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.

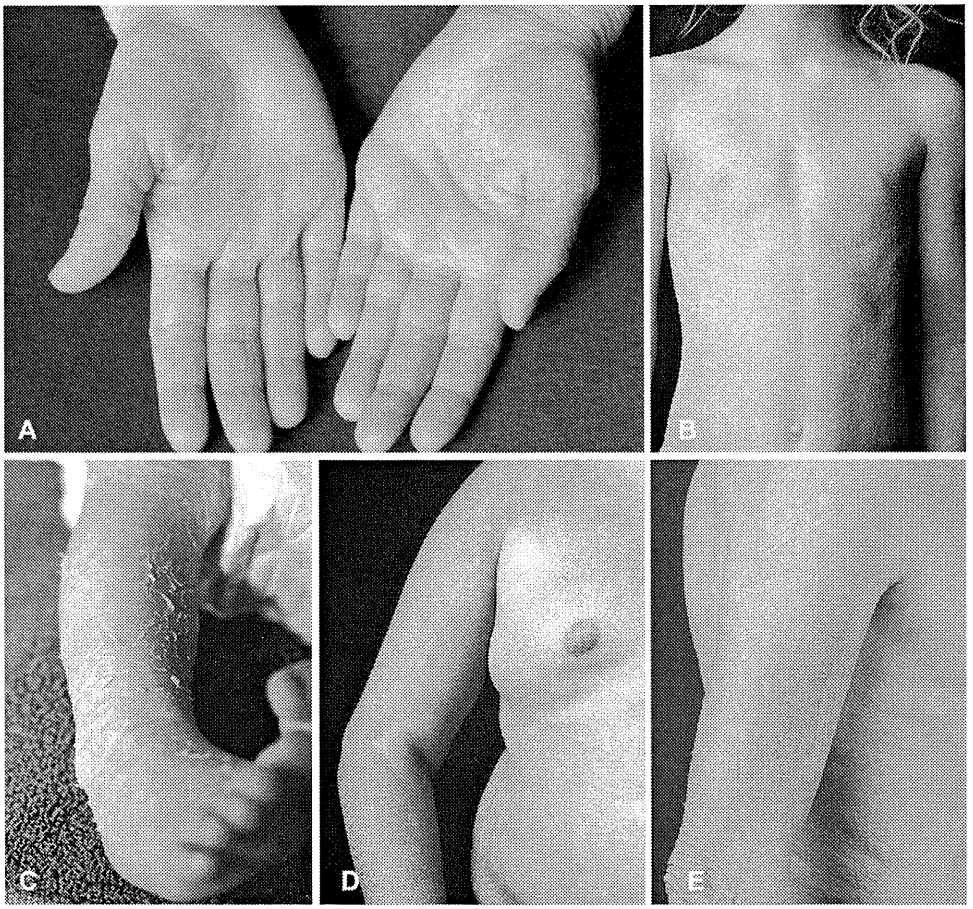

Fig 1. Clinical examples of common ichthyosis: accentuated palmoplantar markings of ichthyosis vulgaris (IV) in white skin (**A**); IV with atopic eczema (**B**); exaggerated scaling after 3 weeks of life as early presentation of recessive X-linked ichthyosis (RXLI) (**C**); RXLI with brownish scales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

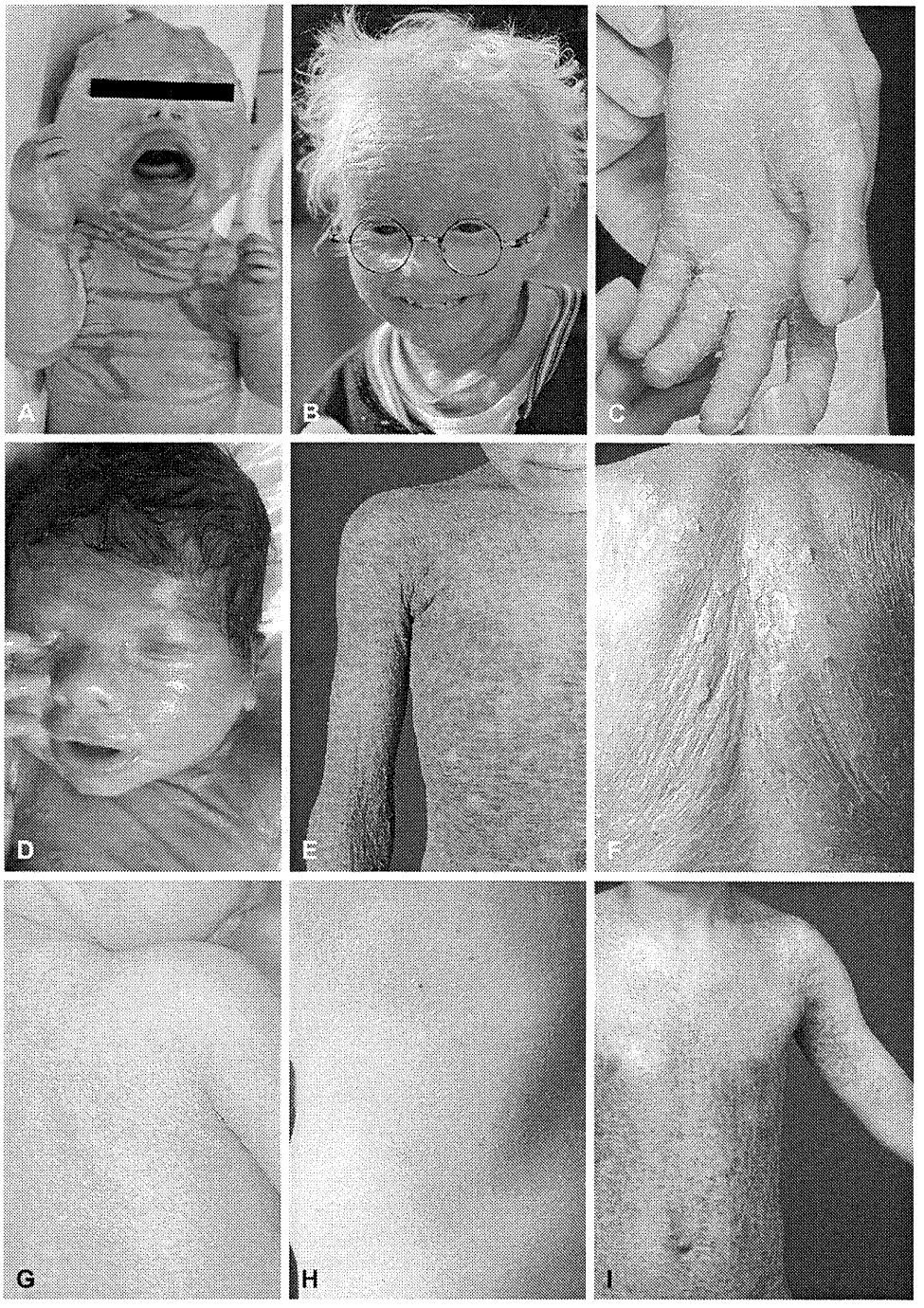

Fig 2. Clinical examples of autosomal recessive congenital ichthyosis: harlequin ichthyosis (HI) at birth (**A**); HI evolves into generalized exfoliating erythrodermic ichthyosis (**B** and **C**) (reprinted from "Menschen mit Ichthyose - ein Bildband 2003" courtesy of Selbsthilfe Ichthyose e. V.); 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

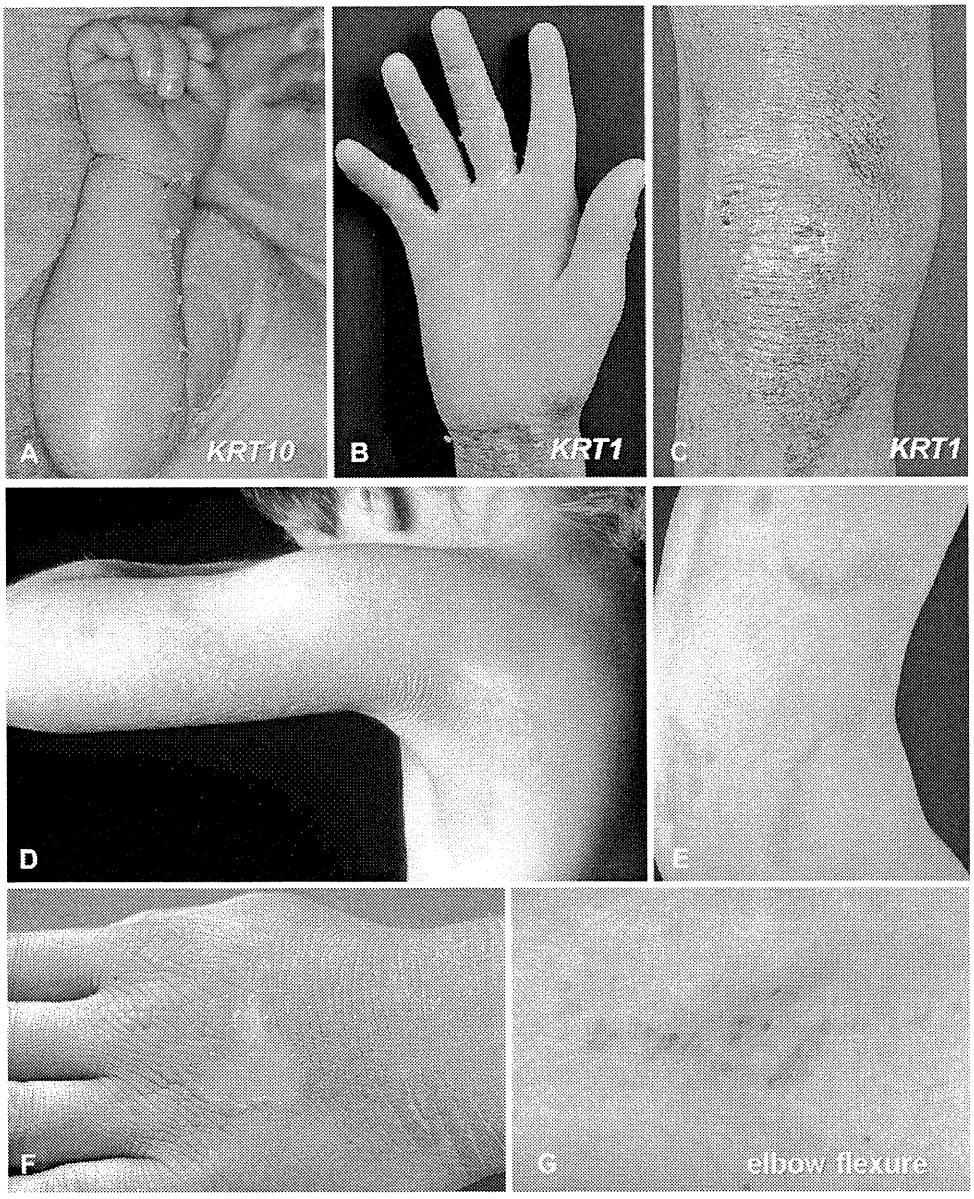

Fig 3. Clinical examples of keratinopathic ichthyosis: superficial blister formation and erythema at birth in epidermolytic ichthyosis (EI) caused by *KRT10* mutation (note that palm is spared) (**A**); palmoplantar keratoderma in EI caused by *KRT1* mutation (**B**); in infancy EI often shows hyperkeratoses 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

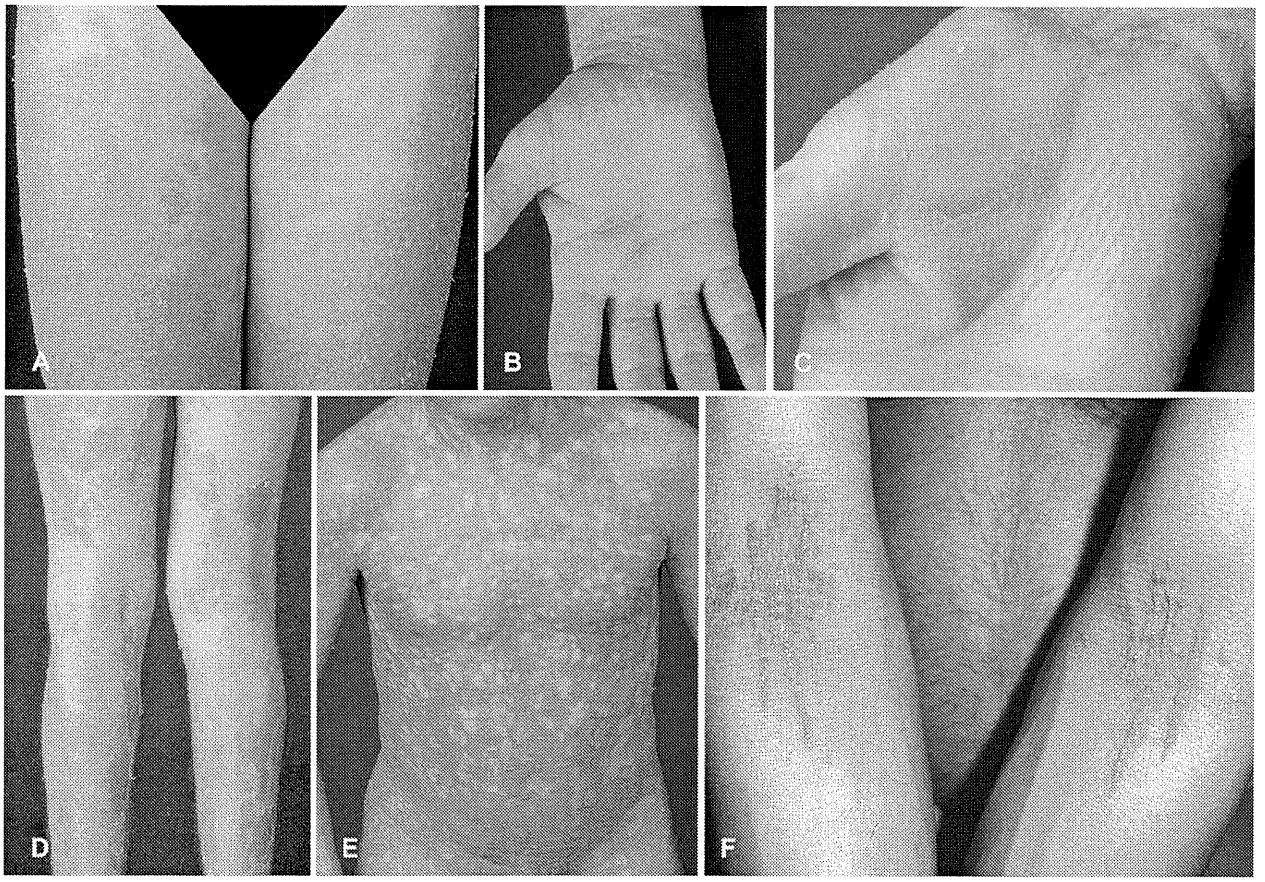

Fig 4. Clinical examples of other nonsyndromic forms of ichthyosis: erythrokeratodermia variabilis (EKV) that evolved like progressive symmetric erythrokeratodermia (**A**); palmoplantar keratoderma in EKV (**B**); palmar honeycomb pattern of loricrin keratoderma (**C**); peeling skin disease (**D**); 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.

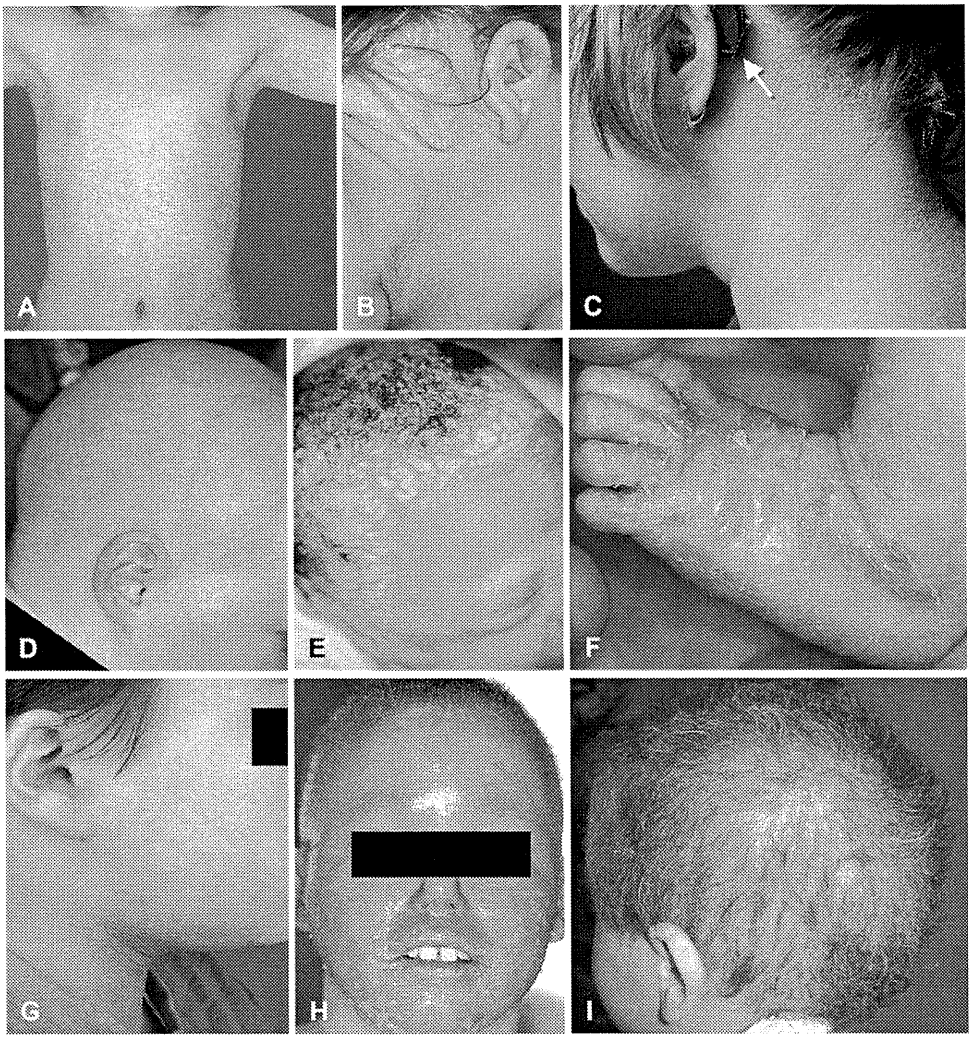

Fig 5. Clinical examples of syndromic forms of ichthyosis: trichothiodystrophy (**A**); Sjögren-Larsson syndrome (**B**); KID syndrome (**C**); ichthyosis follicularis—atrichia—photophobia syndrome (**D**); ichthyosis prematurity syndrome (**E**); Conradi-Hünermann-Happle syndrome (**F**); neutral lipid 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

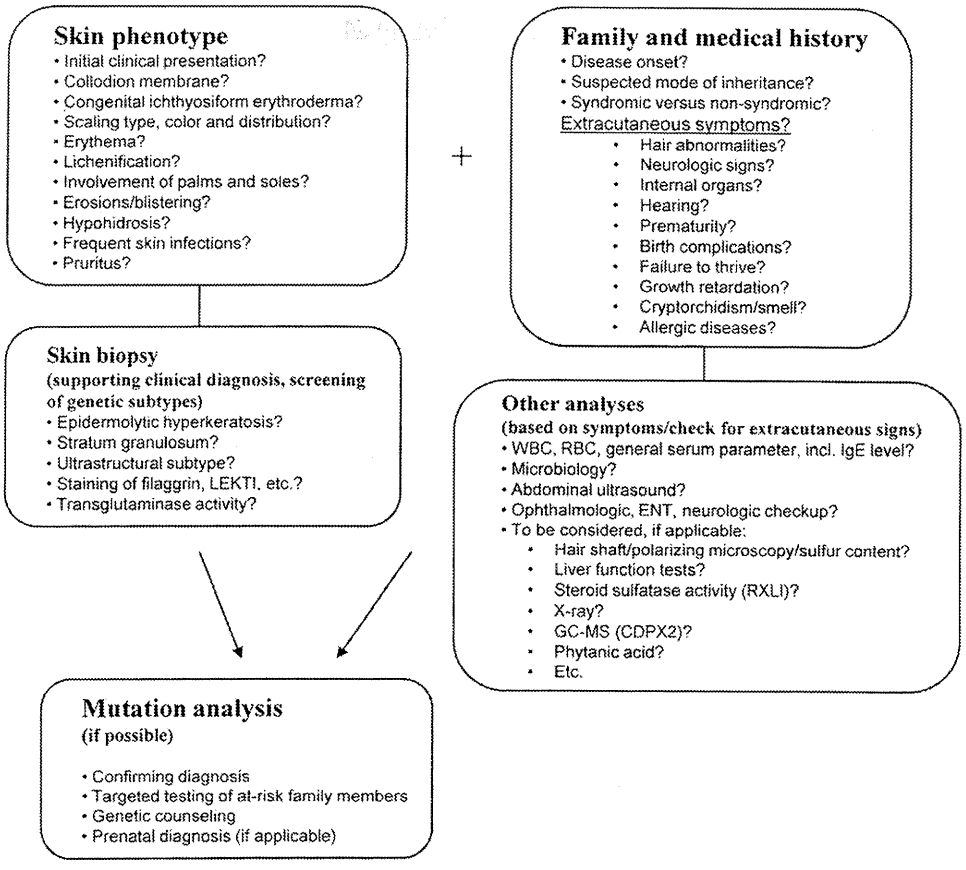

Fig 6. Concept for diagnostic approach. Diagnosis is based on dermatologic evaluation, careful family and medical history, and can be strongly supported by directed morphologic examinations and other special analyses. If available, molecular analyses are suggested to confirm diagnosis, allow for testing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

REFERENCES

1. Williams ML, Elias PM. Ichthyosis: genetic heterogeneity, genodermatoses, and genetic counseling. Arch Dermatol 1986;122:529-31.
2. Willan R. On cutaneous diseases. London: Barnard; 1808.
3. Traupe H. The ichthyoses: a guide to clinical diagnosis, genetic counseling, and therapy. Berlin: Springer Verlag; 1989.
4. Akiyama M, Shimizu H. An update on molecular aspects of the non-syndromic ichthyoses. Exp Dermatol 2008;17:373-82.
5. DiGiovanna JJ, Robinson-Bostom L. Ichthyosis: etiology, diagnosis, and management. Am J Clin Dermatol 2003;4:81-95.
6. DiGiovanna JJ. Ichthyosiform dermatoses: so many discoveries, so little progress. J Am Acad Dermatol 2004;51(Suppl): S31-4.
7. Elias PM, Williams ML, Holleran WM, Jiang YJ, Schmuth M. Thematic review series: skin lipids. Pathogenesis of permeability barrier abnormalities in the ichthyoses: inherited disorders of lipid metabolism. J Lipid Res 2008;49:697-714.
8. Elias PM, Williams ML, Crumrine D, Schmuth M. Ichthyoses - Clinical, Biochemical, Pathogenic and Diagnostic Assessment. Karger. In press.
9. Oji V, Traupe H. Ichthyoses: differential diagnosis and molecular genetics. Eur J Dermatol 2006;16:349-59.
10. Richard G. Molecular genetics of the ichthyoses. Semin Med Genet 2004;131C:32-44.
11. Schmuth M, Gruber R, Elias PM, Williams ML. Ichthyosis update: towards a function-driven model of pathogenesis of the disorders of cornification and the role of corneocyte proteins in these disorders. Adv Dermatol 2007;23:231-56.
12. Siemens HW. Die Vererbung in der Ätiologie der Hautkrankheiten. In: Jadassohn J, editor. Handbuch der Haut- und Geschlechtskrankheiten 3. Berlin: Springer Verlag; 1929. pp. 1-165.
13. Schnyder UW. Inherited ichthyoses. Arch Dermatol 1970;102: 240-52.
14. Riecke E. Über ichthyosis congenita. Arch Dermatol Syph 1900;54:289-340.
15. Kelsell DP, Norgett EE, Unsworth H, Teh MT, Cullup T, Mein CA, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet 2005;76: 794-803.
16. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, McMillan JR, Goto M, Arita K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. J Clin Invest 2005;115:1777-84.
17. Lefevre C, Audebert S, Jobard F, Bouadjar B, Lakhdar H, Boughdene-Stambouli O, et al. Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. Hum Mol Genet 2003;12:2369-78.
18. Parmentier L, Lakhdar H, Blanchet-Bardon C, Marchand S, Dubertret L, Weissenbach J. Mapping of a second locus for lamellar ichthyosis to chromosome 2q33-35. Hum Mol Genet 1996;5:555-9.
19. Natsuga K, Akiyama M, Kato N, Sakai K, Sugiyama-Nakagiri Y, Nishimura M, et al. Novel ABCA12 mutations identified in two cases of non-bullous congenital ichthyosiform erythroderma associated with multiple skin malignant neoplasia. J Invest Dermatol 2007;127:2669-73.
20. Sakai K, Akiyama M, Yanagi T, McMillan JR, Suzuki T, Tsukamoto K, et al. ABCA12 is a major causative gene for non-bullous congenital ichthyosiform erythroderma. J Invest Dermatol 2009;129:2306-9.
21. Lawlor F. Progress of a harlequin fetus to nonbullous ichthyosiform erythroderma. Pediatrics 1988;82:870-3.
22. Huber M, Rettler I, Bernasconi K, Frenk E, Lavrijsen SP, Ponec M, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. Science 1995;267:525-8.
23. Russell LJ, DiGiovanna JJ, Rogers GR, Steinert PM, Hashem N, Compton JG, et al. Mutations in the gene for transglutaminase 1 in autosomal recessive lamellar ichthyosis. Nat Genet 1995;9:279-83.
24. Lefevre C, Bouadjar B, Karaduman A, Jobard F, Saker S, Ozguc M, et al. Mutations in ichthyin a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. Hum Mol Genet 2004;13:2473-82.
25. Lefevre C, Bouadjar B, Ferrand V, Tadini G, Megarbane A, Lathrop M, et al. Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. Hum Mol Genet 2006;15: 767-76.
26. Jobard F, Lefevre C, Karaduman A, Blanchet-Bardon C, Emre S, Weissenbach J, 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 2002;11:107-13.
27. Fischer J. Autosomal recessive congenital ichthyosis. J Invest Dermatol 2009;129:1319-21.
28. Eckl KM, de Juanes S, Kurtenbach J, Natebus M, Lugassy J, Oji V, et al. Molecular analysis of 250 patients with autosomal recessive congenital ichthyosis: evidence for mutation hotspots in ALOXE3 and allelic heterogeneity in ALOX12B. J Invest Dermatol 2009;129:1421-8.
29. Hatsell SJ, Stevens H, Jackson AP, Kelsell DP, Zvulunov A. An autosomal recessive exfoliative ichthyosis with linkage to chromosome 12q13. Br J Dermatol 2003;149:174-80.
30. Mizrachi-Koren M, Geiger D, Indelman M, Bitterman-Deutsch O, Bergman R, Sprecher E. Identification of a novel locus associated with congenital recessive ichthyosis on 12p11.2-q13. J Invest Dermatol 2005;125:456-62.
31. Akiyama M, Sawamura D, Shimizu H. The clinical spectrum of nonbullous congenital ichthyosiform erythroderma and lamellar ichthyosis. Clin Exp Dermatol 2003;28:235-40.
32. Arita K, Jacyk WK, Wessagowit V, van Rensburg EJ, Chaplin T, Mein CA, et al. The South African "bathing suit ichthyosis" is a form of lamellar ichthyosis caused by a homozygous missense mutation, p.R315L, in transglutaminase 1. J Invest Dermatol 2007;127:490-3.

33. Dahlqvist J, Klar J, Hausser I, Anton-Lamprecht I, Pigg MH, Gedde-Dahl T Jr, et al. Congenital ichthyosis: mutations in ichthyin are associated with specific structural abnormalities in the granular layer of epidermis. J Med Genet 2007;44: 615-20.
34. Eckl KM, Krieg P, Kuster W, Traupe H, Andre F, Wittstruck N, et al. Mutation spectrum and functional analysis of epidermis-type lipoxygenases in patients with autosomal recessive congenital ichthyosis. Hum Mutat 2005;26:351-61.
35. Farasat S, Wei MH, Herman M, Liewehr DJ, Steinberg SM, Bale SJ, et al. Novel transglutaminase-1 mutations and genotype-phenotype investigations of 104 patients with autosomal recessive congenital ichthyosis in the USA. J Med Genet 2009; 46:103-11.
36. Frenk E. A spontaneously healing collodion baby: a light and electron microscopical study. Acta Derm Venereol 1981;61: 168-71.
37. Harting M, Brunetti-Pierri N, Chan CS, Kirby J, Dishop MK, Richard G, et al. Self-healing collodion membrane and mild nonbullous congenital ichthyosiform erythroderma due to 2 novel mutations in the ALOX12B gene. Arch Dermatol 2008; 144:351-6.
38. Hennies HC, Kuster W, Wiebe V, Krebsova A, Reis A. Genotype/phenotype correlation in autosomal recessive lamellar ichthyosis. Am J Hum Genet 1998;62:1052-61.
39. Herman ML, Farasat S, Steinbach PJ, Wei MH, Toure O, Fleckman P, et al. Transglutaminase-1 gene mutations in autosomal recessive congenital ichthyosis: summary of mutations (including 23 novel) and modeling of TGase-1. Hum Mutat 2009;30:537-47.
40. Lefevre C, Jobard F, Caux F, Bouadjar B, Karaduman A, Heilig R, 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 2001;69:1002-12.
41. Mazereeuw-Hautier J, Aufenvenne K, Deraison C, Ahvazi B, Oji V, Traupe H, et al. Acral self-healing collodion baby: report of a new clinical phenotype caused by a novel TGM1 mutation. Br J Dermatol 2009;161:456-63.
42. Oji V, Hautier JM, Ahvazi B, Hausser I, Aufenvenne K, Walker T, et al. Bathing suit ichthyosis is caused by transglutaminase-1 deficiency: evidence for a temperature-sensitive phenotype. Hum Mol Genet 2006;15:3083-97.
43. Petit E, Huber M, Rochat A, Bodemer C, Teillac-Hamel D, Muh JP, et al. Three novel point mutations in the keratinocyte transglutaminase (TGK) gene in lamellar ichthyosis: significance for mutant transcript level, TGK immunodetection and activity. Eur J Hum Genet 1997;5:218-28.
44. Raghunath M, Hennies HC, Ahvazi B, Vogel M, Reis A, Steinert PM, et al. Self-healing collodion baby: a dynamic phenotype explained by a particular transglutaminase-1 mutation. J Invest Dermatol 2003;120:224-8.
45. Vahlquist A, Ganemo A, Pigg M, Virtanen M, Westermark P. The clinical spectrum of congenital ichthyosis in Sweden: a review of 127 cases. Acta Derm Venereol Suppl (Stockh) 2003;83(3):34-47.
46. Vahlquist A, Ganemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. Acta Derm Venereol 2008;88:4-14.
47. Jacyk WK. Bathing-suit ichthyosis: a peculiar phenotype of lamellar ichthyosis in South African blacks. Eur J Dermatol 2005;15:433-6.
48. Aufenvenne K, Oji V, Walker T, Becker-Pauly C, Hennies HC, Stocker W, et al. Transglutaminase-1 and bathing suit ichthyosis: molecular analysis of gene/environment interactions. J Invest Dermatol 2009;129:2068-71.
49. Reed WB, Herwick RP, Harville D, Porter PS, Conant M. Lamellar ichthyosis of the newborn: a distinct clinical entity; its comparison to the other ichthyosiform erythrodermas. Arch Dermatol 1972;105:394-9.
50. Anton-Lamprecht I. Prenatal diagnosis of genetic disorders of the skin by means of electron microscopy. Hum Genet 1981; 59:392-405.
51. Anton-Lamprecht I. Genetically induced abnormalities of epidermal differentiation and ultrastructure in ichthyoses and epidermolyses: pathogenesis, heterogeneity, fetal manifestation, and prenatal diagnosis. J Invest Dermatol 1983;81:149-56s.
52. Frost P, Weinstein GD, Van Scott EJ. The ichthyosiform dermatoses, II: autoradiographic studies of epidermal proliferation. J Invest Dermatol 1966;47:561-7.
53. Ishida-Yamamoto A, McGrath JA, Judge MR, Leigh IM, Lane EB, Eady RA. Selective involvement of keratins K1 and K10 in the cytoskeletal abnormality of epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma). J Invest Dermatol 1992;99:19-26.
54. Ishida-Yamamoto A, Takahashi H, Iizuka H. Immunoelectron microscopy links molecules and morphology in the studies of keratinization. Eur J Dermatol 2000;10:429-35.
55. Lapière S. Epidermolyse ichthyosiforme congénitale (erythrodermie ichthyosiforme congénital forme bulleuse de Brocq). Ann Dermatol Syph 1932;3:401-15.
56. Grimberg G, Hausser I, Muller FB, Wodecki K, Schaffrath C, Krieg T, et al. Novel and recurrent mutations in the 1B domain of keratin 1 in palmoplantar keratoderma with tonotubules. Br J Dermatol 2009;160:446-9.
57. Ishida-Yamamoto A, Richard G, Takahashi H, Iizuka H. In vivo studies of mutant keratin 1 in ichthyosis hystrix Curth-Macklin. J Invest Dermatol 2003;120:498-500.
58. Ollendorff-Curth H, Allen FH Jr, Schnyder UW, Anton-Lamprecht I. Follow-up of a family group suffering from ichthyosis hystrix type Curth-Macklin. Humangenetik 1972;17:37-48.
59. Sprecher E, Ishida-Yamamoto A, Becker OM, Marekov L, Miller CJ, Steinert PM, et al. Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. J Invest Dermatol 2001;116:511-9.
60. Schmuth M, Yosipovitch G, Williams ML, Weber F, Hintner H, Ortiz-Urda S, et al. Pathogenesis of the permeability barrier abnormality in epidermolytic hyperkeratosis. J Invest Dermatol 2001;117:837-47.
61. Traupe H, Kolde G, Hamm H, Happle R. Ichthyosis bullosa of Siemens: a unique type of epidermolytic hyperkeratosis. J Am Acad Dermatol 1986;14:1000-5.
62. DiGiovanna JJ, Bale SJ. Clinical heterogeneity in epidermolytic hyperkeratosis. Arch Dermatol 1994;130:1026-35.
63. Arin MJ. The molecular basis of human keratin disorders. Hum Genet 2009;125:355-73.
64. Bale SJ, DiGiovanna JJ. Genetic approaches to understanding the keratinopathies. Adv Dermatol 1997;12:99-113.
65. DiGiovanna JJ, Bale SJ. Epidermolytic hyperkeratosis: applied molecular genetics. J Invest Dermatol 1994;102:390-4.
66. Morais P, Mota A, Baudrier T, Lopes JM, Cerqueira R, Tavares P, et al. Epidermolytic hyperkeratosis with palmoplantar keratoderma in a patient with KRT10 mutation. Eur J Dermatol 2009;19:333-6.
67. Muller FB, Huber M, Kinaciyan T, Hausser I, Schaffrath C, Krieg T, et al. A human keratin 10 knockout causes recessive epidermolytic hyperkeratosis. Hum Mol Genet 2006;15:1133-41.
68. Curth H, Macklin MT. The genetic basis of various types of ichthyosis in a family group. Am J Hum Genet 1954;6:371-82.
69. Jan AY, Amin S, Ratajczak P, Richard G, Sybert VP. Genetic heterogeneity of KID syndrome: identification of a Cx30 gene

(GJB6) mutation in a patient with KID syndrome and congenital atrichia. J Invest Dermatol 2004;122:1108-13.
70. Joh GY, Traupe H, Metze D, Nashan D, Huber M, Hohl D, et al. A novel dinucleotide mutation in keratin 10 in the annular epidermolytic ichthyosis variant of bullous congenital ichthyosiform erythroderma. J Invest Dermatol 1997;108:357-61.
71. Sybert VP, Francis JS, Corden LD, Smith LT, Weaver M, Stephens K, et al. Cyclic ichthyosis with epidermolytic hyperkeratosis: a phenotype conferred by mutations in the 2B domain of keratin K1. Am J Hum Genet 1999;64:732-8.
72. Nazzaro V, Ermacora E, Santucci B, Caputo R. Epidermolytic hyperkeratosis: generalized form in children from parents with systematized linear form. Br J Dermatol 1990;122: 417-22.
73. Paller AS, Syder AJ, Chan YM, Yu QC, Hutton E, Tadini G, et al. Genetic and clinical mosaicism in a type of epidermal nevus. N Engl J Med 1994;331:1408-15.
74. Tsubota A, Akiyama M, Sakai K, Goto M, Nomura Y, Ando S, et al. Keratin 1 gene mutation detected in epidermal nevus with epidermolytic hyperkeratosis. J Invest Dermatol 2007; 127:1371-4.
75. De Laurenzi V, Rogers GR, Hamrock DJ, Marekov LN, Steinert PM, Compton JG, et al. Sjögren-Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. Nat Genet 1996;12:52-7.
76. Sjögren T, Larsson T. Oligophrenia in combination with congenital ichthyosis and spastic disorders: a clinical and genetic study. Acta Psychiatr Neurol Scand 1957;32:1-112s.
77. Refsum S, Salomonsen L, Skatvedt M. Heredopathia atactica polyneuritiformis in children. J Pediatr 1949;35:335-43.
78. Reed WB, Stone VM, Boder E, Ziprkowski L. Hereditary syndromes with auditory and dermatological manifestations. Arch Dermatol 1967;95:456-61.
79. Chanarin I, Patel A, Slavin G, Wills EJ, Andrews TM, Stewart G. Neutral-lipid storage disease: a new disorder of lipid metabolism. Br Med J 1975;1:553-5.
80. Dorfman ML, Hershko C, Eisenberg S, Sagher F. Ichthyosiform dermatosis with systemic lipidosis. Arch Dermatol 1974;110: 261-6.
81. MacLeod JMH. Three cases of 'ichthyosis follicularis' associated with baldness. Br J Dermatol 1909;21:165-89.
82. Hamm H, Meinecke P, Traupe H. Further delineation of the ichthyosis follicularis, atrichia, and photophobia syndrome. Eur J Pediatr 1991;150:627-9.
83. Happle R. X-linked dominant chondrodysplasia punctata: review of literature and report of a case. Hum Genet 1979; 53:65-73.
84. Braverman N, Lin P, Moebius FF, Obie C, Moser A, Glossmann H, et al. Mutations in the gene encoding 3 beta-hydroxysteroid-delta 8, delta 7-isomerase cause X-linked dominant Conradi-Hünermann syndrome. Nat Genet 1999;22:291-4.
85. Castano SE, Segurado RA, Guerra TA, Simon de las HR, Lopez-Rios F. Coll Rosell MJ. Ichthyosis: the skin manifestation of multiple sulfatase deficiency. Pediatr Dermatol 1997;14: 369-72.
86. Dierks T, Schmidt B, Borissenko LV, Peng J, Preusser A, Mariappan M, et al. Multiple sulfatase deficiency is caused by mutations in the gene encoding the human C(alpha)-formylglycine generating enzyme. Cell 2003;113:435-44.
87. Happle R, Kuster W. Ichthyosis variegata: a new name for a neglected disease. J Am Acad Dermatol 1997;36:500.
88. Brusasco A, Tadini G, Cambiaghi S, Ermacora E, Grimalt R, Caputo R. A case of congenital reticular ichthyosiform erythroderma—ichthyosis 'en confettis'. Dermatology 1994; 188:40-5.
89. Bygum A, Westermark P, Brandrup F. Ichthyosis prematurity syndrome: a well-defined congenital ichthyosis subtype. J Am Acad Dermatol 2008;59(Suppl):S71-4.
90. Klar J, Schweiger M, Zimmerman R, Zechner R, Li H, Torma H, et al. Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. Am J Hum Genet 2009;85:248-53.
91. Phadnis SV, Griffin DR, Eady RA, Rodeck CH, Chitty LS. Prenatal diagnosis and management strategies in a family with a rare type of congenital ichthyosis. Ultrasound Obstet Gynecol 2007;30:908-10.
92. Faghri S, Tamura D, Kraemer KH, DiGiovanna JJ. Trichothiodystrophy: a systematic review of 112 published cases characterizes a wide spectrum of clinical manifestations. J Med Genet 2008;45:609-21.
93. Kraemer KH, Patronas NJ, Schiffmann R, Brooks BP, Tamura D, DiGiovanna JJ. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. Neuroscience 2007;145: 1388-96.
94. Morice-Picard F, Cario-André M, Rezvani H, Sarasin A, Lacombe D, Taieb A. New clinico-genetic classification of trichothiodystrophy. Am J Med Genet 2009;149A:2020-30.
95. Camisa C, Hessel A, Rossana C, Parks A. Autosomal dominant keratoderma, ichthyosiform dermatosis and elevated serum beta-glucuronidase. Dermatologica 1988;177:341-7.
96. Korge BP, Ishida-Yamamoto A, Punter C, Dopping-Hepenstal PJ, Iizuka H, Stephenson A, et al. Loricrin mutation in Vohwinkel's keratoderma is unique to the variant with ichthyosis. J Invest Dermatol 1997;109:604-10.
97. Maestrini E, Monaco AP, McGrath JA, Ishida-Yamamoto A, Camisa C, Hovnanian A, et al. A molecular defect in loricrin, the major component of the cornified cell envelope, underlies Vohwinkel's syndrome. Nat Genet 1996;13:70-7.
98. Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M, Rapaport D, Goldsher D, Indelman M, 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 2005;77:242-51.
99. Gissen P, Johnson CA, Morgan NV, Stapelbroek JM, Forshew T, Cooper WN, et al. Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogryposis—renal dysfunction—cholestasis (ARC) syndrome. Nat Genet 2004;36:400-4.
100. Lutz-Richner AR, Landolt RF. Familial bile duct malformation with tubular renal insufficiency (Familiare Gallengansmissbildungen mit tubularer Neireninsuffizienz). Helv Paediatr Acta 1973;28:1-12.
101. Jang JY, Kim KM, Kim GH, Yu E, Lee JJ, Park YS, et al. Clinical characteristics and VPS33B mutations in patients with ARC syndrome. J Pediatr Gastroenterol Nutr 2009;48:348-54.
102. Montpetit A, Cote S, Burstein E, Drouin C, Lapointe L, Boudreau M, et al. Disruption of AP1S1, causing a novel neurocutaneous syndrome, perturbs development of the skin and spinal cord. Proc Natl Acad Sci U S A 2009;4:1-9.
103. Feldmeyer L, Huber M, Fellmann F, Beckmann JS, Frenk E, Hohl D. Confirmation of the origin of NISCH syndrome. Hum Mutat 2006;27:408-10.
104. Hadj-Rabia S, Baala L, Vabres P, Hamel-Teillac D, Jacquemin E, Fabre M, et al. Claudin-1 gene mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. Gastroenterology 2004;127:1386-90.
105. Baala L, Hadj-Rabia S, Hamel-Teillac D, Hadchouel M, Prost C, Leal SM, et al. Homozygosity mapping of a locus for a novel