDP-glucose ceramide glycosyltransferase (ORPHA: -)	*UGCG*[89] (AR, MIM: -)	Manifests as a collodion baby with congenital joint contractures[89]. This newly described condition has largely been lethal during the first months of life, but would be expected to cause severe neurologic effects[89]
Congenital disorder of glycosylation type 1F (CDG-1F, ORPHA: 79323)	*MPDU1*[114] (AR, MIM: 609180)	Characterized by excess muscle tone (hypertonia), psychomotor retardation and ichthyosis[114].

Congenital disorder of glycosylation type 1M (CDG-1M, ORPHA: 91131)	*DOLK*[113] (AR, MIM: 610768)	Also known as dolichol kinase deficiency or hypotonia and ichthyosis due to dolichol phosphate deficiency. It is characterized by reduced muscle strength (hypotonia), inflammation, frequent cardiomyopathy, and ichthyosis[113].
Congenital disorder of glycosylation type 1Q (CDG-1Q, ORPHA: 324737)	*SRD5A3*[112] (AR, MIM: 612379)	Features ocular colobomas, brain malformations leading to mental retardation, hyperplasia of the pituitary gland, and ichthyosis[112].
Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation, and ear anomalies syndrome (CHIME, ORPHA: 3474)	*PIGL*[115] (AR, MIM: 280000)	Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation, and ear anomalies[115]
Other associated signs (ORPHA: 281244)		
Keratitis-ichthyosis-deafness syndrome (KID, ORPHA: 477)	*GJB2* (AD[120] or M[294], MIM: 148210), *GJB6*[123] (AD, MIM: -), *AP1B1*[295] (AR, MIM: 242150)	Also known as Ichthyosis hystrix Rheydt type or Senter syndrome. It is characterized by corneal inflammation (keratitis), spiky hyperkeratosis with palmoplantar keratoderma, and hearing loss[123]. Gene mosaicism for *GJB2* has been associated with keratotic lesions in a blaschkoid distribution and, if more extensive, can be passed to an offspring as KID syndrome[294].
Neutral lipid storage disease with ichthyosis (NLSDI, ORPHA: 98907)	*ABHD5*[86] (AR, MIM: 275630)	Also known as Chanarin-Dorfman disease. It is characterized by ichthyosis with an ARCI phenotype, enlarged liver and spleen (hepatosplenomegaly), muscle weakness (myopathy), hearing loss and cataracts[86]. Histologically, patients show lipid vacuole accumulation in most tissues[86].
Ichthyosis-prematurity syndrome (IPS, ORPHA: 88621)	*SLC27A4*[70] (AR, MIM: 608649)	Characterized by premature birth, neonatal asphyxia, and cobblestone-like plaques of ichthyosis with extensive desquamative scaling that can resemble vernix[70] and tends to improve drastically during the neonatal period to near-normal skin.
Erythrokeratodermia-cardiomyopathy syndrome (EKC, ORPHA: 476096)	*DSP* (AD[158] or AR[292], MIM: 605676)	Characterized by early failure to thrive, wooly hair, erythema with fine scaling, and dilated cardiomyopathy[292].
Hypohidrosis-electrolyte imbalance-lacrimal gland dysfunction-ichthyosis-xerostomia syndrome (HELIX, ORPHA: 528105)	*CLDN10*[118] (AR, MIM: 617671)	Characterized by hypohidrosis, renal loss of Na^+ and Cl^- ions leading to electrolyte imbalance, dry eyes (xerophtalmia), and mouth (xerostomia) and ichthyosis[118].
Ichthyosis-short stature-brachydactyly-microspherophakia syndrome (ORPHA: 363992)	*CERS3*[82] + *ADAMTS17*[82] (HD, MIM: -)	Also known as 15q26.3 microdeletion syndrome. It is characterized by short stature, short fingers (brachydactyly), lens abnormalities (microspherophakia) and myopia, all hallmarks of Weill-Marchesani syndrome (associated with *ADAMTS17*), as well as ichthyosis with CIE phenotype (associated with *CERS3*)[82].
Palmoplantar and perianal keratoderma/harlequin ichthyosis-like ichthyosis with thrombocytopenia (ORPHA: -)	*KDSR*[288] (MIM: -)	Patients presented thrombocytopenia with, either, hyperkeratosis confined to palms, soles, and anogenital skin or harlequin ichthyosis-like cutaneous symptoms.

ORPHA, disease code in the ORPHANET database; MIM, phenotype code in the OMIM database; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; XD, X-linked dominant inheritance; XR, X-linked recessive inheritance; HD, homozygous deletion; M, mosaicism.