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

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Background: Inherited ichthyoses belong to a large, clinically and etiologically heterogeneous group of mendelian disorders of cornification, typically involving the entire integument. Over the recent years, much

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progress has been made defining their molecular causes. However, there is no internationally accepted classification and terminology.

Objective: We sought to establish a consensus for the nomenclature and classification of inherited ichthyoses.

Methods: The classification project started at the First World Conference on Ichthyosis in 2007. A large international network of expert clinicians, skin pathologists, and geneticists entertained an interactive dialogue over 2 years, eventually leading to the First Ichthyosis Consensus Conference held in Sorèze, France, on January 23 and 24, 2009, where subcommittees on different issues proposed terminology that was debated until consensus was reached.

Results: It was agreed that currently the nosology should remain clinically based. "Syndromic" versus "nonsyndromic" forms provide a useful major subdivision. Several clinical terms and controversial disease names have been redefined: eg, the group caused by keratin mutations is referred to by the umbrella term, "keratinopathic ichthyosis"—under which are included epidermolytic ichthyosis, superficial epidermolytic ichthyosis, and ichthyosis Curth-Macklin. "Autosomal recessive congenital ichthyosis" is proposed as an umbrella term for the harlequin ichthyosis, lamellar ichthyosis, and the congenital ichthyosiform erythroderma group.

Limitations: As more becomes known about these diseases in the future, modifications will be needed.

Conclusion: We have achieved an international consensus for the classification of inherited ichthyosis that should be useful for all clinicians and can serve as reference point for future research. (J Am Acad Dermatol 2010;63:607-41.)

Key words: autosomal recessive congenital ichthyosis; epidermolytic ichthyosis; genetics; histology; keratinopathic ichthyosis; mendelian disorders of cornification; superficial epidermolytic ichthyosis; ultrastructure.

The ichthyoses form part of a large, clinically and etiologically heterogeneous group of mendelian disorders of cornification (MEDOC) and typically involve all or most of the integument.[1-3] During the past few years, much progress has been made in defining the molecular basis of these disorders, and in establishing genotype-phenotype correlations.[4-11] However, there is no universally accepted terminology and classification of the diseases considered under the umbrella term "ichthyosis." Classification schemes and terminology continue to vary greatly among European, North American, and Asian countries. For example, the same entity may be referred to as epidermolytic hyperkeratosis, bullous congenital ichthyosiform erythroderma (CIE), or bullous ichthyosis, depending on where it is diagnosed.[9] Therefore, a new consensus project was initiated at the First World Conference on Ichthyosis 2007 in Münster, Germany (http://www.netzwerk-ichthyose.de/fileadmin/nirk/uploads/Program.pdf). The subsequent process of correspondence involved more than 37 dermatologists, skin pathologists, biologists, and geneticists active in the field of ichthyoses. The discussions led to the 2009 Ichthyosis Consensus Conference on the terminology and classification of inherited ichthyoses, held in Sorèze, France (http://www.netzwerk-ichthyose.de/index.php?id=28&L=1).

Abbreviations used:

ARCI:	autosomal recessive congenital ichthyosis
CDPX2:	chondrodysplasia punctata type 2
CIE:	congenital ichthyosiform erythroderma
EI:	epidermolytic ichthyosis
EKV:	erythrokeratodermia variabilis
EM:	electron microscopy
HI:	harlequin ichthyosis
IV:	ichthyosis vulgaris
KPI:	keratinopathic ichthyosis
LB:	lamellar body
LI:	lamellar ichthyosis
MEDOC:	mendelian disorders of cornification
NS:	Netherton syndrome
PPK:	palmoplantar keratoderma
RXLI:	recessive X-linked ichthyosis
SC:	stratum corneum
SG:	stratum granulosum
TGase:	transglutaminase
TTD:	trichothiodystrophy

Subcommittees were formed to address controversial issues including both terminology and nosology. The consensus achieved is presented in Tables I to III. Tables IV to XII summarize the clinical and morphologic findings of the inherited ichthyoses. Importantly, the clinical classification developed at the conference is consistent with current understanding of molecular causes and pathophysiology,

as summarized in Table XIII, and should be amenable to modification as new information emerges.

AIMS AND LIMITATIONS OF THE CONSENSUS REPORT

The overall goal of the revised classification is to clarify the terminology of this heterogeneous group of inherited skin diseases (Table I). The classification scheme and nosology should be easily understandable for all clinicians, biologists, and students. It should guide clinicians toward the correct genotyping of their patients and facilitate communication with investigators. The proposed classification (Tables II and III) will need to be modified or expanded as new information accrues. A pathophysiologic classification of the ichthyoses and all MEDOC should be initiated in the future (Table XIII).

CAPSULE SUMMARY

- Inherited ichthyoses belong to a large and heterogeneous group of mendelian disorders of cornification and involve the entire integument.
- A conference of experts was convened to reach a consensus on terminology and classification and to provide an internationally accepted frame of reference.
- The classification remains clinically based and distinguishes between syndromic and nonsyndromic ichthyosis forms.
- Bullous ichthyosis/epidermolytic hyperkeratosis is redefined as keratinopathic ichthyosis. Autosomal recessive congenital ichthyosis refers to harlequin ichthyosis, lamellar ichthyosis, and congenital ichthyosiform erythroderma.

RECOMMENDED REVISION OF THE TERMINOLOGY AND CLASSIFICATION OF INHERITED ICHTHYOSIS

The generic term "inherited ichthyosis" refers to diseases that are MEDOC affecting all or most of the integument. The skin changes are clinically characterized by hyperkeratosis, scaling, or both. Despite concern among some participants that the term "ichthyosis"[2] is outmoded and sometimes inaccurate, the consensus was to retain it, as it is too firmly entrenched in the literature and minds of clinicians to be abandoned. Inherited ichthyoses are regarded as one disease group within the greater group of MEDOC. For greater clarity, we redefined some important clinical and dermatologic terms that are in common usage (Table I). Specifically, the revised classification is based on consent to a specific definition of the term "autosomal recessive congenital ichthyosis" (ARCI), and a major change to nomenclature of the ichthyoses caused by keratin mutations (see below).

General framework for the revised classification system

At present, molecular diagnosis is not available for all forms of ichthyosis, and access to genetic diagnostics may be impeded by the high cost of analysis. Similarly, ultrastructural techniques are not in common clinical use by pathologists and are not widely available to clinicians. Other laboratory techniques, including light microscopy, narrow the differential diagnoses in some cases (see "Diagnostic Aspects" section), but decisions regarding further testing, ie, molecular diagnostics, rest on an initial, rigorous clinical evaluation. Therefore, the result of the consensus discussion process is a clinically based classification, in which the diseases are referenced with the causative gene or genes. Two principal groups are recognized: nonsyndromic forms (Table II) and syndromic forms (Table III). This algorithm is in the tradition of previous concepts[3,12-14] and based on the following question:

- Is the phenotypic expression of the disorder only seen in the skin (prototypes: lamellar ichthyosis (LI) and epidermolytic ichthyosis [EI]), or is it seen in the skin and in other organs (prototypes: Sjögren-Larsson syndrome and trichothiodystrophy [TTD])?

Noteworthy, recessive X-linked ichthyosis (RXLI) is regarded as syndromic when accompanied by associated manifestations such as testicular maldescent, and nonsyndromic when ichthyosis occurs as an isolated type[3] without extracutaneous signs. To facilitate the readability and understanding of the long list of autosomal ichthyosis syndromes, subheadings have been introduced that point to the prominent associated signs, eg, hair abnormalities or neurologic signs (Table III).

Another question distinguishes between congenital ichthyosis and ichthyoses of delayed onset. This criterion is important for common ichthyoses (Table IV), namely ichthyosis vulgaris (IV) and RXLI, which often have a delayed onset (Fig 1). However, early subtle skin changes may be overlooked, eg, RXLI may present with fine superficial scaling shortly after birth, which may fade within weeks and recur as a clear ichthyosis in later life. Therefore, considering the high variability of the initial disease presentation of some ichthyoses, eg, TTD, the age of onset has not been chosen as a major classification criterion.

Table I. Main definitions, and recommended new terms and disease names

Recommended terms	Definition
General terminology	
Disorder of cornification (DOC)	Disease with abnormal terminal keratinocytic differentiation
MEDOC	Mendelian disorders of cornification
Inherited ichthyosis	MEDOC affecting all or most of integument characterized by hyperkeratosis and/or scaling
Common ichthyoses	Ichthyoses with high prevalence: IV (1:250-1000) and RXLI (1:2000-6000)
Acquired ichthyosis	Noninherited ichthyosis associated with malignancy; autoimmune, inflammatory, nutritional, metabolic, infectious, and neurologic diseases; or medications
Autosomal recessive congenital ichthyosis (ARCI)*	Modified umbrella term for nonsyndromic congenital ichthyoses referring to HI and spectrum of LI and CIE (Tables II and V)
Keratinopathic ichthyosis (KPI)†	New umbrella term for ichthyoses caused by keratin mutations, namely EI, SEI, and other minor variants (Tables II and VI)
Epidermolytic ichthyosis (EI)	New disease name for bullous ichthyosis, bullous CIE, epidermolytic hyperkeratosis, ichthyosis exfoliativa
Superficial epidermolytic ichthyosis (SEI)	New disease name for ichthyosis bullosa Siemens
Diagnostic main criteria for classification	
Nonsyndromic ichthyosis	Phenotypic expression of underlying genetic defect is only seen in skin
Syndromic ichthyosis	Phenotypic expression of underlying genetic defect is seen in skin and other organs
Clinical and dermatologic terms	
Collodion membrane	Tight shiny cast encasing newborn that cracks after some time, resulting in irregularly branched fissures
Congenital	Disorder is evident at birth or soon after birth (<1 wk)
Delayed onset	Disorder becomes evident after weeks, months, or years
Hyperkeratosis	Histopathological: increased thickness of SC Clinical descriptive: thick and horny skin; it is not necessarily accompanied by visible scaling
Hystrix	Massive hyperkeratosis, cobblestone-like or spiky
Keratoderma	Localized form of hyperkeratosis
Lamellar scaling	Phenotype in which scales tend to be coarse and large (platelike scales)
Scaling	Visible flakes of SC of variable size, color, and thickness

CIE, Congenital ichthyosiform erythroderma; *HI*, harlequin ichthyosis; *IV*, ichthyosis vulgaris; *LI*, lamellar ichthyosis; *MEDOC*, mendelian disorders of cornification; *RXLI*, recessive X-linked ichthyosis; *SC*, stratum corneum.

*Previously termed LI/nonbullous ichthyosiform erythroderma.

†Previously used umbrella term: bullous ichthyosis, epidermolytic hyperkeratosis, or exfoliative ichthyosis.

Classification of ARCI

The acronym "ARCI" has been used as an umbrella term for nonsyndromic disorders, eg, LI and CIE, and for syndromic types of ichthyosis, such as Netherton syndrome (NS). We propose that "ARCI" should be used to refer to harlequin ichthyosis (HI) and disorders of the LI/CIE phenotypic spectrum (Table V) exclusively. HI (Fig 2, *A*) was included, because functional null mutations in the *ABCA12* gene cause the disease,[15,16] whereas missense mutations in the same gene may result in a milder phenotype that shows collodion membrane at birth and develops into LI[17,18] or CIE,[19,20] often with palmoplantar keratoderma (PPK). Those infants with HI who survive the perinatal period go on to express a severe and very scaling erythroderma[21] (Fig 2, *B* and *C*).

One difficulty of the ARCI classification is the limited genotype-phenotype correlation within the LI/CIE spectrum. Mutations in 6 genes have been described in non-HI ARCI to date, including *TGM*, the gene encoding transglutaminase (TGase)-1,[22,23] the genes *ABCA12*,[17] *NIPAL4* (also known as *ICHTHYIN*),[24] *CYP4F22*,[25] and the lipoxygenase genes *ALOX12B* and *ALOXE3*.[26] A large cohort of 520 affected families showed a mutation distribution of 32% for *TGM1*, 16% for *NIPAL4*, 12% for *ALOX12B*, 8% for *CYP4F22*, 5% for *ALOXE3*, and 5% for *ABCA12*,[27] which approximately correlated with a recent report of 250 patients.[28] At least 22% of these cases did not exhibit mutations in any of the known ARCI genes,[27] implying that further loci must exist, such as two loci on chromosome 12p11.2-q13.[29,30] A preliminary clinicogenetic correlation based on the

Table II. Clinicogenetic classification of inherited ichthyoses, part A: nonsyndromic forms

Inherited ichthyoses Part A: nonsyndromic forms		
Disease	**Mode of inheritance**	**Gene(s)**
Common ichthyoses*		
IV	Autosomal semidominant	*FLG*
RXLI		
Nonsyndromic presentation	X-linked recessive	*STS*
ARCI		
Major types		
HI	Autosomal recessive	*ABCA12*
LI†	"	*TGM1/NIPAL4‡/ALOX12B/ABCA12/*loci on 12p11.2-q13
CIE	"	*ALOXE3/ALOX12B/ABCA12/CYP4F22/NIPAL4‡/TGM1/*loci on 12p11.2-q13
Minor variants		
SHCB	Autosomal recessive	*TGM1, ALOX12B, ALOXE3*
Acral SHCB	"	*TGM1*
BSI	"	*TGM1*
Keratinopathic ichthyosis (KPI)		
Major types		
EI§	Autosomal dominant	*KRT1/KRT10*
SEI	"	*KRT2*
Minor variants		
AEI§	Autosomal dominant	*KRT1/KRT10*
ICM	"	*KRT1*
AREI	Autosomal recessive	*KRT10*
Epidermolytic nevi//	Somatic mutations	*KRT1/KRT10*)
Other forms		
LK	Autosomal dominant	*LOR*
EKV¶	"	*GJB3/GJB4*
PSD	Autosomal recessive	Locus unknown
CRIE	Autosomal dominant (?) (isolated cases)	Locus unknown
KLICK	Autosomal recessive	*POMP*

AEI, Annular epidermolytic ichthyosis; *ARCI*, autosomal recessive congenital ichthyosis; *AREI*, autosomal recessive epidermolytic ichthyosis; *BSI*, bathing suit ichthyosis; *CIE*, congenital ichthyosiform erythroderma; *CRIE*, congenital reticular ichthyosiform erythroderma; *EI*, epidermolytic ichthyosis; *EKV*, erythrokeratodermia variabilis; *HI*, harlequin ichthyosis; *ICM*, ichthyosis Curth-Macklin; *IV*, ichthyosis vulgaris; *KLICK*, keratosis linearis–ichthyosis congenita–keratoderma; *LI*, lamellar ichthyosis; *LK*, loricrin keratoderma; *PSD*, peeling skin disease; *RXLI*, recessive X-linked ichthyosis; *SEI*, superficial epidermolytic ichthyosis; *SHCB*, self-healing collodion baby.

*Often delayed onset (in RXLI mild scaling and erythroderma may be present already at birth).

†Few cases of autosomal dominant LI described in literature (locus unknown).

‡Also known as *ICHTHYIN* gene.

§*KRT1* mutations are often associated with palmoplantar involvement.

//May indicate gonadal mosaicism, which can cause generalized EI in offspring generation.

¶Whether progressive symmetric erythrokeratodermia represents distinct mendelian disorders of cornification form is debated.

recent literature[17-20,22-45] and our discussions at the consensus conference is given in Tables II and III.

LI is characterized by coarse and brown/dark scaling (Fig 2, *E* and *F*). Affected individuals are often born with collodion membrane and pronounced ectropion (Fig 2, *D*). CIE is characterized by fine, white scaling with varying degrees of erythema (Fig 2, *G* and *H*). Individuals with CIE may also be born with collodion membrane (often less severe), and then transit to generalized fine scaling and pronounced erythroderma.[31,45] The phenotypes can change over time and in response to treatment, eg, LI treated with oral retinoids can evolve into an erythrodermic ichthyosis with a finer scale pattern.[46] In a recent North American study of 104 patients with non-HI ARCI, mutations in *TGM1* were significantly associated with collodion membrane, ectropion, platelike scales, and alopecia. Patients who had at least one mutation predicted to truncate TGase-1 were more likely to have severe

Table III. Clinicogenetic classification of inherited ichthyoses, part B: syndromic forms

Inherited ichthyoses Part B: syndromic forms		
Disease	**Mode of inheritance**	**Gene(s)**
X-linked ichthyosis syndromes		
RXLI*		
- Syndromic presentation	X-linked recessive	*STS* (and others†)
IFAP syndrome	"	*MBTPS2*
Conradi-Hünermann-Happle syndrome (CDPX2)	X-linked dominant	*EBP*
Autosomal ichthyosis syndromes (with)		
Prominent hair abnormalities		
NS	Autosomal recessive	*SPINK5*
IHS‡	"	*ST14*
IHSC syndrome§	"	*CLDN1*
TTD	"	*ERCC2/XPD ERCC3/XPB GTF2H5/TTDA*
*TTD (not associated with congenital ichthyosis)	"	*C7Orf11/TTDN1*
Prominent neurologic signs		
SLS	"	*ALDH3A2*
*Refsum syndrome (HMSN4)	"	*PHYH/PEX7*
MEDNIK syndrome	"	*AP1S1*
Fatal diseases course		
Gaucher syndrome type 2	"	*GBA*
MSD	"	*SUMF1*
CEDNIK syndrome	"	*SNAP29*
ARC syndrome	"	*VPS33B*
Other associated signs		
KID syndrome	Autosomal dominant	*GJB2 (GJB6)*
Neutral lipid storage disease with ichthyosis	Autosomal recessive	*ABHD5*
IPS	"	*SLC27A4*

ARC, Arthrogryposis–renal dysfunction–cholestasis; *CDPX2*, chondrodysplasia punctata type 2; *CEDNIK*, cerebral dysgenesis–neuropathy–ichthyosis–palmoplantar keratoderma; *HMSN4*, hereditary motor and sensory neuropathy type 4; *IFAP*, ichthyosis follicularis–atrichia–photophobia; *IHS*, ichthyosis hypotrichosis syndrome; *IHSC*, ichthyosis–hypotrichosis–sclerosing cholangitis; *IPS*, ichthyosis prematurity syndrome; *MEDNIK*, mental retardation–enteropathy–deafness–neuropathy–ichthyosis–keratodermia; *MSD*, multiple sulfatase deficiency; *NS*, Netherton syndrome; *RXLI*, recessive X-linked ichthyosis; *SLS*, Sjögren-Larsson syndrome; *TTD*, trichothiodystrophy.

*Often delayed onset (in RXLI mild scaling and erythroderma may be present already at birth).

†In context of contiguous gene syndrome.

‡Clinical variant: congenital ichthyosis, follicular atrophoderma, hypotrichosis, and hypohidrosis syndrome.

§Also known as neonatal ichthyosis sclerosing cholangitis syndrome.

hypohidrosis and overheating than those with *TGM1* missense mutations only.[35]

Clinically other minor ARCI variants/subtypes can be distinguished: bathing suit ichthyosis[47] has been attributed to particular *TGM1* mutations that render the enzyme sensitive to ambient temperature (Fig 2, *I*).[32,42,43,48] The self-healing collodion baby representing approximately 10% of all ARCI cases[36,49] has so far been associated with *TGM1* or *ALOX12B* mutations.[37,44] The recently described acral self-healing collodion baby, ie, at birth the collodion membrane is strictly localized to the extremities and then resolves, can also be a result of *TGM1* mutations.[41]

Classification of the keratinopathic ichthyoses

The term "epidermolytic hyperkeratosis" derives from the characteristic light microscopic observation of intracellular vacuolization, clumping of tonofilaments, and formation of small intraepidermal blisters, as commonly seen in ichthyoses as a result of keratin mutations. Therefore the term "epidermolytic hyperkeratosis" is used (by some) as synonymous with bullous ichthyosis, ichthyosis exfoliativa, bullous CIE (of Brocq), or ichthyosis bullosa of Siemens.[50-55] However, the light microscopic features of the cytoskeletal abnormalities as a result of keratin mutations may not be observed in all instances.[56-59] To replace the long list of names, which have been used for these ichthyoses—those that are all a result of keratin mutations—we propose the novel umbrella term and definition "keratinopathic ichthyosis" (KPI) (Table I). In analogy to the prevalent morphologic key features, we suggest the term "epidermolytic ichthyosis" as a novel name for the specific disease

Table IV. Common forms of ichthyosis: summary of clinical and morphologic findings

	IV (prevalence: 1:250-1000)	RXLI (prevalence: 1:2000-6000)
Mode of inheritance	Autosomal semidominant	XR
Onset	After ~2-6 mo	Exaggerated scaling and/or erythroderma in newborn period or late onset after ~2-6 mo, mild collodion-like skin at birth may be possible
Initial clinical presentation	Xerosis, scaling, pruritus, eczema	Scaling
Disease course	Stable, often better in summer	Stable, often better in summer
Cutaneous findings		
Distribution of scaling	Generalized, antecubital or popliteal fossae often spared	Generalized, sparing of body folds, neck is often more severely involved
Scaling type	Fine or light	Large rhomboid scales or fine scaling
Scaling color	White-gray	Dark brown or light gray
Erythema	Absent	Absent
Palmoplantar involvement	Accentuated palmoplantar markings	No accentuated markings
Hypohidrosis	Possible	Possible
Scalp abnormalities	Absent	Absent
Others	Eczema	-
Extracutaneous involvement	Strong association with atopic manifestations	Incidence of cryptorchidism/testicular maldescent seems to be increased (estimated numbers range from 5%-20%), subclinical corneal opacities in ~50%; insufficient cervical dilatation in female carriers *Contiguous gene syndromes have to be ruled out
Ultrastructure	Small or only rudimental KG	Retained corneodesmosomes within SC
Special analyses	Reduced or absent SG, reduced or negative filaggrin staining by antigen mapping	Absent steroid sulfatase (arylsulfatase-C) activity (leukocytes or fibroblasts), FISH test for STS deletion; elevated blood cholesterol sulfate levels (Fetal steroid sulfatase deficiency leads to low maternal serum/urinary estriol levels; therefore, RXLI may be detected in utero, when prenatal screening for Down syndrome and other disorders includes measurement of maternal estriol levels, as in triple-screen blood test)

FISH, Fluorescent in situ hybridization; *IV*, ichthyosis vulgaris; *KG*, keratohyaline granules; *RXLI*, recessive X-linked ichthyosis; *SC*, stratum corneum; *SG*, stratum granulosum; *XR*, X-linked recessive.
*RXLI within context of contiguous gene syndrome (Table III), eg, in Kallmann syndrome, chondrodysplasia punctata (brachytelephalangic type), or ocular albinism type 1.

spectrum that is accompanied by epidermolytic hyperkeratosis at the ultrastructural level. The term "epidermolytic hyperkeratosis" should be used exclusively as an ultrastructural or histopathological descriptor. We propose the novel disease name "superficial epidermolytic ichthyosis" for the well-defined entity ichthyosis bullosa Siemens, which in contrast to EI shows a more superficial pattern of epidermolysis and is caused by mutations in keratin 2, rather than in keratins 1 or 10.

Clinically, KPI show a broad spectrum of skin manifestations and severity (Table VI). Widespread skin blistering is characteristic of neonates with EI (Fig 3, *A*), not seen thereafter except for focal blisters. The blistering phenotype present at birth, which is a result of loss of mechanical resilience in the upper epidermis, evolves into a hyperkeratotic one (phenotypic shift) (Fig 3, *C*); this is suggested to be influenced primarily by abnormal lamellar body (LB) secretion, rather than corneocyte fragility.[60] Superficial EI (Fig 3, *D*) has a milder phenotype than EI and can be distinguished by the lack of erythroderma and by a characteristic "moulting" phenomenon (Fig 3, *F*). Here, light microscopy and ultrastructure reveal cytolysis that correlates with the distinctive expression pattern of keratin 2

Table V. Autosomal recessive congenital ichthyoses: summary of clinical and morphologic findings

	HI	LI	CIE
Mode of inheritance	AR	AR	AR
Onset	At birth, often preterm babies	At birth	At birth
Initial clinical presentation	Severe collodion membrane with armorlike membrane, extreme ectropion and eclabium, and contractures, broadened nose, synechiae of auricles, sometimes toes	Collodion membrane with ectropion and eclabium; less frequently CIE	CIE or less frequently mild collodion membrane
Disease course	Development of exfoliative/very scaling erythroderma similar to severe CIE with fine or large scales	Ranging from very mild to severe (probably never completely heals)	Ranging from very mild to severe
		Minor variants - SHCB: nearly complete resolution of scaling within first 3 mo of life (in ~10% of cases) - Acral SHCB: at birth only acral collodion membranes are observed that later on heal - BSI: collodion membrane at birth and development of LI or CIE Then, within first months of life, skin predominantly of extremities heals, but warmer skin areas, eg, axillary region, scalp, (mid-) trunk, remain involved and show localized form of LI	
Cutaneous findings			
Distribution of scaling	Generalized	Generalized; focally pronounced scaling possible	Generalized; focally pronounced scaling possible
Scaling type	Coarse and large (platelike)	Coarse and large (platelike)	Fine
Scaling color	Gray or yellowish	Brownish or dark	White or gray
Erythema	Severe	Variable, less pronounced	Variable, often pronounced
Palmoplantar involvement	Yes, possibly with synechiae of digits	**NIPAL4*: pronounced keratoderma; *ALOX12B* and *CYP4F22*: pronounced lichenification and mild keratoderma; *ALOXE3*: IV-like; *TGM1*: frequent palmoplantar involvement	
Hypohidrosis	Severe temperature dysregulation	Moderate to severe	Moderate to severe
Scalp abnormalities	Scarring alopecia	Scarring alopecia possible (often with *TGM1*)	Scarring alopecia possible
Other skin findings	Prone to skin infections	-	-
Extracutaneous involvement	Contractures; failure to thrive; short stature	Short stature (if severe)	Failure to thrive, short stature (if severe)
Risk of death	Very high during neonatal period	Elevated during neonatal period	Present during neonatal period
Skin ultrastructure	Vesicular LB ghosts; paucity of secreted lamellar structures in SC	*ABCA12* = absence of LB content; **NIPAL4* = weak correlation with vesicular complexes, defective LB, perinuclear membranes within SG in glutaraldehyde fixation; *TGM1*: thin CE and disorganization of lamellar bilayers (with glutaraldehyde fixation: polygonal clefts within corneocytes)	
Other analyses	None	In situ monitoring of TGase-1 activity in cryostat sections, SDS heating test of scales	

AR, Autosomal recessive; *BSI*, bathing suit ichthyosis; *CE*, cornified cell envelope; *CIE*, congenital ichthyosiform erythroderma; *HI*, harlequin ichthyosis; *IV*, ichthyosis vulgaris; *LB*, lamellar body; *LI*, lamellar ichthyosis; *SC*, stratum corneum; *SG*, stratum granulosum; *SHCB*, self-healing collodion baby; *TGase*, transglutaminase.

**NIPAL4* also known as *ICHTHYIN*.

Table VI. Keratinopathic ichthyoses and congenital reticular ichthyosiform erythroderma: summary of clinical and morphologic findings

	EI	SEI	ICM	CRIE*
Mode of inheritance	AD or rarely AR (*KRT10*) Annular type: AD	AD	AD	AD (?) (isolated cases)
Onset	At birth	At birth	Early childhood	At birth
Initial clinical presentation	Large erosions, mild scaling, erythroderma at birth	Erythroderma, widespread blistering	Striate or diffuse PPK	Exfoliative CIE, larger areas forming reticular pattern predominantly on extremities
Disease course	Resolution of erosions replaced by hyperkeratosis in first months Annular type: development of numerous annular, polycyclic, erythematous, scaly plaques on trunk and extremities that enlarge slowly, and then resolve (intermittent presentations of EI)	Within weeks development of hyperkeratosis particularly over extensor sides of joints	Progressive worsening of PPK and development of hyperkeratotic plaques over joints and/or hyperkeratotic papules on trunk and extremities	During childhood and puberty characteristic patchy pattern starts to evolve
Cutaneous findings				
Distribution of scaling	Generalized, or predilection for friction areas, over joints	Friction areas	Palms and soles, large joints, rarely extremities and/or trunk	Generalized, later reticular ichthyosiform pattern
Scaling type	Adherent, moderate	Adherent, fine to moderate	Thick, spiky hyperkeratosis	Fine
Scaling color	White-brown	Brown (mauserung/moulting)	Yellow-brown hyperkeratoses	Yellow-brown
Erythema	Frequent	Initially, fades	Erythroderma possible	Pronounced
Palmoplantar involvement	*KRT1*: epidermolytic PPK *KRT10*: palms and soles are spared (exceptions possible)	Usually no	Massive PPK leading to deep, bleeding, and painful fissures; flexural contractures; constriction bands	Yes
Hypohidrosis	Possible	Possible	None	-
Scalp abnormalities	Scaling	-	None	Scaling
Other skin findings	Pruritus, blisters after minor trauma, prone to skin infections/impetigo	Pruritus, bullae may occur after minor mechanical trauma (often in summer)	-	-
Extracutaneous involvement	Growth failure with some severe phenotypes		Gangrene and loss of digits	Growth failure with some severe phenotypes
Risk of death	Elevated during neonatal period	-	-	Elevated during neonatal period

Continued

Table VI. Cont'd

	EI	SEI	ICM	CRIE*
Skin ultrastructure	EHK, aggregations and clumping of keratin filaments in suprabasal cells; partly cytolysis, LB accumulation	Superficial EHK, cytolysis in granular cells of affected body areas; no keratin clumping	Binuclear cells, particular concentric perinuclear "shells" of aberrant—putatively—keratin material	Vacuolization of superficial granular cells and (often?) so far unidentified filamentous material in vacuolated cells
Special analyses	-	-	-	-

AD, Autosomal dominant; *AR*, autosomal recessive; *CIE*, congenital ichthyosiform erythroderma; *CRIE*, congenital reticular ichthyosiform erythroderma; *EHK*, epidermolytic hyperkeratosis; *EI*, epidermolytic ichthyosis; *ICM*, ichthyosis Curth-Macklin; *LB*, lamellar body; *PPK*, palmoplantar keratoderma; *SEI*, superficial epidermolytic ichthyosis.
*Also known as ichthyosis variegata and ichthyosis en confettis.

in the stratum granulosum (SG) or upper stratum spinosum.[61] Different features such as distribution, erythema, or blistering were used for separating patients with EI into 6 clinical groups, with the most distinctive characteristic being involvement of palms and soles (1-3 vs non-palms and soles 1-3).[62] PPK is usually predictive of a *KRT1* mutation (Fig 3, *E*). One explanation is that keratin 9, which is expressed in palms and soles, may compensate for a keratin 10 defect, whereas keratin 1 is the only type II keratin expressed in palmoplantar skin.[63-65] However, PPK may occur with *KRT10* mutations as well.[66]

Similar to pachyonychia congenita or the epidermolysis bullosa simplex group, the vast majority of the KPI arise from autosomal dominant mutations. The resulting mutant keratin is normally expressed but interferes with the assembly and/or function of keratin intermediate filaments, often leading to keratin intermediate filament aggregation and cytolysis. However, *KRT10* nonsense mutations have been observed that do not lead to the usual dominant negative effect and cause an autosomal recessive KPI form.[67] Therefore, autosomal recessive EI is listed as a new separate KPI. For ichthyosis Curth-Macklin,[57-59,68] which represents a very rare form of KPI and shows a characteristic ultrastructure (Table VI), we propose to omit the adjective "hystrix" and retain the eponym Curth-Macklin. Hystrix skin changes can be observed in other ichthyoses, eg, KID syndrome (Table XII), or in particular types of ectodermal dysplasia.[69] The annular EI (Fig 3, *E*), which is a result of *KRT1* or *KRT10* mutations,[70,71] is classified as a clinical variant of EI.

Importantly, linear epidermolytic nevi, ie, those epidermal nevi exhibiting the histopathology of epidermolytic hyperkeratosis, may indicate a somatic type 1 mosaicism for mutations in *KRT1* or *KRT10*, which, if also gonadal, can result in generalized EI in the patient's offspring (Fig 3, *A* and *G*).[72-74] Because recognition of this risk is important for genetic counseling, epidermolytic nevi have been included (in brackets) in the classification of KPI (Table II).

Other diseases considered in the classification of inherited ichthyoses

The inclusion of disease entities into this classification of inherited ichthyosis rests on an appropriate clinical disease description and our definition of inherited ichthyosis (Table I). A detailed overview of the disease onset, initial clinical presentation, disease course, cutaneous and extracutaneous findings, and of the skin ultrastructure is given for each entity: (1) common forms of ichthyosis (Table IV); (2) ARCI (Table V); (3) KPI and congenital reticular

Table VII. Other nonsyndromic ichthyosis forms: summary of clinical and morphologic findings

	LK	EKV	KLICK	PSD*
Mode of inheritance	AD	AD	AR	AR
Onset	At birth	At birth or within first year of life	At birth	At birth (or first weeks of life)
Initial clinical presentation	CIE or collodion baby	Co-occurrence of transient, migratory erythematous patches and hyperkeratosis limited to geographic outlined plaques or generalized	Congenital ichthyosis	IE, atopic dermatitis-like lesions
Disease course	Improvement and development of PPK	Relapsing-remitting, erythema are fleeting (hours-days), hyperkeratosis more stable (months to years)	Mild	Mild to moderate, spontaneous remissions, and relapses
Cutaneous findings				
Skin distribution	Generalized mild scaling with accentuated hyperkeratosis over joints, flexural areas	Generalized or focally accented hyperkeratosis, predominantly on extremities, buttocks	Generalized, accentuated linear keratoses in skin folds, (sclerosing) PPK	Generalized (to be differentiated from acral PSS)
Scaling type	Fine	Rough, thickened skin, possibly hystrix skin; occasionally peeling		Large peeling scales
Scaling color	White	White to gray, yellow or brown	White-brown	White
Erythema	Uncommon	Focal migratory	Uncommon	Varying from mild to moderate, may improve with age
Palmoplantar involvement	Noninflammatory diffuse PPK with honeycomb pattern, mild digital constriction, brown hyperkeratosis, knuckle pads over back aspects	Diffuse PPK present in about 50% of patients	—	Yes
Hypohidrosis	-	No	Yes	No
Scalp abnormalities	No	No	No	No hair abnormalities
Other skin findings	Keratoderma (thickening), pseudo-ainhum or (mild) linear constrictions	No	Linear keratosis	Pruritus
Extracutaneous involvement	-	None	None	Associated atopic diathesis, short stature (single cases)
Risk of death	Normal	Normal	Normal	Elevated during neonatal period

Continued

Table VII. Cont'd

	LK	EKV	KLICK	PSD*
Skin ultrastructure	Electron dense intranuclear granules in granular cells, thin CE in lower SC, abnormal extracellular lamellae	Mostly nonspecific changes with various degrees of deviations or suppression of keratinization and reduction of LB in SG	Hypergranulosis and abnormally big KG	Superficial exfoliation, separation directly above SG or within SC; between, adjacent, or within corneocytes
Other analyses	Histology: parakeratosis, and hypergranulosis	-	-	Immunohistochemistry: LEKTI is normal or even elevated

Acral PSS, Acral peeling skin syndrome; *AD*, autosomal dominant; *AR*, autosomal recessive; *CE*, cornified cell envelope; *CIE*, congenital ichthyosiform erythroderma; *EKV*, erythrokeratodermia variabilis; *IE*, ichthyosiform erythroderma; *KG*, keratohyaline granules; *KLICK*, keratosis linearis–ichthyosis congenita–keratoderma; *LB*, lamellar body; *LK*, loricrin keratoderma; *PPK*, palmoplantar keratoderma; *PSD*, peeling skin disease; *SC*, stratum corneum; *SG*, stratum granulosum.
*We propose to classify disorder as nonsyndromic form and therefore modified name "peeling skin syndrome (PSS)" into "peeling skin disease."

ichthyosiform erythroderma (Table VI); (4) other nonsyndromic ichthyosis forms (Table VII); (5) X-linked ichthyosis syndromes (Table VIII); and (6) autosomal ichthyosis syndromes with prominent hair abnormalities (Table IX), prominent neurologic signs (Table X), fatal disease course (Table XI), and other associated signs (Table XII).

Diseases that are classically regarded as ichthyosis in the previously published scientific literature and that will continue to be included are shown in Figs 4 and 5. They include Sjögren-Larsson syndrome[75,76] (Fig 5, *B*), Refsum syndrome,[77,78] neutral lipid storage disease with ichthyosis (also referred to as Chanarin-Dorfman syndrome) (Fig 5, *G*),[40,79,80] ichthyosis follicularis–atrichia–photophobia syndrome (Fig 5, *D*),[81,82] Conradi-Hünermann-Happle syndrome (CDPX2) (Fig 5, *F*),[83,84] multiple sulfatase deficiency,[85,86] congenital reticular ichthyosiform erythroderma also referred to as ichthyosis variegata[87] (or ichthyosis en confettis[88]) (Fig 4, *E*), and ichthyosis prematurity syndrome[89,90] (Fig 5, *E*). In ichthyosis prematurity syndrome, affected pregnancies exhibit abnormal amniotic fluid both on ultrasound imaging and clinically.[91] It must be distinguished from the self-healing collodion baby, because in both diseases the skin heals almost completely soon after birth.[89] Many advances in the heterogeneous field of the TTDs (Fig 5, *A*) have been made.[92,93] Recent studies on genotype-phenotype correlation distinguish the TTD syndromes associated with ichthyosis of delayed onset or accompanied with collodion membrane from other forms of TTD.[94]

Diseases relatively new in the list of ichthyoses are loricrin keratoderma, also referred to as Camisa variant of Vohwinkel keratoderma (Fig 4, *C*),[95-97] the cerebral dysgenesis–neuropathy–ichthyosis–PPK syndrome,[98] the arthrogryposis–renal dysfunction–cholestasis syndrome,[99-101] the mental retardation–enteropathy–deafness–neuropathy–ichthyosis–keratodermia syndrome,[102] the ichthyosis–hypotrichosis–sclerosing cholangitis syndrome (also known as neonatal ichthyosis sclerosing cholangitis syndrome),[103-105] the ichthyosis hypotrichosis syndrome (Fig 5, *I*)[106] and its allelic variant congenital ichthyosis–follicular atrophoderma–hypotrichosis–hypohidrosis syndrome,[107,108] and keratosis linearis–ichthyosis–congenital sclerosing keratoderma (Fig 4, *F*).[109,110]

Erythrokeratodermia variabilis (EKV),[111-113] which is characterized by migratory erythematous patches and more fixed, symmetric hyperkeratotic plaques often with palmoplantar involvement (Fig 4, *B*), is genetically heterogeneous and can in 50% to 65% of cases[114] be caused by mutations in *GJB3* coding for the gap junction protein connexin 31,[115] or *GJB4* coding for connexin 30.3.[116] Whether

Table VIII. X-linked ichthyosis syndromes (for recessive X-linked ichthyosis see Table IV): summary of clinical and morphologic findings

	IFAP syndrome	Conradi-Hünermann-Happle syndrome (CDPX2)
Mode of inheritance	XR*	XD
Onset	At birth	At birth
Initial clinical presentation	Mild collodion skin, congenital atrichia	Ichthyosiform erythroderma may be severe
Disease course	Development of generalized follicular keratosis that can be severe or improves during first year of life	CIE clears up after few months, lifelong hyperkeratosis distributed in linear, blotchy pattern, follicular atrophoderma
Cutaneous findings		
Distribution of scaling	Generalized (mosaic in carriers)	Generalized or mosaic pattern of skin lesions
Scaling type	Mild to moderate	Discrete IV-like scaling
Scaling color	Whitish	Variable
Erythema	Mild	Resolving after birth
Palmoplantar involvement	Inflammatory focal to diffuse (also possible in carriers)	Unusual
Hypohidrosis	Mild	No
Scalp abnormalities	Follicular keratoses, atrichia, occasionally some sparse and thin hair may be present	Patchy areas of cicatricial alopecia
Other skin findings	Disturbed nail growth (possible), prone to infections	Sparse eyelashes and eyebrows, nail anomalies
Extracutaneous involvement	Severe photophobia (vascularizing keratitis or anomalies in Bowman membrane), retarded psychomotor development, in some cases: cerebral atrophy, temporal lobe malformation, hypoplasia of corpus callosum, failure to thrive, atopic manifestations, inguinal hernia, aganglionic megacolon, testicular or renal anomalies	Stippled calcifications of enchondral bone formation, chondrodysplasia punctata, short stature, asymmetric shortening of legs, kyphoscoliosis, dysplasia of hip joints, sectorial cataracts, asymmetric facial appearance as result of unilateral hypoplasia, flattened nose bridge
Risk of death	Present during neonatal period	Present during neonatal period
Skin ultrastructure	Nonepidermolytic hyperkeratosis	Cytoplasmic vacuoles of keratinocytes in SG
Other analyses	Histology: numerous atrophic hair follicles and absence of sebaceous glands	Histology: calcification in follicular keratoses (in neonates); roentgenographic examination; serum GC-MS for high 8-DHC and cholesterol level

DHC, Dehydrocholesterol; *CDPX2*, chondrodysplasia punctata type 2; *CIE*, congenital ichthyosiform erythroderma; *GC-MS*, gas chromatography-mass spectrometry; *IFAP*, ichthyosis follicularis—atrichia—photophobia; *IV*, ichthyosis vulgaris; *SG*, stratum granulosum; *XD*, X-linked dominant; *XR*, X-linked recessive.

*Female carriers may present with linear pattern of mild follicular ichthyosis, mild atrophoderma, hypotrichosis, and hypohidrosis (X-chromosomal lyonization effect).

progressive symmetric erythrokeratodermia,[111,112] which has a considerable clinical overlap with EKV,[113] represents a distinct MEDOC form is debated and depends on future genetic data. At present, it is known that progressive symmetric erythrokeratodermia is heterogeneous and patients of two families given the diagnosis of progressive symmetric erythrokeratodermia were found to have the same GJB4 mutation as others with EKV.[114,117] Previously, erythrokeratodermia was differentiated from the ichthyosis group as it is not generalized in most cases. However, the majority of the participants thought that the inclusion of EKV into this classification is appropriate and useful and in accordance with the inclusion of KID (keratitis—ichthyosis—deafness) syndrome[118,119] (Fig 5, *C*), which is identical to ichthyosis hystrix type Rheydt[120] or hystrixlike ichthyosis deafness syndrome.[3] KID syndrome is caused by heterozygous mutations in *GJB2* (connexin 26)[121] and patients with congenital presentation in particular have generalized skin involvement. In some cases, it may overlap with Clouston syndrome, which is caused by mutations in *GJB6* (connexin 30).[69,122]

One could argue that NS[123] (Fig 5, *H*) should not be classified with the ichthyoses, because it is characterized by premature desquamation and a thinner rather than thicker stratum corneum (SC). However, the clinical features often overlap with the CIE phenotype, and scaling is a common clinical feature. The consensus was to retain the disorder in the

Table IX. Autosomal ichthyosis syndromes with prominent hair abnormalities: summary of clinical and morphologic findings

	NS	IHS	IHSC syndrome*
Mode of inheritance	AR	AR	AR
Onset	At birth (or later)	At birth	At birth (or shortly after)
Initial clinical presentation	CIE in most of cases, collodion membrane rare, ILC, atopic dermatitis-like lesions	LI, severe hypotrichosis, absent eyebrows and eyelashes	Mild scaling, neonatal jaundice with hepatomegaly, frontal alopecia in early childhood
Disease course	Mild to severe, spontaneous remissions, and relapses	Over time, scalp hair growth and appearance/color may improve	Mild ichthyosis, liver involvement variable
Cutaneous findings			
Skin distribution	Localized (ILC type) or generalized (CIE type)	Generalized, including scalp, face may be unaffected	Predominant on trunk
Scaling type	Fine or large, double-edged scales (ILC)	Coarse, platelike, adherent	Fine to polygonal, thin
Scaling color	White	Brown to dark	Normal
Erythema	Frequent, varying from moderate to severe, may improve with age	Unusual	Unusual
Palmoplantar involvement	Possible	No	No
Hypohidrosis	No	Yes	No
Scalp abnormalities	Short, fragile, and brittle hair; alopecia (hair, lashes, and eyebrows); spontaneous remissions and relapses	Hypotrichosis in youth, sparse, unruly hair in adolescence, recessing frontal hairline in adults	Major criterion: coarse thick hair, frontotemporal scarring alopecia; hypotrichosis, curly/woolly hair
Other skin findings	Severe pruritus, prone to bacterial and viral (HPV) skin infections	Follicular atrophoderma	
Extracutaneous involvement	HS abnormalities, failure to thrive, severe atopic diathesis, increased IgE level and eosinophilia, frequent skin infections (*Staphylococcus aureus* or HPV)	Sparse and curly eyebrows, occasionally photophobia and pingueculum	Major criterion: sclerosing cholangitis or congenital paucity of bile ducts†
Risk of death	Life-threatening neonatal hypernatremic dehydration, and sepsis	Normal	Not observed, but theoretically possible from liver involvement
Skin ultrastructure	Suppressed keratinization, thin or absent SC and SG, reduction of corneodesmosomes, intercorneal clefts	High presence of intact corneodesmosomes in upper SC, residues of membranous structures in SC	Splitting of desmosomal anchoring plaques in SG
Other analyses	Trichorrhexis invaginata: highly diagnostic (usually after 1 y), but inconsistent; skin immunochemistry: absent or reduced expression of LEKTI	Hair microscopy may reveal dysplastic hair, pili torti, or pili bifurcate	Liver function tests, cholangiography, liver biopsy

AR, Autosomal recessive; *CIE*, congenital ichthyosiforme erythroderma; *HPV*, human papillomavirus; *HS*, hair shaft; *IHS*, ichthyosis hypotrichosis syndrome; *IHSC*, ichthyosis—hypotrichosis—sclerosing cholangitis; *ILC*, ichthyosis linearis circumflexa; *LI*, lamellar ichthyosis; *NS*, Netherton syndrome; *SC*, stratum corneum; *SG*, stratum granulosum.

*Also known as neonatal ichthyosis sclerosing cholangitis or ichthyosis, leukocyte vacuoles, alopecia and sclerosing cholangitis (ILVASC) syndrome.

†Previously described leukocyte vacuoles are probably artifact and no longer diagnostic criteria.

Table X. Autosomal ichthyosis syndromes with prominent hair abnormalities and/or neurologic signs: summary of clinical and morphologic findings

	TTD	TTD (not associated with CI)	SLS	Refsum syndrome (HMSN4)	MEDNIK syndrome
Mode of inheritance	AR	AR	AR	AR	AR
Onset	At birth	Childhood or late adulthood	At birth	Childhood or late adulthood	At birth or within first weeks of life
Initial clinical presentation	Collodion baby, CIE	Xerosis, scaling, IV-like	CI of mild type, focal accentuation of hyperkeratosis on scalp and neck	Xerosis, scaling	Erythematous rashes, similar to EKV
Disease course	Postneonatal improvement in most cases, mild LI possible	Progressive	Mild to moderate	Progressive	Progressive
Cutaneous findings					
Distribution of scaling	Generalized	Generalized	Generalized but more severe on trunk and neck	Generalized	Generalized,
Scaling type	Fine, rarely lamellar	Fine or light	Velvetlike, fine scaling	Fine or light	EKV-like
Scaling color	White, gray	White-gray	Grayish	White-gray	"
Erythema	Caused by photosensitivity	Absent	Yes	Absent	"
Palmoplantar involvement	Possible PPK	Accentuated palmoplantar markings	Yes	Accentuated palmoplantar markings	Not specifically
Hypohidrosis	No	No	Yes	Unusual	?
Scalp abnormalities	Hair fragility, variable	Hair fragility, variable	-	Absent	Not specifically
Other skin findings	Photosensitivity, atopic dermatitis	-	Pruritus	-	Nail thickening, mucous membrane affected
Extracutaneous involvement	Growth and developmental delay, short stature, recurrent infections, cataracts		Spastic paraplegia, mental retardation, ocular involvement	Development of night blindness (retinitis pigmentosa), anosmia, progressive deafness, peripheral neuropathy, cerebellar ataxia	Congenital sensorineural deafness, peripheral neuropathy, psychomotor and growth retardation, chronic diarrhea, mental retardation
Risk of death	High risk of death in childhood because of infection		Increased	Without treatment present	Life-threatening congenital diarrhea
Skin ultrastructure	Limited studies: perinuclear vacuoles in cytoplasm of keratinocytes, irregularly arranged bundles of tonofilaments (?)		Not specific: abnormal LB, cytoplasmic lipid vacuoles and lamellar/nonlamellar phase separations layers	Mostly nonspecific: lipid vacuoles in melanocytes, basal keratinocytes and dermal cells	Histology: hyperkeratosis with hypergranulosis

Continued

Table X. Cont'd

	TTD	TTD (not associated with CI)	SLS	Refsum syndrome (HMSN4)	MEDNIK syndrome
Other analyses	Hair shafts with alternating light and dark bands under polarizing microscopy and structural abnormalities such as trichoschisis, low-sulfur hair content		Eye examination; increased fatty alcohols (blood); reduced aldehyde dehydrogenase or fatty alcohol NAD oxidoreductase (leukocytes)	Increased phytanic acid levels (blood)	Elevation of VLCFAs (blood)

AR, Autosomal recessive; *CI*, congential ichthyosis; *CIE*, congenital ichthyosiform erythroderma; *EKV*, erythrokeratodermia variabilis; *HMSN4*, hereditary motor and sensory neuropathy type 4; *IV*, ichthyosis vulgaris; *LB*, lamellar body; *LI*, lamellar ichthyosis; *MEDNIK*, mental retardation–enteropathy–deafness–neuropathy–ichthyosis–keratodermia (~EKV 3, Kamouraska type); *NAD*, nicotinamid-adenin-dinucleotid; *PPK*, palmoplantar keratoderma; *SLS*, Sjögren-Larsson syndrome; *TTD*, trichothiodystrophy; *VLCFA*, very long chain fatty acids.

classification. Peeling skin disease (Fig 4, *D*)[124] has to be differentiated from NS. Unlike NS, peeling skin disease does not show hair anomalies, is not caused by *SPINK5* mutations,[125] and has different immunochemical features,[126] but may also be accompanied by atopic diathesis.[3,124]

Diseases related to inherited ichthyoses

A certain number of MEDOC forms can be regarded as phenotypically and/or etiologically related to ichthyosis, or have to be considered as differential diagnoses. Examples are the PPKs, which sometimes show nonacral involvement, eg, Vohwinkel keratoderma[127] caused by a particular dominant *GJB2* mutation (connexin 26),[128] Mal de Meleda[129] caused by recessive *SLURP1* mutations,[130] and Papillon-Lefèvre syndrome[131] caused by recessive *CTSC* mutations encoding cathepsin C.[132] Mutations in keratin 5 or 14 cause epidermolysis bullosa simplex,[133,134] which can present with severe neonatal blistering clinically indistinguishable from EI.[62,65,135] Importantly, hypohidrosis—a common symptom in ichthyoses, especially ARCI[136]—represents one main criterion for the heterogeneous group of the ectodermal dysplasia.[137,138] Generalized erythroderma with scaling, and even collodion membranes, have been described in single cases of hypohidrotic ectodermal dysplasia.[139,140] One important differential diagnosis of HI (or severe collodion babies) is lethal restrictive dermopathy,[141-143] which is associated with intrauterine growth retardation, congenital contractures, tight skin, and ectropion, but does not develop hyperkeratosis and scaling. Another perinatal lethal syndrome, the Neu-Laxova syndrome, should be considered in neonates with ichthyosis and multiple anomalies, including tight translucent skin similar to that in restrictive dermopathy, abnormal facies with exophthalmos, marked intrauterine growth retardation, limb deformities, and central nervous system anomalies.[144] CHILD (congenital hemidysplasia—ichthyosiform nevus—limb defect) syndrome[145] is strictly limited to one half of the body and does not fulfill the ichthyosis criterion of a generalized cornification disorder; it is here considered ichthyosis related. Conradi-Hünermann-Happle (CDPX2) and CHILD syndrome are both caused by an enzyme defect within the distal cholesterol biosynthetic pathway as a result of X-linked dominant mutations in the *EBP* (CDPX2) and *NSDHL* (CHILD) genes, respectively.[84,146] However, CDPX2 may present with severe CIE or collodion membrane and is therefore regarded as an ichthyosis (Fig 4, *F*).[147] Darier disease[148,149] and Hailey—Hailey disease[150] are autosomal dominant genodermatoses

Table XI. Autosomal recessive ichthyosis syndromes with fatal disease course: summary of clinical and morphologic findings

	Gaucher syndrome type 2	Multiple sulfatase syndrome	CEDNIK syndrome	ARC syndrome
Mode of inheritance	AR	AR	AR	AR
Onset	At birth, or later	At birth, or later	After 5-11 mo	At birth, can sometimes be late
Initial clinical presentation	CIE or less frequently mild collodion membrane	Prevailing neurologic symptoms, skin similar to RXLI	Until up to age 1 y, normal-appearing skin; thereafter LI type	Xerosis and scaling within few days of birth
Disease course	Ranging from mild to moderate	Fatal	Fatal	Fatal
Cutaneous findings				
Distribution of scaling	Generalized	Generalized, sparing of body folds	Generalized with sparing of skin folds	Generalized with sparing of skin folds
Scaling type	Fine or moderate; scaling may resolve after neonatal period	Large rhomboid scales or fine scaling	Coarse and large (platelike)	Fine or platelike (extensor sites)
Scaling color	White or gray or brown	Dark brown or light gray	Whitish	White or brownish
Erythema	Unusual	Absent	Absent	Absent
Palmoplantar involvement	-	-	Yes	Spared
Hypohidrosis	Yes	-	Not studied (no heat stroke)	Not studied
Scalp abnormalities	-	Absent	Fine, sparse hair	Mild scarring alopecia
Other skin findings	-	Possible	None	Ectropion
Extracutaneous involvement	Hydrops fetalis; progressive neurologic deterioration; hepatosplenomegaly, hypotonia, respiratory distress, arthrogryposis, facial anomalies	Metachromatic leukodystrophy, mucopolysaccharidoses, progressive psychomotor deterioration	Sensorineural deafness; cerebral dysgenesis; neuropathy; microcephaly; neurogenic muscle atrophy; optic nerve atrophy; cachexia	Arthrogryposis (wrist, knee, or hip); intrahepatic bile duct hypoplasia with cholestasis; renal tubular degeneration; metabolic acidosis; abnormal platelet function; cerebral malformation
Risk of death	Death often by age 2 y	Death within first year of life	Lethal within first decade	Lethal within first year of life
Skin ultrastructure	Lamellar/nonlamellar phase separations in SC	Same ultrastructural features as RXLI	Impaired lipid loading onto LB and defective LB secretion	Defective LB secretion
Special analyses	Liver function tests; decreased beta-glucocerebrosidase activity (leukocytes); Gaucher cells (bone marrow); increased acid phosphatase (serum)	Diagnostic urinary metabolites	Absent RAB protein on immunohistochemistry, MRI	Liver and renal biopsy

AR, Autosomal recessive; *ARC*, arthrogryposis–renal dysfunction–cholestasis; *CEDNIK*, cerebral dysgenesis–neuropathy–ichthyosis–palmoplantar keratoderma; *CIE*, congenital ichthyosiform erythroderma; *LB,* lamellar body; *LI*, lamellar ichthyosis; *MRI*, magnetic resonance imaging; *RAB*, ras-related gtp-binding protein; *RXLI*, recessive X-linked ichthyosis; *SC*, stratum corneum.

Table XII. Autosomal ichthyosis syndromes with other associated signs: summary of clinical and morphologic findings

	KID syndrome*	Neutral lipid storage disease with ichthyosis	IPS†
Mode of inheritance	AD	AR	AR
Onset	At birth or within first year of life	At birth, or shortly after	At birth (polyhydramnios, prematurity, >6 wk)
Initial clinical presentation	Severe generalized (or localized) (erythro)keratoderma with spiky hyperkeratosis, PPK, keratitis, ectropion, nail dystrophy	CIE, EKV-like changes or less frequently mild collodion membrane	Respiratory distress, generalized skin hyperkeratosis with focal accentuation on scalp, eyebrows
Disease course	Lethal in neonatal period in some cases, progressive hyperkeratosis, PPK and keratitis in some, improvement in others	Ranging from mild to moderate	Severe at birth, spontaneous improvement
Cutaneous findings			
Distribution of scaling	Generalized or focally accented hyperkeratosis	Generalized	Focal accentuation (see above)
Scaling type	Hystrix or cobblestone	Fine or moderate	Caseous (vernix caseosa-like)
Scaling color	Brown-yellow-gray	White or gray or brown	Whitish
Erythema	Generalized-focal	Unusual	Mild to moderate
Palmoplantar involvement	Diffuse PPK with grainy surface, very common	Yes	Yes, initially
Hypohidrosis	No	Yes	No
Scalp abnormalities	Hypotrichosis possible, scarring alopecia in association with follicular occlusion syndrome	-	Extensive at birth
Other skin findings	Recurrent fungal, bacterial and viral infections, association with follicular occlusion syndrome (eg, hidradenitis suppurativa), mucocutaneous squamous cell carcinoma in 10%-20% of patients	Rhomboid lichenification of nuchal skin	Follicular keratosis (“toad skin”), atopic eczema, asthma, eosinophilia
Extracutaneous involvement	Photophobia, keratitis, variable degree of SNHL (mostly bilateral), absence of corpus callosum and shortened heel cords possible	Jordan anomaly, variable hepatosplenomegaly, mild myopathy, cataract; occasionally: developmental delay, short stature	Pulmonary involvement and asphyxia at birth, later on atopic asthma, eosinophilia, and occasionally hyper-IgE
Risk of death	Lethal in some severe congenital presentations (eg, in case of G45E mutation)	Normal	Perinatally potentially fatal because of respiratory asphyxia; otherwise normal
Skin ultrastructure	Limited studies: abnormal KG and tonofilaments	Keratinocytes with lipid droplets, abnormal LB	Deposits of trilamellar membranous curved lamellae in swollen corneocytes and perinuclearly in edematous granular cells

Other analyses	None	Abnormal liver function tests; increased CPK, fasting test (reduced lipolysis), lipid vacuoles within polymorphonuclear leukocytes and monocytes (Jordan anomaly) Blood cell count (eosinophilia)

AD, Autosomal dominant; *AR*, autosomal recessive; *CIE*, congenital ichthyosiform erythroderma; *CPK*, creatine phosphokinase; *EKV*, erythrokeratodermia variabilis; *IPS*, ichthyosis prematurity syndrome; *KG*, keratohyaline granules; *LB*, lamellar body; *PPK*, palmoplantar keratoderma; *SNHL*, sensorineural hearing loss.
*May overlap with Clouston syndrome in rare cases.
†To be differentiated from self-healing collodion baby (Table V).

often referred to as acantholytic disorders. They represent MEDOC forms, in which the formation and/or stability of the keratinocytic desmosomal adhesion is altered by a defect of a sarco(endo)plasmic reticulum Ca^{2+}-ATPase pump (Darier: *ATP2A2* gene) or a secretory Ca^{2+}/Mn^{2+}-ATPase pump of the Golgi apparatus (Hailey-Hailey: *ATP2C1* gene).[151,152] The typical lesions of Darier disease—usually beginning in adolescence—are tiny keratotic papules with a firmly adherent keratin cap, and are most often found on the seborrheic areas, scalp, and extremities; generalized involvement is very rare.

MODERN PATHOPHYSIOLOGIC VIEW

Basic aspects for a functional understanding

Ichthyoses exhibit a generalized impaired desquamation as clinically evidenced by hyperkeratosis, scaling, or both. Desquamation is achieved by proteolytic degradation of the intercellular connectors, corneodesmosomes, aided by friction and corneocyte hydration. The process is based on normal epidermal differentiation and regulated by the balance of pH, protease inhibitors, and the generation of small hygroscopic molecules within the corneocyte.[8,11] Through one defective pathway or another, all the ichthyoses result in varying degrees of abnormal epidermal differentiation and abnormal desquamation, eg, showing impaired corneocyte shedding (retention hyperkeratosis) or accelerated production (epidermal hyperplasia).

Concept of the impaired permeability barrier and homeostatic response

The SC provides a barrier, which abruptly impedes the outward movement of interstitial fluid at the SG/SC interface,[153-156] and is formed by a series of highly hydrophobic lipid lamellae deposited through secretion of LB contents at the SG/SC interface between a mechanically resilient, yet pliable, scaffold of corneocytes.[157,158] In recent years, it has become evident that this most critical SC function—the permeability barrier—is impaired in most ichthyosis forms.[11,60,159-164] Several murine knockout models for ichthyosis [*Spink5* (−/−), *Tgm1* (−/−), *Abca12* (−/−) mice,[165-167] *Alox12b* (−/−),[168] *Cldn1*(−/−)[169]] have demonstrated neonatal lethality as a result of dehydration, underscoring the critical role of these genes in permeability barrier competence. Mutations that either alter the lipid composition of the SC membranes—disorders of lipid metabolism—or affect the function of the corneocyte structural proteins—disorders of keratinocyte proteins—result in increased water movement through the intercellular pathway. Therefore, the phenotypic expression

Table XIII. Overview of molecular basis and pathophysiologic aspects of inherited ichthyoses and related mendelian disorders of cornification (refer to "Modern Pathophysiologic View" section)

Primary defect	Pathophysiologic aspects of epidermis	Affected gene(s)	Diseases
1.) Disorders of keratinocyte proteins ("bricks")			
Cytoskeleton	Weakening or collapse of cytoskeleton and decreased	*KRT1/10*	EI
KIF disorder	mechanical stability of epidermis; affecting LB secretion	*KRT1*	ICM
	resulting in paucity of SC lamellar material and CDSN	*KRT2*	SEI
	retention		
Cornified lipid/cell envelope	Weak CE with reduced lamellar membrane and NLPS	*TGM1*	LI, CIE, SHCB, BSI
TGase-1 deficiency Loricrin disorder	Weak CE with reduced lamellar membrane and NLPS	*LOR*	LK
	Possible cytotoxic effect through gain of function of mutant loricrin molecules		
Protease/protease inhibitors	Increased serine protease activity with premature loss of	*SPINK5*	NS
LEKTI deficiency	CDSN and induction of inflammation	*ST14*	IHS
Matriptase deficiency	Defective filaggrin processing	*CTSC*	Papillon-Lefèvre
Cathepsin C deficiency	Impaired innate immune response and desquamation		syndrome
Keratohyaline	Decreased corneocyte hydration as result of low NMF; high SC	*FLG*	IV
Filaggrin deficiency	pH resulting in increased protease activity		
2.) Disorders of lipid metabolism, assembly, and/or transport ("mortar")			
Lipid synthesis/modification	Defect of different enzymes (or receptors) within lipoxygenase	*ALOX12B*	LI; CIE
Hepoxilin pathway defect	pathway, impaired processing of profilaggrin to monomeric	*ALOXE3*	RXLI
Steroid sulfatase deficiency	filaggrin (abnormal SC lipid composition likely)	*CYP4F22*	IPS
Fatty acid transporter defect	Abnormal SC lipid composition with lamellar/NLPS; inhibition	*NIPAL4*	
	of proteases causes persistence of CDSN	*STS*	
	Impaired transport and activation of fatty acids (critical	*SLC27A4*	
	fetal/neonatal period), defective SC lipid homeostasis		
Lipid transport and secretion	Disturbed transport of lipids and proteases, protease	*ABCA12*	HI; LI/CIE
Primary LB defect	inhibitors, and antimicrobial peptides; paucity of SC	(nonsense vs	
	lamellar structures	missense)	
Cholesterol biosynthesis and homeostasis	Defective "Kandutsch" pathway	*EBP*	CDPX2
disorders	Interference with sonic hedgehog	*NSDHL*	CHILD syndrome
8-7 sterol isomerase	Impaired transcription factors (SREBF1and2) affect sterol/ER	*MBTPS2*	IFAP syndrome
C3 sterol dehydrogenase	homeostasis and cell differentiation		
Zinc endopeptidase/site-2-protease defect			
Triglyceride metabolism	Abnormal SC lipid composition with lamellar/NLPS	*ABHD5*	Neutral lipid storage
Neutral lipid storage disease			disease with ichthyosis
Lysosomal storage	Disturbance of SC lipid composition of ceramides, cholesterol,	*GBA*	Gaucher syndrome
Glucocerebrosidase deficiency	and free fatty acids		type 2
Peroxisomal hydroxylation	Phytanic acid excess disturbs cholesterol/cholesterol sulfate,	*PHYH*	Refsum syndrome
Phytanoyl-CoA hydroxylase deficiency	or alters lipid degradation	*PEX7*	

Microsomal oxidation	SC lamellar phase separation or NLPS	*ALDH3A2*	SLS
Fatty aldehyde dehydrogenase deficiency			
Intracellular membrane trafficking	Impaired LB function	*AP1S1*	MEDNIK syndrome
Secretory (SNARE) pathway defects		*SNAP29*	CEDNIK syndrome
		VPS33B	ARC syndrome
3.) Disorders of cell-cell junctions			
Gap junctions	(?) Increased sensitivity to apoptosis, reactive	*GJB2 (GJB6)*	KID syndrome
Connexin disorders	hyperproliferation, impaired calcium regulation	*GJB3/GJB4*	EKV
Tight junctions	(?) Impaired regulation of paracellular permeability,	*CLDN1*	IHSC syndrome
Claudin disorders	defective epithelial polarization		
4.) Disorders of DNA transcription/repair			
Nucleus	?	C7Orf11	TTDs/ TFIIH related
Nucleotide excision repair defect		*ERCC2/XPD*	
		ERCC3/XPB	
Transcription defect (?)	?	*C7Orf11*	TTD without CI

ARC, Arthrogryposis–renal dysfunction–cholestasis*; BSI*, bathing suit ichthyosis; *CDSN*, corneodesmosome; *CE,* cornified cell envelope; *CEDNIK*, cerebral dysgenesis–neuropathy–ichthyosis–palmoplantar keratoderma; *CI*, congential ichthyosis; *CIE*, congenital ichthyosiform erythroderma; *EI*, epidermolytic ichthyosis; *EKV*, erythrokeratodermia variabilis; *ER,* endoplasmatic reticulum; *HI*, harlequin ichthyosis; *ICM*, ichthyosis Curth-Macklin; *IFAP*, ichthyosis follicularis–atrichia–photophobia; *IHS*, ichthyosis hypotrichosis syndrome; *IHSC*, ichthyosis–hypotrichosis–sclerosing cholangitis; *IPS*, ichthyosis prematurity syndrome; *IV*, ichthyosis vulgaris; *KIF*, keratin intermediate filament; *LB*, lamellar body; *LI*, lamellar ichthyosis; *LK*, loricrin keratoderma; *MEDNIK*, mental retardation–enteropathy–deafness–neuropathy–ichthyosis–keratodermia; *NLPS*, nonlamellar phase separations; *NMF*, natural moisturizing factor; *NS*, Netherton syndrome; *RXLI*, recessive X-linked ichthyosis; *SC*, stratum corneum; *SEI*, superficial epidermolytic ichthyosis; *SHCB*, self-healing collodion baby; *SLS*, Sjögren-Larsson syndrome; *TGase*, transglutaminase; *TFIIH*, transcription factor II H; *TTD*, trichothiodystrophy.

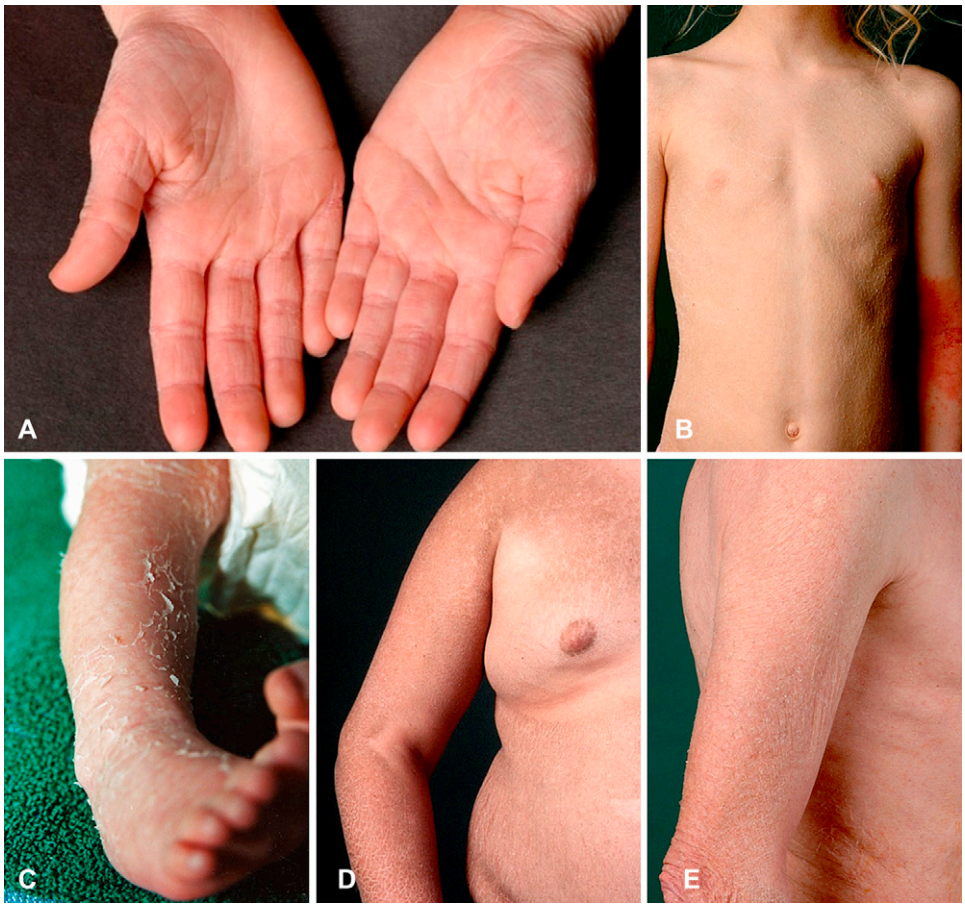

Fig 1. Clinical examples of common ichthyosis: accentuated palmoplantar markings of ichthyosis vulgaris (IV) in white skin (**A**); IV with atopic eczema (**B**); exaggerated scaling after 3 weeks of life as early presentation of recessive X-linked ichthyosis (RXLI) (**C**); RXLI with brownish scales in 14-year-old boy (**D**); RXLI with white to gray scales in elderly patient (**E**).

of many ichthyoses should be analyzed within the context of stereotypical homeostatic response mechanisms that are activated by barrier abrogation in an attempt to restore the impaired barrier (and avoid lethal desiccation). For example, these mechanisms include delivery of preformed LB (within minutes), up-regulation of epidermal lipid synthesis (within hours), epidermal hyperproliferation (within days), and/or inflammation.[7,8,170] Healthy epidermis may need 3 to 7 days for complete barrier repair,[171] but in ichthyosis, where a genetic mutation produces an inherent epidermal barrier defect, repair efforts are continuously stimulated and do not terminate.[8] Differences in the pathogenetic mechanisms of these disorders have to be considered, but from a functional viewpoint, the ichthyosis skin phenotype may be regarded as a summation of the genetic epidermal barrier defect and the homeostatic response.[8,172] This concept is illustrated by a recent mouse model, where *Alox12b* (−/−) skin was transplanted on nude mice. The neonatal *Alox12b* (−/−) mouse phenotype presented with thin, highly inflamed skin leading to dehydration and death within several hours (genetically impaired SC barrier), but the transplanted rescued adult phenotype of the lipoxygenase-deficient skin developed a mouse ichthyosis with severe hyperkeratosis (homeostatic response).[173] Such functional models correlate with the phenotypic shift in EI (or HI), where differences in barrier requirements between the wet intrauterine versus the dry postnatal environments produce strikingly different phenotypes at birth versus thereafter.

Toward a pathophysiologic classification

Unraveling the pathogenic sequence of each disorder from the responsible genetic cause to clinical disease expression is important for the development of new targeted therapies. A pathophysiologic/functional classification of all MEDOC is a long-term goal, which will require further studies before it can be fully realized. Currently, an initial pathophysiologic scheme for

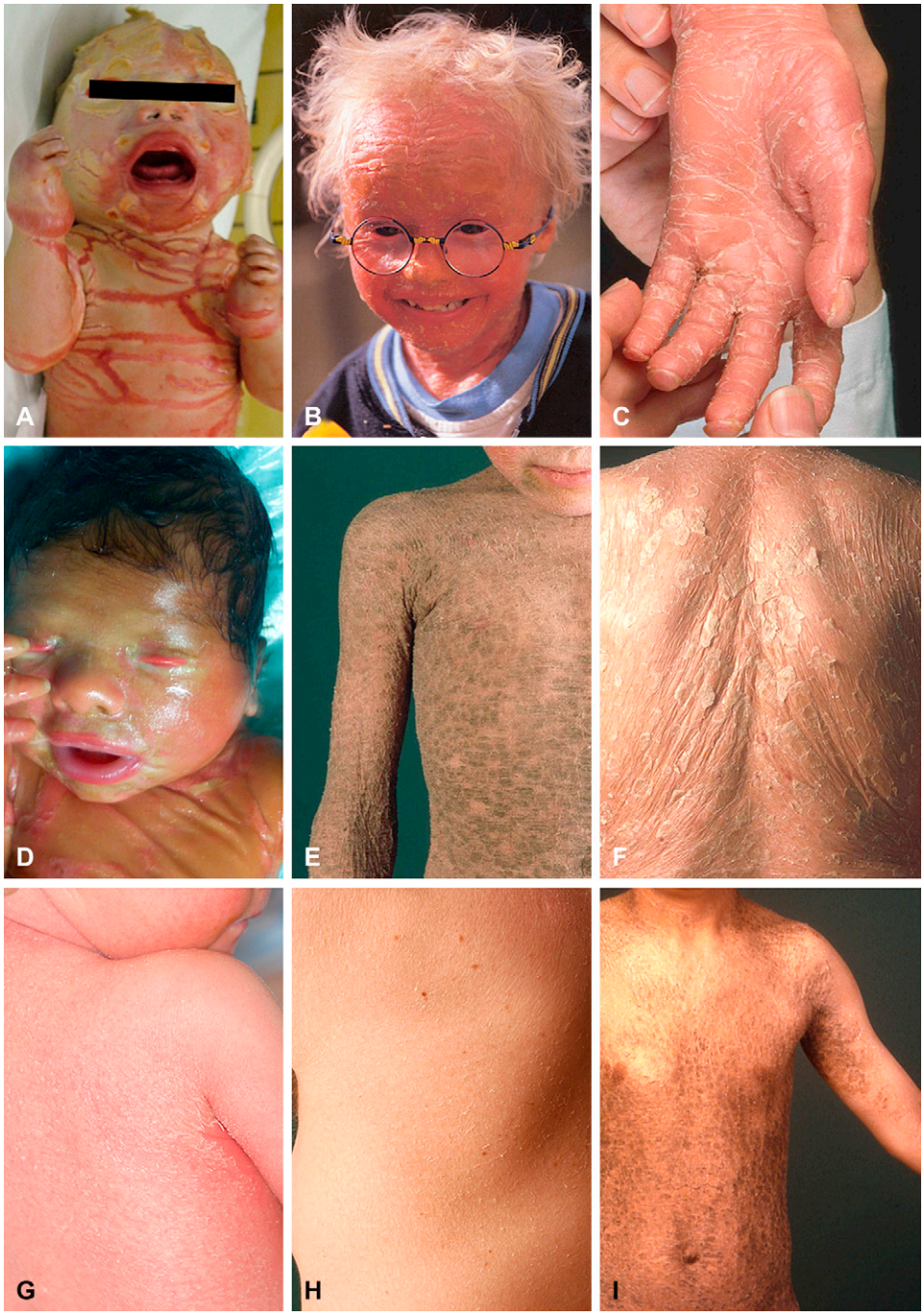

Fig 2. Clinical examples of autosomal recessive congenital ichthyosis: harlequin ichthyosis (HI) at birth (**A**); HI evolves into generalized exfoliating erythrodermic ichthyosis (**B** and **C**) (reprinted from "Menschen mit Ichthyose - ein Bildband 2003" courtesy of Selbsthilfe Ichthyose e. V.); collodion membrane with ectropion and eclabion in lamellar ichthyosis (LI) (courtesy of Dr Hagen Ott) (**D**); LI in childhood (**E**); LI caused by severe mutations in *TGM1* in 79-year-old man (**F**); congenital ichthyosiform erythroderma (CIE) in early infancy (**G**); mild CIE in adult patient with *ALOXE3* mutations (**H**); bathing suit ichthyosis represents LI variant characterized by localized healing of extremities (**I**).

ichthyoses and related diseases is proposed recognizing the following main categories: disorders of keratinocyte proteins ("bricks"), eg, referring to cytoskeleton, cornified lipid/cell envelope, proteases/protease inhibitors, keratohyaline, and disorders of lipid metabolism, assembly, and/or transport

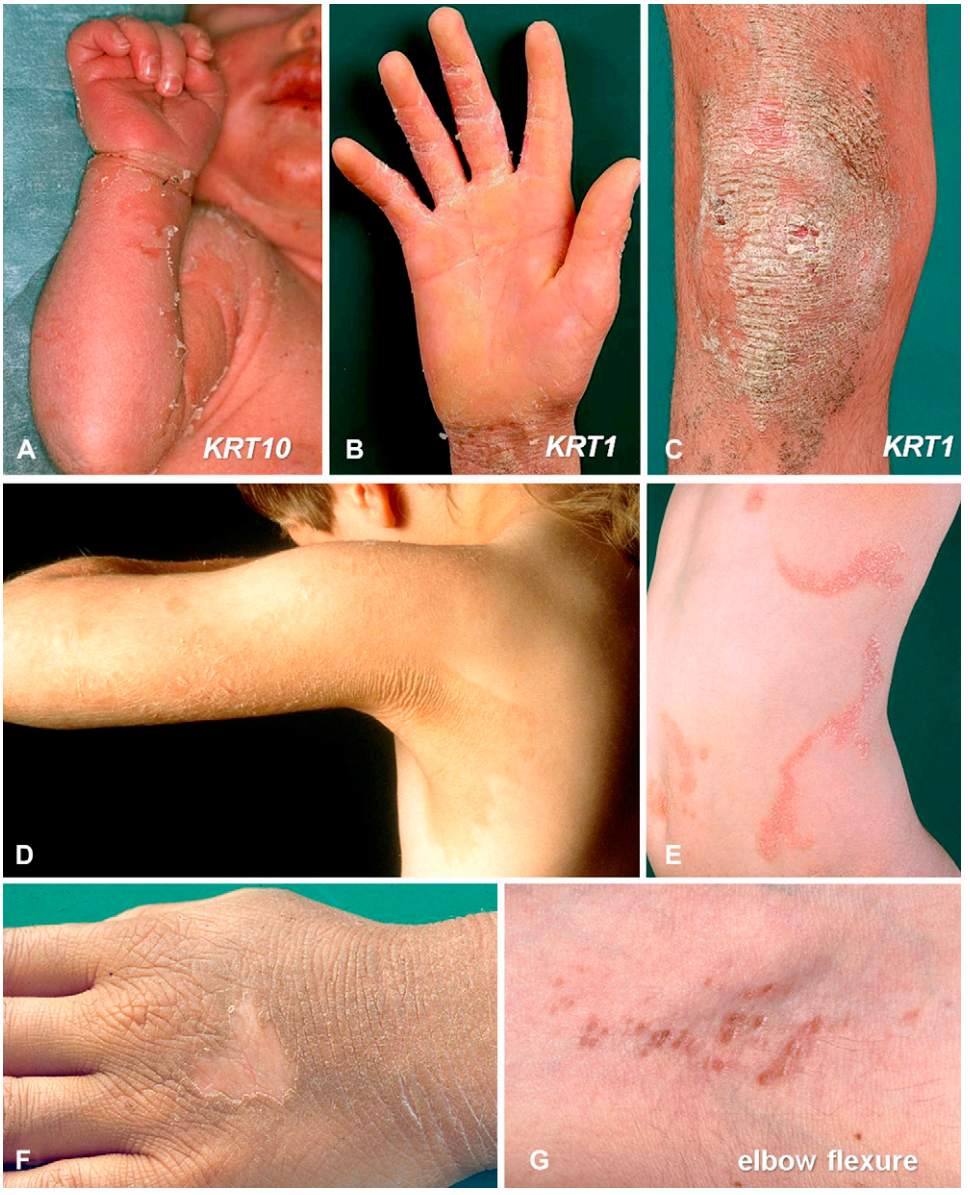

Fig 3. Clinical examples of keratinopathic ichthyosis: superficial blister formation and erythema at birth in epidermolytic ichthyosis (EI) caused by *KRT10* mutation (note that palm is spared) (**A**); palmoplantar keratoderma in EI caused by *KRT1* mutation (**B**); in infancy EI often shows hyperkeratoses with predilection of friction areas and over joints (**C**); superficial EI (SEI) confined to particular skin areas of arm and axillary region (**D**); annular EI represents intermittent or transient presentation of EI (**E**); moulting phenomenon in SEI (**F**); epidermolytic nevi may indicate gonadal mosaicism (elbow flexure of parent of patient shown in *A*) (**G**).

("mortar"), eg, referring to steroid sulfatase deficiency, the proposed hepoxilin pathway,[24] LB defects, and a variety of multisystem lipid metabolism defects such as lysosomal or neutral lipid storage disease. The inclusion of the connexin disorders, ie, EKV and KID, the ichthyosis–hypotrichosis–sclerosing cholangitis syndrome, and TTDs into the ichthyosis family indicates the additional categories of disorders of cell-cell junctions, and disorders of DNA transcription/repair, respectively. Table XII, open for inclusion of future new categories, summarizes the different groups and specifies the most important pathophysiologic aspects of each disorder as known to date.

DIAGNOSTIC ASPECTS

Molecular genetics

The genetic causes, meaning the genes and pathogenic mutations, for most of the 36 forms of inherited ichthyoses (Tables I and II) have

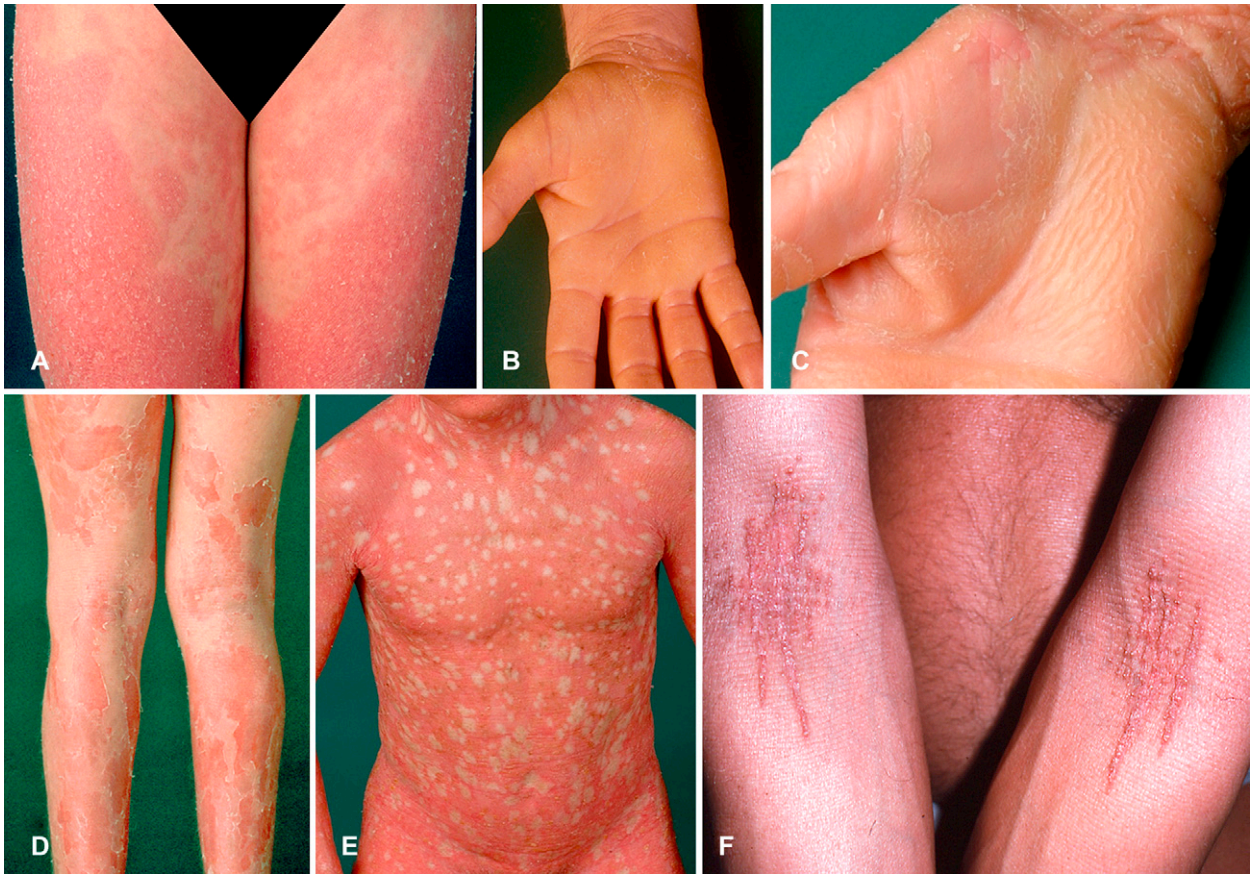

Fig 4. Clinical examples of other nonsyndromic forms of ichthyosis: erythrokeratodermia variabilis (EKV) that evolved like progressive symmetric erythrokeratodermia (**A**); palmoplantar keratoderma in EKV (**B**); palmar honeycomb pattern of loricrin keratoderma (**C**); peeling skin disease (**D**); congenital reticular ichthyosiform erythroderma (**E**); keratosis linearis–ichthyosis congenita–keratoderma (**F**).

been successfully identified within the last two decades.* The molecular bases of only a few remain to be elucidated. The current classification was designed to reference each clinical diagnosis with the associated gene defect (Tables II and III). Nevertheless, because of the genetic diversity and costs of testing, an initial carefully made clinical diagnosis, assisted by relevant laboratory and pathological evaluations, is essential to narrow the search for the affected gene (Fig 6). Helpful contacts to initiate molecular diagnostic procedures are listed in Table XIV or can be provided by the authors (see http://www.netzwerk-ichthyose.de/index.php?id=27&L=1). In consanguineous populations, homozygosity mapping may be a screening test to identify the causative gene, while saving time and reducing diagnostic costs.[187,188] It is of note that in some patients with an ichthyosis with a well-defined genetic basis, even extensive gene sequencing does not identify the pathogenic mutation or mutations, eg, in KPI.[189]

In summary, molecular diagnosis is a crucial diagnostic tool and has become in some countries the gold standard for the diagnosis of the ichthyoses and MEDOC in general. It provides a firm basis for genetic counseling of affected individuals and families and permits DNA-based prenatal diagnosis for families at risk, as has been demonstrated in NS,[190-192] KPI,[193-195] Sjögren-Larsson syndrome,[196] HI,[197,198] and others.

Use of ultrastructural analyses

In disorders of cornification, subcellular changes that occur in the keratinocyte organelles and structural proteins are even more heterogeneous than expected from the clinical and light microscopic view alone. Transmission electron microscopy (EM) is therefore a valuable tool and may provide important clues to the clinical diagnosis of the ichthyoses by

*References 15-17,22-26,32,37,40-42,44,53,57,59,67,69-71,73,75,84,86,90,96,98,99,102,104,106,114-116,121,125,174-186.

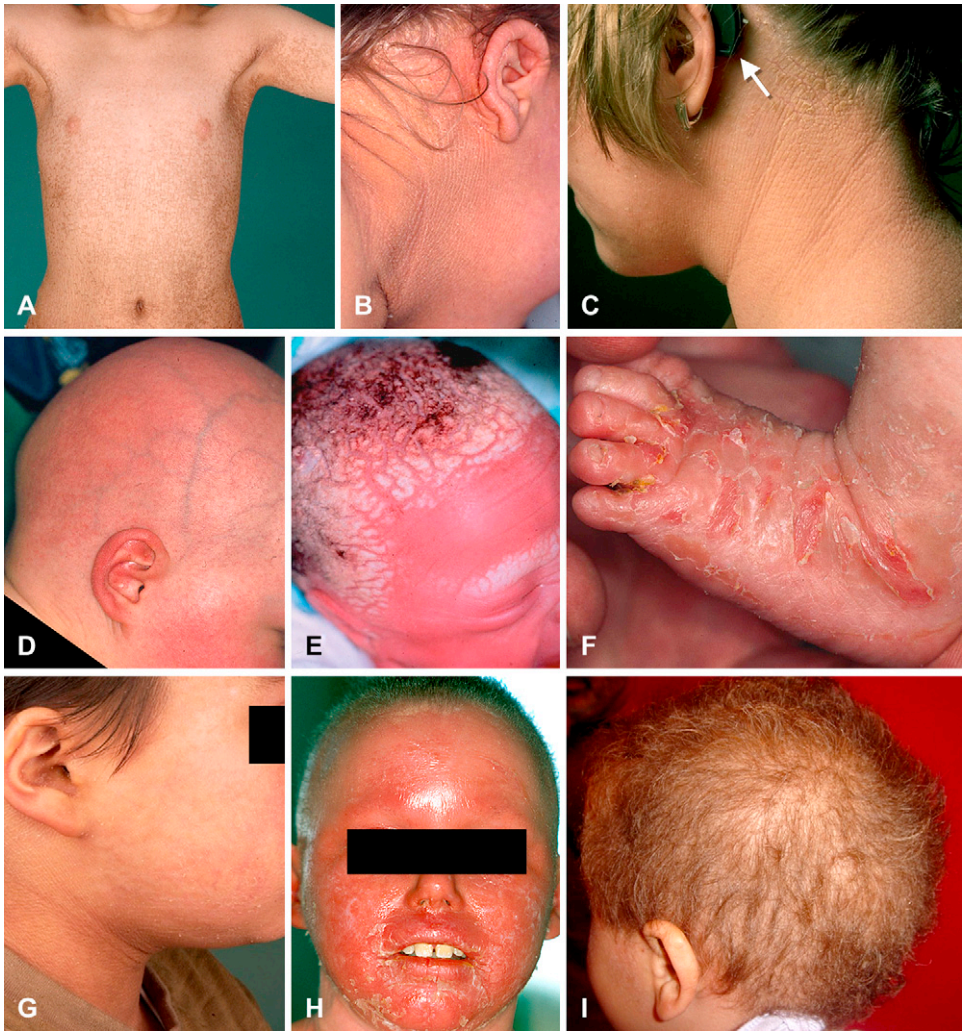

Fig 5. Clinical examples of syndromic forms of ichthyosis: trichothiodystrophy (**A**); Sjögren-Larsson syndrome (**B**); KID syndrome (**C**); ichthyosis follicularis—atrichia—photophobia syndrome (**D**); ichthyosis prematurity syndrome (**E**); Conradi-Hünermann-Happle syndrome (**F**); neutral lipid storage disease with ichthyosis (**G**); Netherton syndrome (**H**); ichthyosis hypotrichosis syndrome (**I**) (courtesy of Dr Dan Ben Amitai).

identification of consistent and sometimes highly specific ultrastructural markers.[54,164,199,200] Given appropriate expertise, about 30% to 40% of patients with a suspected form of ichthyosis can be classified based on conventional ultrastructural criteria, ie, certain types of ichthyosis may be excluded, or the list of differential diagnoses may be narrowed. For example, in IV a pronounced rarefaction of keratohyaline granules can be visualized,[201] and the extent of this ultrastructural abnormality correlates with the presence of one or two loss-of-function mutations in the *FLG* gene, encoding filaggrin.[202] RXLI typically shows retained corneodesmosomes within the SC and nonlamellar phase separation in the SC interstices, provided that a ruthenium tetroxide fixation (see below) has been performed.[7,8] HI exhibits abnormal LB,[203] with a marked deficiency of intercellular lamellae in the SC.[16,204] Disruption of the keratin cytoskeleton, with detachment from the desmosomal plaques and often perinuclear shell formation is observed in the KPI.[50,51,53,54,62,65,176] Abnormal intranuclear granules seen in the SG and SC are observed in loricrin keratoderma, which is ultrastructurally further characterized by a reduced thickness of the cornified cell envelope.[96,205] A markedly thinned cornified cell envelope throughout the SC is typical for TGase-1 deficiency.[160] The ultrastructural features of the so-called EM classification described by the Heidelberg group are based on a glutaraldehyde fixation of the skin biopsy specimen.[206-210] With this technique polygonal clefts in the SC can be observed as an ultrastructural key

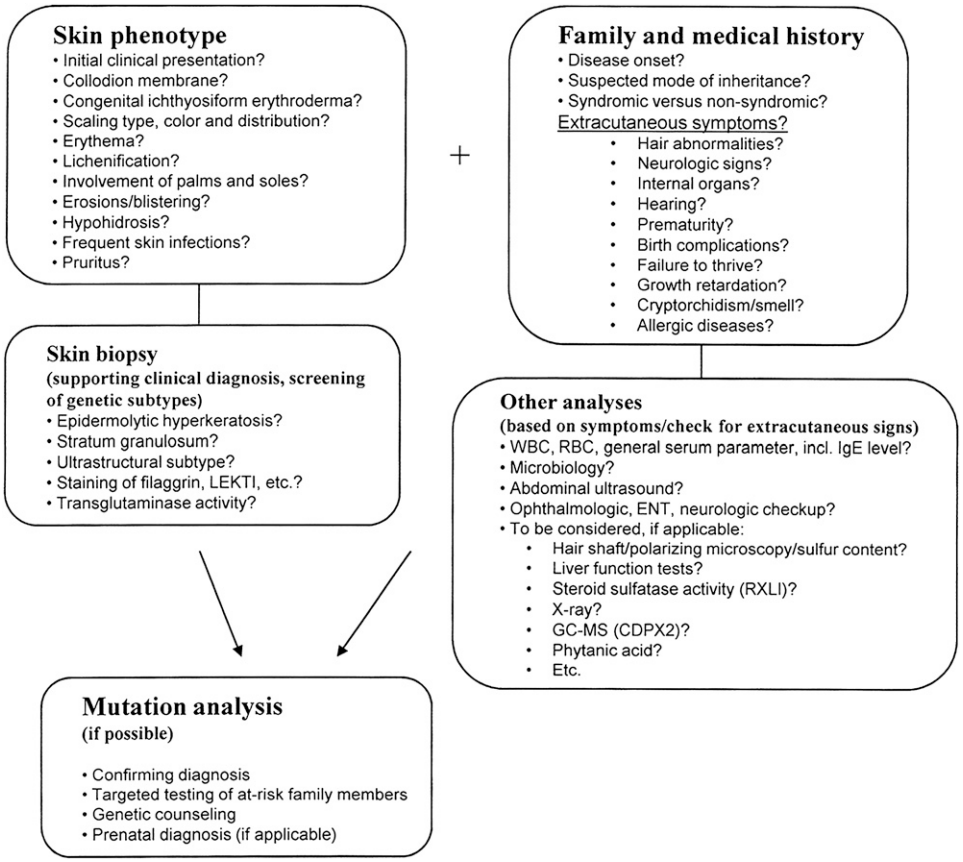

Fig 6. Concept for diagnostic approach. Diagnosis is based on dermatologic evaluation, careful family and medical history, and can be strongly supported by directed morphologic examinations and other special analyses. If available, molecular analyses are suggested to confirm diagnosis, allow for testing of family members, and prenatal diagnosis.

feature of TGase-1 deficiency,[211] aberrant vesicular structures may indicate *NIPAL4* (~*ICHTHYIN*) mutations in ARCI,[33] and trilamellar membrane aggregations in the SC and SG (EM type IV) are pathognomonic for ichthyosis prematurity syndrome.[89] Detachment of the SC from the SG with asymmetric cleavage of corneodesmosomes is a specific feature of NS.[165,212]

The image of the SC as viewed by conventional EM is still artifactual. In frozen sections, where lipid extraction is avoided, eg, by hydrophilic staining procedures, the compact structure of the SC can be appreciated. Similarly, the recent development of both osmium tetroxide and ruthenium tetroxide postfixation enables improved visualization of extracellular lipids, postsecretory changes in LB contents, and alterations of the lamellar bilayers in the SC, eg, lamellar/nonlamellar phase separation.[7] The combination of all alterations observed with this technique may be diagnostic for many forms of ichthyosis.[8] Most importantly, the ultrastructural demonstration of disturbances of lipid metabolism gives valuable insights into the pathophysiologic basis of many ichthyoses[11,60,159-164] and enables a function-driven approach.[7,8,11]

Histopathology, immunochemistry, and other nongenetic analyses

Routine histopathological findings in most ichthyoses are nondiagnostic, often demonstrating only epidermal hyperplasia and varying degrees of orthohyperkeratosis. In combination with characteristic features, routine histology can give an important clue for IV[213,214] or EI.[52,61,62,215,216] However, one should consider that a reduced or absent SG suggestive for IV can also be seen in acquired ichthyosis, NS, Refsum syndrome, TTDs, or Conradi-Hünermann-Happle syndrome. Hair mounts can demonstrate bamboo hairs (trichorrhexis invaginata) in NS[123]; although not invariably present, bamboo hairs are pathognomonic of this disorder. Parakeratosis and hypergranulosis is regarded a histopathological clue to loricrin keratoderma.[96,205] Polarization microscopy can demonstrate the tiger-tail pattern of TTD,[217,218] which

Table XIV. Examples of foundations, patient organizations, and useful Internet links

Foundations and registries	
United States: Foundation for Ichthyosis and Related Skin Types (www.scalyskin.org), Registry for Ichthyosis and Related Disorders (www.skinregistry.org)	
Germany (Europe): Network for Ichthyoses and Related Keratinization Disorders (www.netzwerk-ichthyose.de/)	
Japan: Registry for Autosomal Recessive Congenital Ichthyosis and Keratinopathic Ichthyosis supported by Health and Labor Science Research Grants, Research on Intractable Diseases, Ministry of Health, Labor, and Welfare	
Austria: National Registry for Genodermatoses Including Ichthyoses	
Patient organizations for ichthyosis	
Austria	www.selbsthilfe-tirol.at/Selbsthilfegruppen/Gruppen/Ichthyose.htm
Belgium	www.devidts.com/ichthyosis
Denmark	www.iktyosis.dk
Finland	www.iholiitto.fi/
France	www.anips.net/
Germany	www.ichthyose.de
Italy	www.ittiosi.it/
Japan	www.gyorinsen.com
Monaco	www.aaimonaco.org
Spain	www.ictiosis.org
Sweden	www.iktyos.nu//
Switzerland	www.ichthyose.ch
United Kingdom	www.ichthyosis.org.uk/
United States	www.scalyskin.org
Other databases and Internet links	
World Wide Web site hosted at National Center for Biotechnology Information (NCBI):	www.genetests.org
Portal for rare diseases and orphan drugs:	www.orpha.net
Human intermediated filament database:	www.interfil.org
German guidelines for diagnosis and treatment of ichthyoses:	www.uni-duesseldorf.de/AWMF/ll/013-043.htm

corresponds to the diagnostic low-sulfur protein content of the hair.[219,220] Special immunohistochemical procedures can be combined, eg, to confirm filaggrin deficiency in IV,[202,221] or demonstrate absent or reduced expression of LEKTI that supports the diagnosis of NS.[222-224] To screen for TGase-1 deficiency in ARCI unfixed cryostat sections are used for the enzyme activity assay.[225,226] Alternatively, superficial SC material can be subjected to a SDS heating test that visualizes absent cross-linked envelopes in TGase-1 deficiency.[227]

There are special useful analyses given in Tables IV to XII. For instance, steroid sulfatase deficiency underlying RXLI can be demonstrated by reduced arylsulfatase-C activity of leukocytes, or can readily be diagnosed by the widely available fluorescent in situ hybridization test for the STS gene region, because more than 90% of the cases are caused by a gene deletion. Gas chromatography-mass spectrometry reveals elevated serum levels of 8-dehydrocholesterol and cholesterol in Conradi-Hünermann-Happle syndrome and can identify a somatic *EBP* gene mosaicism in unaffected individuals.[228]

RESOURCES FOR CLINICIANS AND PATIENTS

Currently, therapy of most ichthyoses is neither type-specific nor corrective, but rather its goal is to relieve symptoms.[6,35,46,229-232] Importantly, clinicians have to consider the functional consequences of the epidermal barrier defect, such as increased risk of systemic absorption and toxicity, especially in infants.[231-233] Neonates with severe congenital phenotypes may require intensive care using humidified isolettes (incubators) to avoid temperature instability and hypernatremic dehydration, and observation for signs of cutaneous infection and septicemia. Caloric insufficiency as a result of evaporative energy losses places infants with severe phenotypes at risk for growth failure and requires early intervention.[234,235]

Affected individuals and/or their families should be offered genetic counseling to explain the nature of the disorder, its mode of inheritance, and the probability of future disease manifestations in the family.[1,3] They should be offered psychologic support and be informed of patient organizations or foundations (Table XIV).

We would like to dedicate this classification to all our patients and their families, and thank all colleagues and friends, who are helping to achieve optimal clinical care for affected individuals and/or promote through their research our knowledge about the disorders of cornification. We are deeply grateful for the generous financial support of the Laboratories Pierre Fabre, and would like to say "grand merci" to Anita Couteau, Didier Coustou, and Pascal Lefrancois—and to Brigitte Willis from the Network for Ichthyoses and Related Keratinization Disorders Center in Münster, who together perfectly organized the wonderful, unforgettable conference in Sorèze. Moreover, we would like to acknowledge the help of Dr Dan Ben Amitai and Dr Hagen Ott for providing photographs, and Jutta Bückmann for the help with the slides from the Department of Dermatology, Münster (head Thomas A. Luger). We also express gratitude to Meral Arin, Steffen Emmert, Rudolf Happle, Peter Höger, and Dieter Metze for their support and helpful comments. The first author wants to thank his wonderful family, namely Melody, Alanna, and Amechi.

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