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Primer

Ichthyosis

In the format provided by the authors and unedited

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 [1,2]
KRT10	Keratin 10	Contributes to the intermediate filament cell cytoskeleton in suprabasal epidermal cells, less important in palmoplantar skin. [1,2]
KRT2	Keratin 2	Contributes to the intermediate filament cell cytoskeleton in the uppermost suprabasal epidermal cells [1,2]
Filaggrin		
ASPRV1	Aspartic Peptidase Retroviral Like 1	Protease involved in filaggrin processing, due to phenotype it probably targets additional proteins[3]
CASP14	Caspase 14	Protease involved in filaggrin processing[4]
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[5]
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[6]
Cornified envelope		
LORICRIN	Loricrin Cornified Envelope Precursor Protein	Precursor protein of the CE[7]
TGM5	Transglutaminase 5	Enzyme that crosslinks precursor proteins of and to the CE[8]
Lipid metabolism		
Ceramides		
ABCA12	ATP Binding Cassette Subfamily A Member 12	Enzyme involved in ceramide loading to the lamellar bodies[9]
ABHD5	Abhydrolase Domain Containing 5	Functions as an acyltransferase and as a coactivator of adipocyte triglyceride lipase[10]
ALDH3A2	Aldehyde Dehydrogenase 3 Family Member A2	Enzyme involved in fatty acid synthesis, which some studies suggest are used as ceramide precursors[11]
ALOX12B	Arachidonate 12-Lipoxygenase	Enzyme involved in ceramide crosslinking to the CE to form the CLE[12]
ALOXE3	Arachidonate Lipoxygenase 3	Enzyme involved in ceramide crosslinking to the CE to form the CLE[12]
CERS3	Ceramide Synthase 3	Synthesizes ceramide from modified ULC-fatty acid and dihydrosphingosine[13–15]
CYP4F22	Cytochrome P450 Family 4 Subfamily F Member 22	ω-hydroxylation of ULC-fatty acids for acylceramide synthesis[16,17]
ELOVL1	ELOVL Fatty Acid Elongase 1	Fatty acid elongase involved in ULC-fatty acid synthesis, which are ceramide precursors[18]

ELOVL4	ELOVL Fatty Acid Elongase 4	Fatty acid elongase involved in ULC-fatty acid synthesis, which are ceramide precursors[19]
GBA1	Acid beta-glucoderebrosidase	Catalyzes the breakdown of the glycolipid glucosylceramide to ceramide and glucose[20]
KDSR	3-Ketodihydrosphingosine Reductase	Synthesizes ceramide precursor dihydrosphingosine from serine[21]
LIPN	Lipase Family Member N	Unclear role in ceramide synthesis[22]
NIPAL4	NIPA Like Domain Containing 4	Unclear role in ceramide synthesis[23,24]
PEX7	Peroxisomal Biogenesis Factor 7	Plays an essential role in peroxisomal protein import (including phytanoyl-CoA hydroxylase)[25]
PHGDH	Phosphoglycerate Dehydrogenase	Enzyme involved in serine synthesis, which is used as a ceramide precursor[26–28]
PHYH	Phytanoyl-CoA 2-Hydroxylase	Enzyme involved in synthesis of peroxisomal fatty acids, which are used as ceramide precursors[29,30]
PNPLA1	Patatin Like Phospholipase Domain Containing 1	Catalyzes ω-O-esterification with linoleic acid to form acylceramides[31,32]
PSAT1	Phosphoserine Aminotransferase 1	Enzyme involved in serine synthesis, which is used as a ceramide precursor[26–28]
PSPH	Phosphoserine Phosphatase	Enzyme involved in serine synthesis, which is used as a ceramide precursor[26–28]
SDR9C7	Short Chain Dehydrogenase/Reductase Family 9C Member 7	Enzyme involved in ceramide crosslinking to the CE to form the CLE[33]
SLC27A4	Solute Carrier Family 27 Member 4	Adds coenzyme A (CoA) to ULC-fatty acids for ceramide synthesis[34,35]
TGM1	Transglutaminase 1	Enzyme with poorly understood functions in ceramide crosslinking to the CE to form the CLE[36]
UGCG	UDP-Glucose Ceramide Glucosyltransferase	Glycosylates acyl-ceramide[37]
Cholesterol		
EBP	EBP Cholestenol Delta-Isomerase	Enzyme involved in cholesterol synthesis[38,39]
MBTPS2	Membrane Bound Transcription Factor Peptidase, Site 2	Membrane metalloprotease involved in activation of transcription factors involved in cholesterol enzyme transcription[40]
NSDHL	NAD(P) Dependent Steroid Dehydrogenase-Like	Enzyme involved in cholesterol synthesis[38,39]
SREBF1	Sterol Regulatory Element Binding Transcription Factor 1	Transcription factor involved in cholesterol enzyme transcription[41]
STS	Steroid Sulfatase	Synthesizes cholesterol from cholesterol sulfate[42]
SULT2B1	Sulfotransferase Family 2B Member 1	Responsible for cholesterol sulfation, which plays a major role in the regulation of epidermal differentiation[43]
SUMF1	Sulfatase Modifying Factor 1	Responsible for modifying various sulfatases[44,45]
Lamellar bodies		
SNAP29	Synaptosome Associated Protein 29	Mediates lamellar body fusion events[46]
VIPAS39	VPS33B Interacting Protein, Apical-Basolateral Polarity Regulator, Spe-39 Homolog	Mediates lamellar body fusion events[47]
VPS33B	VPS33B Late Endosome And Lysosome Associated	Mediates lamellar body fusion events[48]
Dolichol		

DOLK	Dolichol Kinase	Phosphates dolichol[49]
MPDU1	Mannose-P-Dolichol Utilization Defect 1	Adds mannose to dolichols as preparation for protein O-glycosylation and N-mannosylation[50]
PIGL	Phosphatidylinositol Glycan Anchor Biosynthesis Class L	Involved in GPI anchor synthesis[51]
SRD5A3	Steroid 5 Alpha-Reductase 3	Involved in dolichol synthesis[52]
Intercellular junctions		
Tight junctions		
CLDN1	Claudin 1	Tight junction protein, controls paracellular permeability[53]
CLDN10	Claudin 10	Tight junction protein, controls paracellular permeability[54]
Gap junctions		
GJA1	Gap Junction Protein Alpha 1 (Connexin 43)	Gap junction protein, controls intercellular communication[55]
GJB2	Gap Junction Protein Beta 2 (Connexin 26)	Gap junction protein, controls intercellular communication[56]
GJB3	Gap Junction Protein Beta 3 (Connexin 31)	Gap junction protein, controls intercellular communication[57]
GJB4	Gap Junction Protein Beta 4 (Connexin 30.3)	Gap junction protein, controls intercellular communication[58]
GJB6	Gap Junction Protein Beta 6 (Connexin 30)	Gap junction protein, controls intercellular communication[59]
Desmosomes		
CDSN	Corneodesmosin	Component of corneodesmosomes in the SC, increases mechanical resistance[60]
DSG1	Desmoglein 1	Desmosome protein, ensures intercellular adhesion[61,62]
DSP	Desmoplakin	Desmosome protein, ensures intercellular adhesion[61,62]
FLG2	Filaggrin 2	Ensures cell-cell adhesion in the upper epidermal layers in a corneodesmosin-dependent fashion[63]
PERP	P53 Apoptosis Effector Related To PMP22	Promotes desmosome assembly[64]
Proteases and inhibitors		
SPINK5	Serine Peptidase Inhibitor Kazal Type 5	Serine protease inhibitor, prevents junction degradation[65,66]
CAST	Calpastatin	Cysteine protease inhibitor, prevents junction degradation[67]
CSTA	Cystatin A	Cysteine protease inhibitor, prevents junction degradation[68]
SERPINB8	Serpin Family B Member 8	Serine protease inhibitor, prevents junction degradation[69]
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[70]
Transcription / translation		
AARS1	Alanyl-TRNA Synthetase 1	Alanyl-tRNA synthetase[71]

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[72]
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[73]
GTF2E2	General Transcription Factor IIE Subunit 2	Component of the TFIIE complex involved in type 2 gene transcription[74]
GTF2H5	General Transcription Factor IIH Subunit 5	Component of the TFIIH complex involved in nucleotide excision repair and type 2 gene transcription[75]
MARS1	Methionyl-TRNA Synthetase 1	Methionyl-tRNA synthetase[71]
RNF113A	Ring Finger Protein 113A	Ring finger protein involved in pre-mRNA splicing[76]
TARS1	Threonyl-TRNA Synthetase 1	Threonyl-tRNA synthetase[77]
Miscellaneous		
AP1B1	Adaptor Related Protein Complex 1 Subunit Beta 1	Part of clathrin-coated vesicle adaptor complex[78,79]
AP1S1	Adaptor Related Protein Complex 1 Subunit Sigma 1	Part of clathrin-coated vesicle adaptor complex[78,79]
MPLKIP	M-Phase Specific PLK1 Interacting Protein	Interacts with cyclin dependent and polo kinases, maintains cell cycle integrity[80]
TRPM4	Transient Receptor Potential Cation Channel Subfamily M Member 4	Calcium activated-ion channel, associated with proliferation regulation[81]

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*[5] (SD, MIM: 146700), *CASP14*[4] (AR, MIM: 617320), *ASPRV1*[3] (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[82]. 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[4]. *ASPRV1* (MIM: 146750), causes ichthyosis that resembles lamellar ichthyosis (see below), but has hyperlinear palms and no collodion membrane at birth[3].
Recessive X-linked ichthyosis (RXLI, ORPHA: 461)	*STS*[42] (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[82,83]. 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[82,83].
Autosomal recessive congenital ichthyosis (ARCI, ORPHA: 281097)		This heterogeneous subgroup often presents at birth[84] as a collodion baby, characterized by encasement in a shiny membrane that peels off within a few weeks after birth[83] 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*[9] (AR, MIM: 601277), *ALOX12B*[85] (AR, MIM: 242100), *ALOXE3*[86] (AR, MIM: 606545), *CYP4F22*[16] (AR, MIM: 604777), *LIPN*[22] (AR, MIM: 613943), *NIPAL4*[23] (AR, MIM: 612281), *SDR9C7*[33] (AR, MIM: 617574), *SULT2B1*[43] (AR, MIM: 617571), *TGM1*[36] (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[84].
Congenital ichthyosiform erythroderma (CIE, ORPHA: 79394)	*ABCA12*[87] (AR, MIM: 601277), *ALOX12B*[12] (AR, MIM: 242100), *ALOXE3*[12] (AR, MIM: 606545), *CERS3*[15] (AR, MIM: 615023), *CYP4F22*[88] (AR, MIM: 604777), *NIPAL4*[23] (AR, MIM: 612281), *PNPLA1*[31] (AR, MIM: 615024), *TGM1*[89] (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[84]. While homozygosity mapping identified an additional causative locus at 12p11.2-q13.1 (MIM: 615022)[90], it has later been revealed that *SDR9C7* and *ALOX12B* were the genes responsible for those cases[91].
Harlequin ichthyosis (HI, ORPHA: 457)	*ABCA12*[92] (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)[83]. 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[83].
Self-healing collodion baby (SHCB, ORPHA: 281122)	*ALOX12B*[93] (AR, MIM: 242100), *ALOXE3*[94] (AR, MIM: 606545), *CYP4F22*[95] (AR, MIM: 604777), *TGM1*[96] (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[82]. 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[96].

Acral self-healing collodion baby (ASHCB, ORPHA: 281127)	*TGM1*[97] (AR, MIM: 242300)	A very rare variant similar to the SHCB, but the collodion membrane affects only the extremities[84]
Bathing suit ichthyosis (BSI, ORPHA: 100976)	*TGM1*[98] (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[82] because of temperature-sensitive pathogenic variants that affect warmer body areas.
Keratinopathic ichthyoses (KPI, ORPHA: 281103)		
Autosomal dominant epidermolytic ichthyosis (EI, ORPHA: 312)	*KRT1*[1] (AD, MIM: 113800), *KRT10*[1] (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[1]. 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)[1]
Autosomal recessive epidermolytic ichthyosis (AREI, ORPHA: 512103)	*KRT10*[99] (AR, MIM: 113800)	Shows similar symptoms to EI[99].
Superficial epidermolytic ichthyosis (SEI, ORPHA: 455)	*KRT2*[2] (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)[84].
Annular epidermolytic ichthyosis (AEI, ORPHA: 281139)	*KRT1*[100] (AD, MIM: 607602), *KRT10*[101] (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[100].
Ichthyosis Curth-Macklin (ICM, ORPHA: 79503)	*KRT1*[102] (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[102].
Epidermolytic nevus (EN, ORPHA: 497737)	*KRT1*[103] (M, MIM: -), *KRT10*[104] (M, MIM: -), *KRT2*[105] (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[82,84]. 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[104]
Ichthyosis with confetti (IWC, ORPHA: 281190)	*KRT1*[106] (AD, MIM: 609165), *KRT10*[107] (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[106]. This "confetti" patches of normal skin result from loss of heterozygosity of the disease-causing allele by mitotic recombination[106]. 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[63] . They are further subdivided depending on the affected areas
Generalized peeling skin syndrome (generalized PSS, ORPHA: 263543)	*CDSN*[60] (AR, MIM: 270300), *FLG2*[63] (AR, MIM: 618084)	Peeling involves the entire surface of the skin[63] 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*[108] (AR, MIM: 607936), *TGM5*[8] (AR, MIM: 609796)	The shedding affects primarily the plantar and dorsal surfaces of the hands and feet[63].
Exfoliative ichthyosis (ORPHA: 289586)	*CSTA*[68] (AR, MIM: 607936), *SERPINB8*[69] (AR, MIM: 617115)	Characterized by shedding of the skin and generalized dry, scaling skin[68]. It is not typically classified as a PSS, but exfoliative ichthyosis shares signs and underlying molecular basis with acral PSS[68].
Peeling skin-leukonychia-acral punctate keratoses-cheilitis-knuckle pads syndrome (PLACK, ORPHA: 44138)	*CAST*[67] (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*[7] (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[7]
Erythrokeratoderma variabilis et progressiva (EKVP, ORPHA: 308166)	*GJA1*[55] (AD, MIM: 617525), *GJB3*[57] (AD or AR, MIM: 133200), *GJB4*[58] (AD, MIM: 617524), *KDSR*[21] (AR, MIM: 617526), *PERP*[64] (AR, MIM: 619209), *TRPM4*[81] (AD, MIM: 618531)	An umbrella term that includes patients with similar clinical findings: migratory erythema and hyperkeratotic lesions, which change size over time[109] (sometimes called erythrokeratoderma variabilis (EKV)) and/or fixed brown-red hyperkeratotic plaques[58] (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*[110] or *ABCA12*[111] mutations
Keratosis linearis-ichthyosis congenita-sclerosing keratoderma syndrome (KLICK, ORPHA: 281201)	*POMP*[6] (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[6].

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*[112] (HD, MIM: 308100) + contiguous genes	Results from X-chromosomal deletions that include *STS*, which is responsible for the ichthyotic phenotype, and contiguous genes[112]. Clinical manifestations will depend on the spectrum of genes deleted along with *STS*[112], 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[113] with other manifestations.
Ichthyosis follicularis-alopecia-photophobia syndrome (IFAP, ORPHA: 2273)	*MBTPS2*[40] (XR, MIM: 308205), *SREBF1*[41] (AD, MIM: 619016)	Characterized by generalized skin thickening and erythema, with follicular-based accentuation, palmoplantar keratoderma, usually total baldness (alopecia) and light sensitivity (photophobia)[40]. 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*[39] (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[39].
Male EBP disorder with neurological defects (MEND, ORPHA:) 401973	*EBP*[114] (XR, MIM: 300960)	Characterized by ichthyosis, neurological symptoms (delayed development and seizures), and craniofacial dysmorphism, with possible involvement of other organs[114].
Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD, ORPHA: 139)	*NSDHL*[38] (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)[38].
Autosomal ichthyosis syndromes (with)		
Prominent hair abnormalities (ORPHA: 281222)		
Netherton syndrome (NS, ORPHA: 634)	*SPINK5*[65] (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[65]. 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[65]. 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)[65] and verrucous lesions.
Severe dermatitis-multiple allergies-metabolic wasting syndrome (SAM, ORPHA: 369992)	*DSG1*[61] (AR, MIM: 615508), *DSP*[62] (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[61].
Ichthyosis-hypotrichosis syndrome (IHS, ORPHA: 91132)	*ST14*[70] (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[70].
Ichthyosis, leukocyte vacuoles, alopecia, and sclerosing cholangitis; (ILVASC, ORPHA: 59303)	*CLDN1*[53] (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[53].
Trichothiodystrophy (TTD, ORPHA: 33364)	*AARS1*[71] (AR, MIM: 619691), *ERCC2*[72] (AR, MIM: 601675), *ERCC3*[73] (AR, MIM: 616390),	Characterized by sulfur deficiency leading to ichthyosis and brittle hair and nails[71]. Some forms of this disease are photosensitive, with progressive neuropathy and accelerated aging, associated with defects in DNA repair[71]. This subgroup is caused by variants in *ERCC2*, *ERCC3*, and *GTF2H5*.

	GTF2E2[74] (AR, MIM: 616943), *GTF2H5*[75] (AR, MIM: 616395), *MAARS1*[71] (AR, MIM: 619692), *MPLKIP*[80] (AR, MIM: 234050), *RNF113A*[76] (XR, MIM: 300953), *TARS1*[77] (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*[11] (AR, MIM: 270200)	Also known as fatty acid alcohol oxidoreductase deficiency. It is characterized by intellectual disability, spasticity and skin thickening[11].
Refsum disease (ORPHA: 773)	*PEX7*[25] (AR, MIM: 308100), *PHYH*[29,30] (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[25].
Cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma syndrome (CEDNIK, ORPHA: 66631)	*SNAP29*[46] (AR, MIM: 609528)	Typically leads to early death from aspiration pneumonia[46].
Mental disability-enteropathy-deafness-peripheral neuropathy-ichthyosis-keratoderma syndrome (MEDNIK, ORPHA: 171851)	*AP1S1*[78] (AR, MIM: 609313), *AP1B1*[79] (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*[18] (AD, MIM: 618527)	Ichthyotic keratoderma, spastic paraplegia - hypomyelination - dysmorphic facies
Congenital ichthyosis-intellectual disability-spastic quadriplegia syndrome (ORPHA: 352333)	*ELOVL4*[19] (AR, MIM: 614457)	Also known as ELOVL4-related neuro-ichthyosis, this disease also features seizures.
Arthrogryposis-renal dysfunction-cholestasis syndrome (ARC, ORPHA: 2697)	*VIPAS39*[47] (AR, MIM: 613404), *VPS33B*[48] (AR, MIM: 208085)	Characterized by neurogenic arthrogryposis, renal tubular dysfunction, bile production defects (cholestasis), ichthyosis and death within the first year of life[48]. This disease is allelic to autosomal recessive-keratoderma-ichthyosis-deafness (ARKID, ORPHA: -), also caused by recessive pathogenic variants in *VPS33B*[115].
Fetal Gaucher disease (FGD, ORPHA: 85212)	*GBA1*[20] (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[20]. These neonates and infants experience progressive neurologic deterioration.
Multiple sulfatase deficiency (MSD, ORPHA: 585)	*SUMF1*[44] (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[116].
Neu-Laxova syndrome (NLS, ORPHA: 2671)	*PHGDH*[27] (AR, MIM: 256520), *PSAT1*[28] (AR, MIM: 616038), *PSPH*[26] (AR, MIM: -)	Characterized by collodion membrane, severe malformations, microcephaly, and intra uterine growth retardation that lead to death *in utero* or shortly after birth[26].
Disorders of glycosylation		
Deficiency of UDP-glucose ceramide glycosyltransferase (ORPHA: -)	*UGCG*[37] (AR, MIM: -)	Manifests as a collodion baby with congenital joint contractures[37]. This newly described condition has largely been lethal during the first months of life, but would be expected to cause severe neurologic effects[37]
Congenital disorder of glycosylation type 1F (CDG-1F, ORPHA: 79323)	*MPDU1*[50] (AR, MIM: 609180)	Characterized by excess muscle tone (hypertonia), psychomotor retardation and ichthyosis[50].

Congenital disorder of glycosylation type 1M (CDG-1M, ORPHA: 91131)	*DOLK*[49] (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[49].
Congenital disorder of glycosylation type 1Q (CDG-1Q, ORPHA: 324737)	*SRD5A3*[52] (AR, MIM: 612379)	Features ocular colobomas, brain malformations leading to mental retardation, hyperplasia of the pituitary gland, and ichthyosis[52].
Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation, and ear anomalies syndrome (CHIME, ORPHA: 3474)	*PIGL*[51] (AR, MIM: 280000)	Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation, and ear anomalies[51]
Other associated signs (ORPHA: 281244)		
Keratitis-ichthyosis-deafness syndrome (KID, ORPHA: 477)	*GJB2* (AD[56] or M[117], MIM: 148210), *GJB6*[59] (AD, MIM: -), *AP1B1*[118] (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[59]. 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[117].
Neutral lipid storage disease with ichthyosis (NLSDI, ORPHA: 98907)	*ABHD5*[10] (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[10]. Histologically, patients show lipid vacuole accumulation in most tissues[10].
Ichthyosis-prematurity syndrome (IPS, ORPHA: 88621)	*SLC27A4*[34] (AR, MIM: 608649)	Characterized by premature birth, neonatal asphyxia, and cobblestone-like plaques of ichthyosis with extensive desquamative scaling that can resemble vernix[34] and tends to improve drastically during the neonatal period to near-normal skin.
Erythrokeratodermia-cardiomyopathy syndrome (EKC, ORPHA: 476096)	*DSP* (AD[119] or AR[120], MIM: 605676)	Characterized by early failure to thrive, wooly hair, erythema with fine scaling, and dilated cardiomyopathy[120].
Hypohidrosis-electrolyte imbalance-lacrimal gland dysfunction-ichthyosis-xerostomia syndrome (HELIX, ORPHA: 528105)	*CLDN10*[54] (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[54].
Ichthyosis-short stature-brachydactyly-microspherophakia syndrome (ORPHA: 363992)	*CERS3*[15] + *ADAMTS17*[15] (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*)[15].
Palmoplantar and perianal keratoderma/harlequin ichthyosis-like ichthyosis with thrombocytopenia (ORPHA: -)	*KDSR*[121] (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.

References

1. Rothnagel, J. A. *et al.* Mutations in the Rod Domains of Keratins 1 and 10 in Epidermolytic Hyperkeratosis. *Science (80-.).* **257**, 1128–1130 (1992).

2. Rothnagel, J. A. *et al.* Mutations in the rod domain of keratin 2e in patients with ichthyosis bullosa of Siemens. *Nat. Genet. 1994 74* **7**, 485–490 (1994).

3. Boyden, L. M. *et al.* Mutations in ASPRV1 Cause Dominantly Inherited Ichthyosis. *Am. J. Hum. Genet.* **107**, 158 (2020).

4. Kirchmeier, P., Zimmer, A., Bouadjar, B., Rösler, B. & Fischer, J. Whole-exome-sequencing reveals small deletions in CASP14 in patients with autosomal recessive inherited ichthyosis. *Acta Derm. Venereol.* **97**, 102–104 (2017).

5. Sybert, V. P., Dale, B. A. & Holbrook, K. A. Ichthyosis vulgaris: identification of a defect in synthesis of filaggrin correlated with an absence of keratohyaline granules. *J. Invest. Dermatol.* **84**, 191–194 (1985).

6. Dahlqvist, J. *et al.* A single-nucleotide deletion in the POMP 5' UTR causes a transcriptional switch and altered epidermal proteasome distribution in KLICK genodermatosis. *Am. J. Hum. Genet.* **86**, 596–603 (2010).

7. Maestrini, E. *et al.* A molecular defect in loricrin, the major component of the cornified cell envelope, underlies Vohwinkel's syndrome. *Nat. Genet. 1996 131* **13**, 70–77 (1996).

8. Cassidy, A. J. *et al.* A homozygous missense mutation in TGM5 abolishes epidermal transglutaminase 5 activity and causes acral peeling skin syndrome. *Am. J. Hum. Genet.* **77**, 909–917 (2005).

9. Lefèvre, C. *et al.* Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Hum. Mol. Genet.* **12**, 2369–2378 (2003).

10. Lefèvre, C. *et al.* Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. *Am. J. Hum. Genet.* **69**, 1002–1012 (2001).

11. De Laurenzi, V. *et al.* Sjögren-Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nat. Genet.* **12**, 52–57 (1996).

12. Jobard, F. *et al.* Lipoxygenase-3 (ALOXE3) and 12(R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13.1. *Hum. Mol. Genet.* **11**, 107–113 (2002).

13. Rabionet, M., Gorgas, K. & Sandhoff, R. Ceramide synthesis in the epidermis. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* **1841**, 422–434 (2014).

14. Linn, S. C. *et al.* Regulation of de novo sphingolipid biosynthesis and the toxic consequences of its disruption. *Biochem. Soc. Trans.* **29**, 831 (2001).

15. Radner, F. P. W. *et al.* Mutations in CERS3 Cause Autosomal Recessive Congenital Ichthyosis in Humans. *PLOS Genet.* **9**, e1003536 (2013).

16. Lefèvre, C. *et al.* Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. *Hum. Mol. Genet.* **15**, 767–776 (2006).

17. Ohno, Y. *et al.* Essential role of the cytochrome P450 CYP4F22 in the production of acylceramide, the key lipid for skin permeability barrier formation. *Proc. Natl. Acad. Sci. U. S. A.* **112**, 7707–7712 (2015).

18. Mueller, N. *et al.* De novo mutation in ELOVL1 causes ichthyosis, acanthosis nigricans, hypomyelination, spastic paraplegia, high frequency deafness and optic atrophy. *J. Med. Genet.* **56**, 164–175 (2019).

19. Aldahmesh, M. A. *et al.* Recessive Mutations in ELOVL4 Cause Ichthyosis, Intellectual Disability, and Spastic Quadriplegia. *Am. J. Hum. Genet.* **89**, 745–750 (2011).

20. Sidransky, E. *et al.* The clinical, molecular, and pathological characterisation of a family with two cases of lethal perinatal type 2 Gaucher disease. *J Med Genet* **33**, 132–136 (1996).

21. Boyden, L. M. *et al.* Mutations in KDSR Cause Recessive Progressive Symmetric Erythrokeratoderma. *Am. J. Hum. Genet.* **100**, 978–984 (2017).

22. Israeli, S. *et al.* A Mutation in LIPN, Encoding Epidermal Lipase N, Causes a Late-Onset Form of Autosomal-Recessive Congenital Ichthyosis. *Am. J. Hum. Genet.* **88**, 482 (2011).

23. Lefèvre, C. *et al.* Mutations in ichthyin a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. *Hum. Mol. Genet.*

13, 2473–2482 (2004).

24. Honda, Y. *et al.* Decreased Skin Barrier Lipid Acylceramide and Differentiation-Dependent Gene Expression in Ichthyosis Gene Nipal4-Knockout Mice. *J. Invest. Dermatol.* **138**, 741–749 (2018).

25. Van Den Brink, D. M. *et al.* Identification of PEX7 as the Second Gene Involved in Refsum Disease. *Am. J. Hum. Genet.* **72**, 471–477 (2003).

26. Acuna-Hidalgo, R. *et al.* Neu-Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the L-serine biosynthesis pathway. *Am. J. Hum. Genet.* **95**, 285–293 (2014).

27. Shaheen, R. *et al.* Neu-Laxova syndrome, an inborn error of serine metabolism, is caused by mutations in PHGDH. *Am. J. Hum. Genet.* **94**, 898–904 (2014).

28. Hart, C. E. *et al.* Phosphoserine Aminotransferase Deficiency: A Novel Disorder of the Serine Biosynthesis Pathway. *Am. J. Hum. Genet.* **80**, 931 (2007).

29. Jansen, G. A. *et al.* Refsum disease is caused by mutations in the phytanoyl–CoA hydroxylase gene. *Nat. Genet. 1997 172* **17**, 190–193 (1997).

30. Mihalik1, S. J. *et al.* Identification of PAHX, a Refsum disease gene. *Nat. Genet. 1997 172* **17**, 185–189 (1997).

31. Grall, A. *et al.* PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. *Nat. Genet. 2012 442* **44**, 140–147 (2012).

32. Kien, B. *et al.* ABHD5 stimulates PNPLA1-mediated ω- O-acylceramide biosynthesis essential for a functional skin permeability barrier. *J. Lipid Res.* **59**, 2360–2367 (2018).

33. Shigehara, Y. *et al.* Mutations in SDR9C7 gene encoding an enzyme for vitamin A metabolism underlie autosomal recessive congenital ichthyosis. *Hum. Mol. Genet.* **25**, 4484–4493 (2016).

34. Klar, J. *et al.* Mutations in the Fatty Acid Transport Protein 4 Gene Cause the Ichthyosis Prematurity Syndrome. *Am. J. Hum. Genet.* **85**, 248–253 (2009).

35. Yamamoto, H., Hattori, M., Chamulitrat, W., Ohno, Y. & Kihara, A. Skin permeability barrier formation by the ichthyosis-causative gene FATP4 through formation of the barrier lipid ω-O-acylceramide. *Proc. Natl. Acad. Sci. U. S. A.* **117**, 2914–2922 (2020).

36. Huber, M. *et al.* Mutations of Keratinocyte Transglutaminase in Lamellar Ichthyosis. *Science (80-.).* **267**, 525–528 (1995).

37. Monies, D. *et al.* Identification of a novel lethal form of autosomal recessive ichthyosis caused by UDP-glucose ceramide glucosyltransferase deficiency. *Clin. Genet.* **93**, 1252–1253 (2018).

38. Kö, A., Happle, R., Bornholdt, D., Engel, H. & Grzeschik, K.-H. Mutations in the NSDHL Gene, Encoding a 3-Hydroxysteroid Dehydrogenase, Cause CHILD Syndrome. *J. Med. Genet* **90**, 339–346 (2000).

39. Derry, J. M. J. *et al.* Mutations in a delta 8-delta 7 sterol isomerase in the tattered mouse and X-linked dominant chondrodysplasia punctata. *Nat. Genet.* **22**, 286–290 (1999).

40. Oeffner, F. *et al.* IFAP syndrome is caused by deficiency in MBTPS2, an intramembrane zinc metalloprotease essential for cholesterol homeostasis and ER stress response. *Am. J. Hum. Genet.* **84**, 459–467 (2009).

41. Wang, H. *et al.* Mutations in SREBF1, Encoding Sterol Regulatory Element Binding Transcription Factor 1, Cause Autosomal-Dominant IFAP Syndrome. *Am. J. Hum. Genet.* **107**, 34–45 (2020).

42. Mohandas, T., Shapiro, L. J., Sparkes, R. S. & Sparkes, M. C. Regional assignment of the steroid sulfatase—X-linked ichthyosis locus: Implications for a noninactivated region on the short arm of human X chromosome. *Proc. Natl. Acad. Sci.* **76**, 5779–5783 (1979).

43. Heinz, L. *et al.* Mutations in SULT2B1 Cause Autosomal-Recessive Congenital Ichthyosis in Humans. *Am. J. Hum. Genet.* **100**, 926–939 (2017).

44. Dierks, T. *et al.* Multiple Sulfatase Deficiency Is Caused by Mutations in the Gene Encoding the Human Cα-Formylglycine Generating Enzyme. *Cell* **113**, 435–444 (2003).

45. Cosma, M. P. *et al.* The Multiple Sulfatase Deficiency Gene Encodes an Essential and Limiting Factor for the Activity of Sulfatases. *Cell* **113**, 445–456 (2003).

46. Sprecher, E. *et al.* A mutation in SNAP29, coding for a SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma. *Am. J. Hum. Genet.* **77**, 242–251 (2005).

47. Cullinane, A. R. *et al.* Mutations in VIPAR cause an arthrogryposis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization. *Nat. Genet. 2010 424* **42**, 303–312 (2010).

48. Gissen, P. *et al.* Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome. *Nat. Genet. 2004 364* **36**, 400–404 (2004).

49. Kranz, C. *et al.* A Defect in Dolichol Phosphate Biosynthesis Causes a New Inherited Disorder with Death in Early Infancy. *Am. J. Hum. Genet.* **80**, 433 (2007).

50. Schenk, B. *et al.* MPDU1 mutations underlie a novel human congenital disorder of glycosylation, designated type If. *J. Clin. Invest.* **108**, 1687–1695 (2001).

51. Ng, B. G. *et al.* Mutations in the Glycosylphosphatidylinositol Gene PIGL Cause CHIME Syndrome. *Am. J. Hum. Genet.* **90**, 685–688 (2012).

52. Al-Gazali, L., Hertecant, J., Algawi, K., El Teraifi, H. & Dattani, M. A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnormalities in an inbred Emirati family. *Am. J. Med. Genet. Part A* **146A**, 813–819 (2008).

53. Baala, L. *et al.* Homozygosity mapping of a locus for a novel syndromic ichthyosis to chromosome 3q27-q28. *J. Invest. Dermatol.* **119**, 70–76 (2002).

54. Hadj-Rabia, S. *et al.* Multiplex epithelium dysfunction due to CLDN10 mutation: the HELIX syndrome. *Genet. Med. 2018 202* **20**, 190–201 (2017).

55. Boyden, L. M. *et al.* Dominant De Novo Mutations in GJA1 Cause Erythrokeratodermia Variabilis et Progressiva, without Features of Oculodentodigital

Dysplasia. *J. Invest. Dermatol.* **135**, 1540–1547 (2015).

56. Richard, G. *et al.* Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. *Am. J. Hum. Genet.* **70**, 1341–1348 (2002).

57. Richard, G. *et al.* Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis. *Nat. Genet.* **20**, 366–369 (1998).

58. Macari, F. *et al.* Mutation in the Gene for Connexin 30.3 in a Family with Erythrokeratodermia Variabilis. *Am. J. Hum. Genet.* **67**, 1296–1301 (2000).

59. Jan, A. Y., Amin, S., Ratajczak, P., Richard, G. & Sybert, V. P. Genetic heterogeneity of KID syndrome: identification of a Cx30 gene (GJB6) mutation in a patient with KID syndrome and congenital atrichia. *J. Invest. Dermatol.* **122**, 1108–1113 (2004).

60. Oji, V. *et al.* Loss of Corneodesmosin Leads to Severe Skin Barrier Defect, Pruritus, and Atopy: Unraveling the Peeling Skin Disease. *Am. J. Hum. Genet.* **87**, 274–281 (2010).

61. Samuelov, L. *et al.* Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat. Genet. 2013 4510* **45**, 1244–1248 (2013).

62. McAleer, M. A. *et al.* Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin. *J. Allergy Clin. Immunol.* **136**, 1268 (2015).

63. Alfares, A. *et al.* Peeling skin syndrome associated with novel variant in FLG2 gene. *Am. J. Med. Genet. Part A* **173**, 3201–3204 (2017).

64. Duchatelet, S. *et al.* Mutations in PERP Cause Dominant and Recessive Keratoderma. *J. Invest. Dermatol.* **139**, 380–390 (2019).

65. Chavanas, S. *et al.* Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat. Genet. 2000 252* **25**, 141–142 (2000).

66. Deraison, C. *et al.* LEKTI Fragments Specifically Inhibit KLK5, KLK7, and KLK14 and Control Desquamation through a pH-dependent Interaction. *Mol. Biol. Cell* **18**, 3607 (2007).

67. Lin, Z. *et al.* Loss-of-function mutations in CAST cause peeling skin, leukonychia, acral punctate keratoses, cheilitis, and knuckle pads. *Am. J. Hum. Genet.* **96**, 440–447 (2015).

68. Blaydon, D. C. *et al.* Mutations in CSTA, encoding Cystatin A, underlie exfoliative ichthyosis and reveal a role for this protease inhibitor in cell-cell adhesion. *Am. J. Hum. Genet.* **89**, 564–571 (2011).

69. Pigors, M. *et al.* Loss-of-Function Mutations in SERPINB8 Linked to Exfoliative Ichthyosis with Impaired Mechanical Stability of Intercellular Adhesions. *Am. J. Hum. Genet.* **99**, 430–436 (2016).

70. Basel-Vanagaite, L. *et al.* Autosomal Recessive Ichthyosis with Hypotrichosis Caused by a Mutation in ST14, Encoding Type II Transmembrane Serine Protease Matriptase. *Am. J. Hum. Genet.* **80**, 467 (2007).

71. Botta, E. *et al.* Protein instability associated with AARS1 and MARS1 mutations causes trichothiodystrophy. *Hum. Mol. Genet.* **30**, 1711–1720 (2021).

72. K. Takayama, D. M. Danks, E. P. Salazar, J. E. Cleaver, C. A. W. DNA repair characteristics and mutations in the ERCC2 DNA repair and transcription gene in a trichothiodystrophy patient. *Hum. Mutat.* **9**, 519–25 (1997).

73. Weeda, G. *et al.* A mutation in the XPB/ERCC3 DNA repair transcription gene, associated with trichothiodystrophy. *Am. J. Hum. Genet.* **60**, 320 (1997).

74. Kuschal, C. *et al.* GTF2E2 Mutations Destabilize the General Transcription Factor Complex TFIIE in Individuals with DNA Repair-Proficient Trichothiodystrophy. *Am. J. Hum. Genet.* **98**, 627–642 (2016).

75. Giglia-Mari, G. *et al.* A new, tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. *Nat. Genet. 2004 367* **36**, 714–719 (2004).

76. Corbett, M. A. *et al.* A novel X-linked trichothiodystrophy associated with a nonsense mutation in RNF113A. *J. Med. Genet.* **52**, 269–274 (2015).

77. Theil, A. F. *et al.* Bi-allelic TARS Mutations Are Associated with Brittle Hair Phenotype. *Am. J. Hum. Genet.* **105**, 434–440 (2019).

78. Montpetit, A. *et al.* Disruption of AP1S1, Causing a Novel Neurocutaneous Syndrome, Perturbs Development of the Skin and Spinal Cord. *PLOS Genet.* **4**, e1000296 (2008).

79. Alsaif, H. S. *et al.* Homozygous Loss-of-Function Mutations in AP1B1, Encoding Beta-1 Subunit of Adaptor-Related Protein Complex 1, Cause MEDNIK-like Syndrome. *Am. J. Hum. Genet.* **105**, 1016–1022 (2019).

80. Nakabayashi, K. *et al.* Identification of C7orf11 (TTDN1) Gene Mutations and Genetic Heterogeneity in Nonphotosensitive Trichothiodystrophy. *Am. J. Hum. Genet.* **76**, 510 (2005).

81. Wang, H. *et al.* Gain-of-Function Mutations in TRPM4 Activation Gate Cause Progressive Symmetric Erythrokeratodermia. *J. Invest. Dermatol.* **139**, 1089–1097 (2019).

82. Oji, V. & Traupe, H. Ichthyosis: clinical manifestations and practical treatment options. *Am. J. Clin. Dermatol.* **10**, 351–364 (2009).

83. Traupe, H., Fischer, J. & Oji, V. Nonsyndromic types of ichthyoses - an update. *J. Dtsch. Dermatol. Ges.* **12**, 109–121 (2014).

84. Oji, V. *et al.* Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorze 2009. *J. Am. Acad. Dermatol.* **63**, 607–641 (2010).

85. Lesueur, F. *et al.* Novel mutations in ALOX12B in patients with autosomal recessive congenital ichthyosis and evidence for genetic heterogeneity on chromosome 17p13. *J. Invest. Dermatol.* **127**, 829–834 (2007).

86. Sugiura, K. & Akiyama, M. Lamellar ichthyosis caused by a previously unreported homozygous ALOXE3 mutation in East Asia. *Acta Derm. Venereol.* **95**, 858–859 (2015).

87. Akiyama, M. ABCA12 mutations and autosomal recessive congenital ichthyosis: A review of genotype/phenotype correlations and of pathogenetic concepts. *Hum. Mutat.* **31**, 1090–1096 (2010).

88. Hellström Pigg, M. *et al.* Spectrum of Autosomal Recessive Congenital Ichthyosis in Scandinavia: Clinical Characteristics and Novel and Recurrent Mutations in 132 Patients. *Acta Derm. Venereol.* **96**, 932–937 (2016).

89. Laiho, E. *et al.* Transglutaminase 1 mutations in autosomal recessive congenital ichthyosis: private and recurrent mutations in an isolated population. *Am. J. Hum. Genet.* **61**, 529–538 (1997).

90. Mizrachi-Koren, M. *et al.* Identification of a Novel Locus Associated with Congenital Recessive Ichthyosis on 12p11.2–q13. *J. Invest. Dermatol.* **125**, 456–462 (2005).

91. Mohamad, J., Malchin, N., Shalev, S., Sarig, O. & Sprecher, E. ARCI7 Revisited and Repositioned. *J. Invest. Dermatol.* **137**, 970–972 (2017).

92. Kelsell, D. P. *et al.* Mutations in ABCA12 Underlie the Severe Congenital Skin Disease Harlequin Ichthyosis. *Am. J. Hum. Genet.* **76**, 794–803 (2005).

93. Harting, M. *et al.* Self-Healing Collodion Membrane and Mild Nonbullous Congenital Ichthyosiform Erythroderma Due to 2 Novel Mutations in the ALOX12B Gene. *Arch. Dermatol.* **144**, 351–356 (2008).

94. Vahlquist, A. *et al.* Genotypic and clinical spectrum of self-improving collodion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients. *J. Invest. Dermatol.* **130**, 438–443 (2010).

95. Noguera-Morel, L. *et al.* Two cases of autosomal recessive congenital ichthyosis due to CYP4F22 mutations: Expanding the genotype of self-healing collodion baby. *Pediatr. Dermatol.* **33**, e48–e51 (2016).

96. Raghunath, M. *et al.* Self-healing collodion baby: a dynamic phenotype explained by a particular transglutaminase-1 mutation. *J. Invest. Dermatol.* **120**, 224–228 (2003).

97. Mazereeuw-Hautier, J. *et al.* Acral self-healing collodion baby: report of a new clinical phenotype caused by a novel TGM1 mutation. *Br. J. Dermatol.* **161**, 456–463 (2009).

98. Oji, V. *et al.* Bathing suit ichthyosis is caused by transglutaminase-1 deficiency: evidence for a temperature-sensitive phenotype. *Hum. Mol. Genet.* **15**, 3083–3097 (2006).

99. Müller, F. B. *et al.* A human keratin 10 knockout causes recessive epidermolytic hyperkeratosis. *Hum. Mol. Genet.* **15**, 1133–1141 (2006).

100. Sybert, V. P. *et al.* Cyclic ichthyosis with epidermolytic hyperkeratosis: A phenotype conferred by mutations in the 2B domain of keratin K1. *Am. J. Hum. Genet.* **64**, 732 (1999).

101. Joh, G. Y. *et al.* A Novel Dinucleotide Mutation in Keratin 10 in the Annular Epidermolytic Ichthyosis Variant of Bullous Congenital Ichthyosiform Erythroderma. *J. Invest. Dermatol.* **108**, 357–361 (1997).

102. Sprecher, E. *et al.* Evidence for Novel Functions of the Keratin Tail Emerging from a Mutation Causing Ichthyosis Hystrix. *J. Invest. Dermatol.* **116**, 511–519 (2001).

103. Tsubota, A. *et al.* Keratin 1 Gene Mutation Detected in Epidermal Nevus with Epidermolytic Hyperkeratosis. *J. Invest. Dermatol.* **127**, 1371–1374 (2007).

104. Paller, A. S. *et al.* Genetic and Clinical Mosaicism in a Type of Epidermal Nevus. *http://dx.doi.org/10.1056/NEJM199411243312103* **331**, 1408–1415 (1994).

105. Diociaiuti, A. *et al.* First Case of KRT2 Epidermolytic Nevus and Novel Clinical and Genetic Findings in 26 Italian Patients with Keratinopathic Ichthyoses. *Int. J. Mol. Sci. 2020, Vol. 21, Page 7707* **21**, 7707 (2020).

106. Choate, K. A. *et al.* Frequent somatic reversion of KRT1 mutations in ichthyosis with confetti. *J. Clin. Invest.* **125**, 1703–1707 (2015).

107. Choate, K. A. *et al.* Mitotic Recombination in Patients with Ichthyosis Causes Reversion of Dominant Mutations in KRT10. *Science* **330**, 94 (2010).

108. Muttardi, K., Nitoiu, D., Kelsell, D. P., O'Toole, E. A. & Batta, K. Acral peeling skin syndrome associated with a novel CSTA gene mutation. *Clin. Exp. Dermatol.* **41**, 394–398 (2016).

109. Van Steensel, M. A. M., Oranje, A. P., Van der Schroeff, J. G., Wagner, A. & Van Geel, M. The missense mutation G12D in connexin30.3 can cause both erythrokeratodermia variabilis of Mendes da Costa and progressive symmetric erythrokeratodermia of Gottron. *Am. J. Med. Genet. Part A* **149A**, 657–661 (2009).

110. Boyden, L. M. *et al.* Phenotypic spectrum of autosomal recessive congenital ichthyosis due to PNPLA1 mutation. *Br. J. Dermatol.* **177**, 319–322 (2017).

111. Sun, Q. *et al.* The Genomic and Phenotypic Landscape of Ichthyosis: An Analysis of 1000 Kindreds. *JAMA dermatology* **158**, 16–25 (2022).

112. Elias, P. M. *et al.* Basis For Abnormal Desquamation And Permeability Barrier Dysfunction in RXLI. *J. Invest. Dermatol.* **122**, 314–319 (2004).

113. Ma, W. *et al.* Novel Microdeletion in the X Chromosome Leads to Kallmann Syndrome, Ichthyosis, Obesity, and Strabismus. *Front. Genet.* **11**, 596 (2020).

114. Milunsky, J. M., Maher, T. A. & Metzenberg, A. B. Molecular, biochemical, and phenotypic analysis of a hemizygous male with a severe atypical phenotype for X-linked dominant Conradi-Hunermann-Happle syndrome and a mutation in EBP. *Am. J. Med. Genet. Part A* **116A**, 249–254 (2003).

115. Gruber, R. *et al.* Autosomal Recessive Keratoderma-Ichthyosis-Deafness (ARKID) Syndrome Is Caused by VPS33B Mutations Affecting Rab Protein Interaction and Collagen Modification. *J. Invest. Dermatol.* **137**, 845–854 (2017).

116. Schlotawa, L. *et al.* A systematic review and meta-analysis of published cases reveals the natural disease history in multiple sulfatase deficiency. *J. Inherit. Metab. Dis.* **43**, 1288–1297 (2020).

117. Titeux, M. *et al.* Keratitis-ichthyosis-deafness syndrome caused by GJB2 maternal mosaicism. *J. Invest. Dermatol.* **129**, 776–779 (2009).

118. Boyden, L. M. *et al.* Recessive Mutations in AP1B1 Cause Ichthyosis, Deafness, and Photophobia. *Am. J. Hum. Genet.* **105**, 1023 (2019).

119. Boyden, L. M. *et al.* Dominant de novo DSP mutations cause erythrokeratodermia-cardiomyopathy syndrome. *Hum. Mol. Genet.* **25**, 348 (2016).

120. Norgett, E. E. *et al.* Recessive mutation in desmoplakin disrupts desmoplakin–intermediate filament interactions and causes dilated cardiomyopathy,

woolly hair and keratoderma. *Hum. Mol. Genet.* **9**, 2761–2766 (2000).

121. Takeichi, T. *et al.* Biallelic Mutations in KDSR Disrupt Ceramide Synthesis and Result in a Spectrum of Keratinization Disorders Associated with Thrombocytopenia. *J. Invest. Dermatol.* **137**, 2344 (2017).