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

Continued

Table XII. Cont'd

	KID syndrome*	Neutral lipid storage disease with ichthyosis	IPS†
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 mechanical stability of epidermis; affecting LB secretion resulting in paucity of SC lamellar material and CDSN retention	KRT1/10	EI
KIF disorder		KRT1	ICM
		KRT2	SEI
Cornified lipid/cell envelope	Weak CE with reduced lamellar membrane and NLPS	TGM1	LI, CIE, SHCB, BSI
TGase-1 deficiency Loricrin disorder	Possible cytotoxic effect through gain of function of mutant loricrin molecules	LOR	LK
Protease/protease inhibitors	Increased serine protease activity with premature loss of CDSN and induction of inflammation	SPINK5	NS
LEKTI deficiency	Defective filaggrin processing	ST14	IHS
Matriptase deficiency	Impaired innate immune response and desquamation	CTSC	Papillon-Lefèvre syndrome
Cathepsin C deficiency			
Keratohyaline	Decreased corneocyte hydration as result of low NMF; high SC pH resulting in increased protease activity	FLG	IV
Filaggrin deficiency			
2.) Disorders of lipid metabolism, assembly, and/or transport ("mortar")			
Lipid synthesis/modification	Defect of different enzymes (or receptors) within lipoxygenase pathway, impaired processing of profilaggrin to monomeric filaggrin (abnormal SC lipid composition likely)	ALOX12B ALOXE3 CYP4F22 NIPAL4	LI; CIE
Hepoxilin pathway defect	Abnormal SC lipid composition with lamellar/NLPS; inhibition of proteases causes persistence of CDSN	STS	RXLI
Steroid sulfatase deficiency			
Fatty acid transporter defect	Impaired transport and activation of fatty acids (critical fetal/neonatal period), defective SC lipid homeostasis	SLC27A4	IPS
Lipid transport and secretion	Disturbed transport of lipids and proteases, protease inhibitors, and antimicrobial peptides; paucity of SC lamellar structures	ABCA12 (nonsense vs missense)	HI; LI/CIE
Primary LB defect			
Cholesterol biosynthesis and homeostasis disorders	Defective "Kandutsch" pathway	EBP	CDPX2
8-7 sterol isomerase	Interference with sonic hedgehog	NSDHL	CHILD syndrome
C3 sterol dehydrogenase	Impaired transcription factors (SREBF1 and 2) affect sterol/ER homeostasis and cell differentiation	MBTPS2	IFAP syndrome
Zinc endopeptidase/site-2-protease defect			
Triglyceride metabolism	Abnormal SC lipid composition with lamellar/NLPS	ABHD5	Neutral lipid storage disease with ichthyosis
Neutral lipid storage disease			
Lysosomal storage	Disturbance of SC lipid composition of ceramides, cholesterol, and free fatty acids	GBA	Gaucher syndrome type 2
Glucocerebrosidase deficiency			
Peroxisomal hydroxylation	Phytanic acid excess disturbs cholesterol/cholesterol sulfate, or alters lipid degradation	PHYH PEX7	Refsum syndrome
Phytanoyl-CoA hydroxylase deficiency			

Table XIII. Cont'd

Primary defect	Pathophysiologic aspects of epidermis	Affected gene(s)	Diseases
Microsomal oxidation Fatty aldehyde dehydrogenase deficiency	SC lamellar phase separation or NLPS	ALDH3A2	SLS
Intracellular membrane trafficking Secretory (SNARE) pathway defects	Impaired LB function	AP1S1 SNAP29 VPS33B	MEDNIK syndrome CEDNIK syndrome ARC syndrome
3.) Disorders of cell-cell junctions			
Gap junctions Connexin disorders	(?) Increased sensitivity to apoptosis, reactive hyperproliferation, impaired calcium regulation	GJB2 (GJB6) GJB3/GJB4	KID syndrome EKV
Tight junctions Claudin disorders	(?) Impaired regulation of paracellular permeability, defective epithelial polarization	CLDN1	IHSC syndrome
4.) Disorders of DNA transcription/repair			
Nucleus Nucleotide excision repair defect	?	C7Orf11 ERCC2/XPD ERCC3/XPB	TTDs/ TFIIH related
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,* congenital 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.
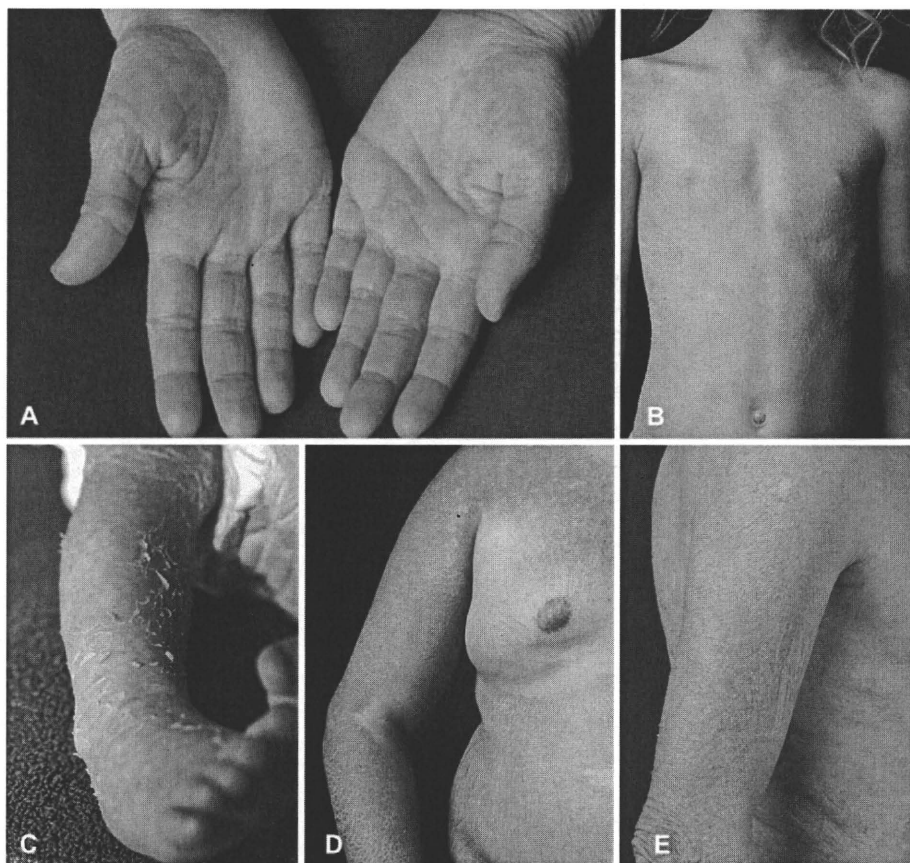
Fig 1. Clinical examples of common ichthyosis: accentuated palmoplantar markings of ichthyosis vulgaris (IV) in white skin (**A**); IV with atopic eczema (**B**); exaggerated scaling after 3 weeks of life as early presentation of recessive X-linked ichthyosis (RXLI) (**C**); RXLI with brownish scales 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
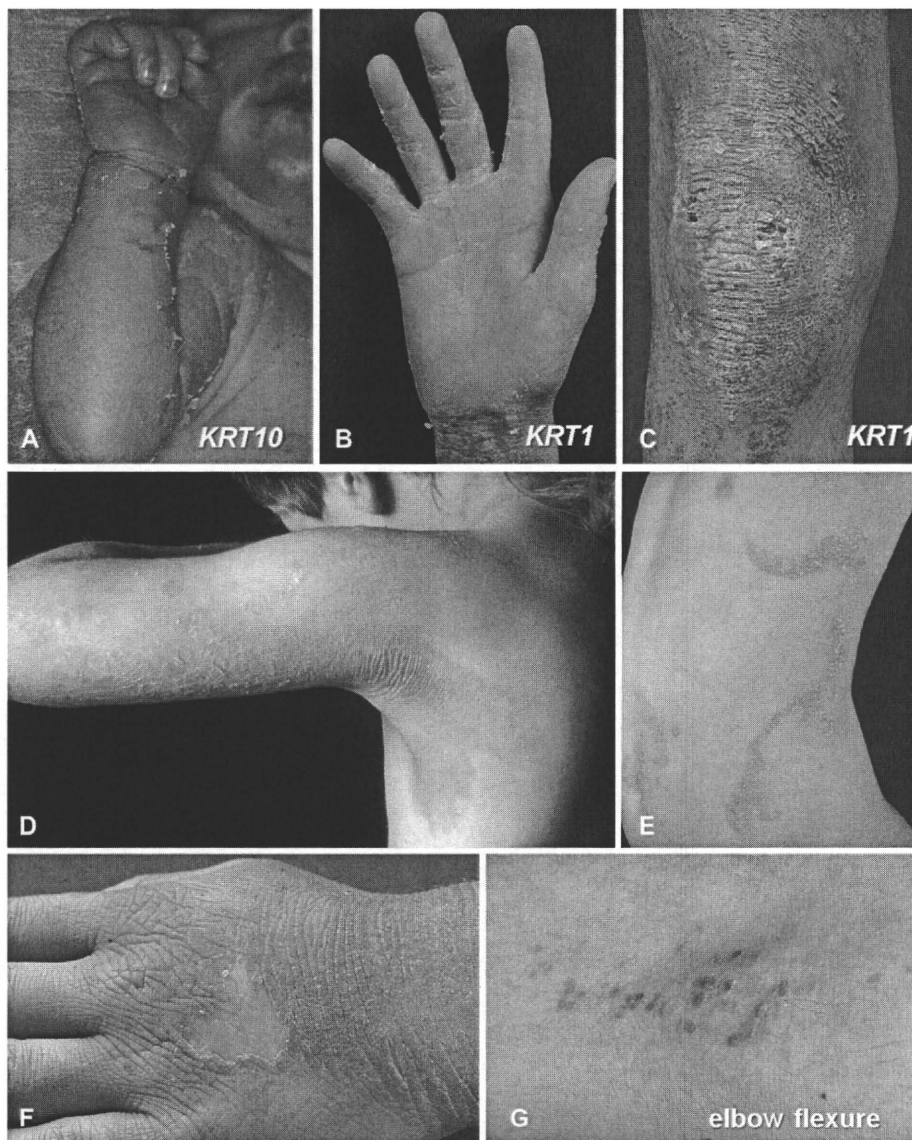
Fig 3. Clinical examples of keratinopathic ichthyosis: superficial blister formation and erythema at birth in epidermolytic ichthyosis (EI) caused by *KRT10* mutation (note that palm is spared) (**A**); palmoplantar keratoderma in EI caused by *KRT1* mutation (**B**); in infancy EI often shows hyperkeratoses 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
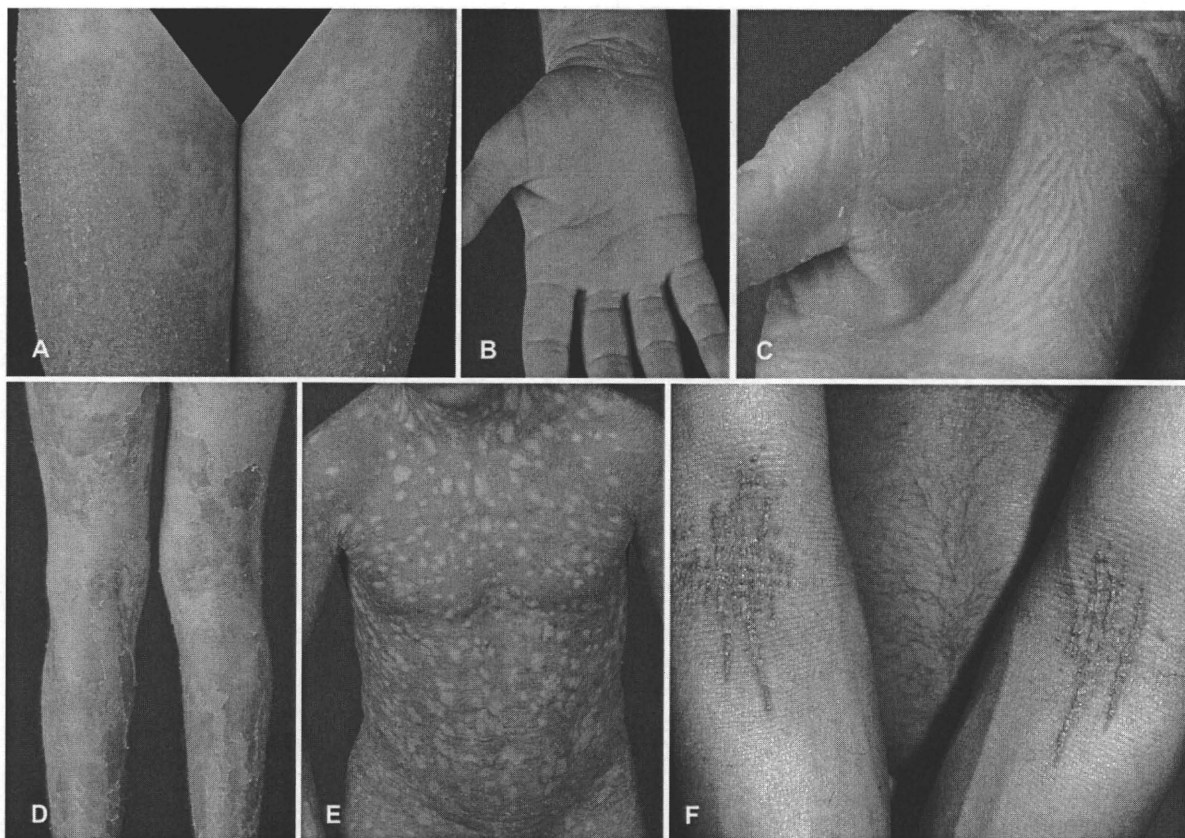
Fig 4. Clinical examples of other nonsyndromic forms of ichthyosis: erythrokeratodermia variabilis (EKV) that evolved like progressive symmetric erythrokeratodermia (**A**); palmoplantar keratoderma in EKV (**B**); palmar honeycomb pattern of loricrin keratoderma (**C**); peeling skin disease (**D**); 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.
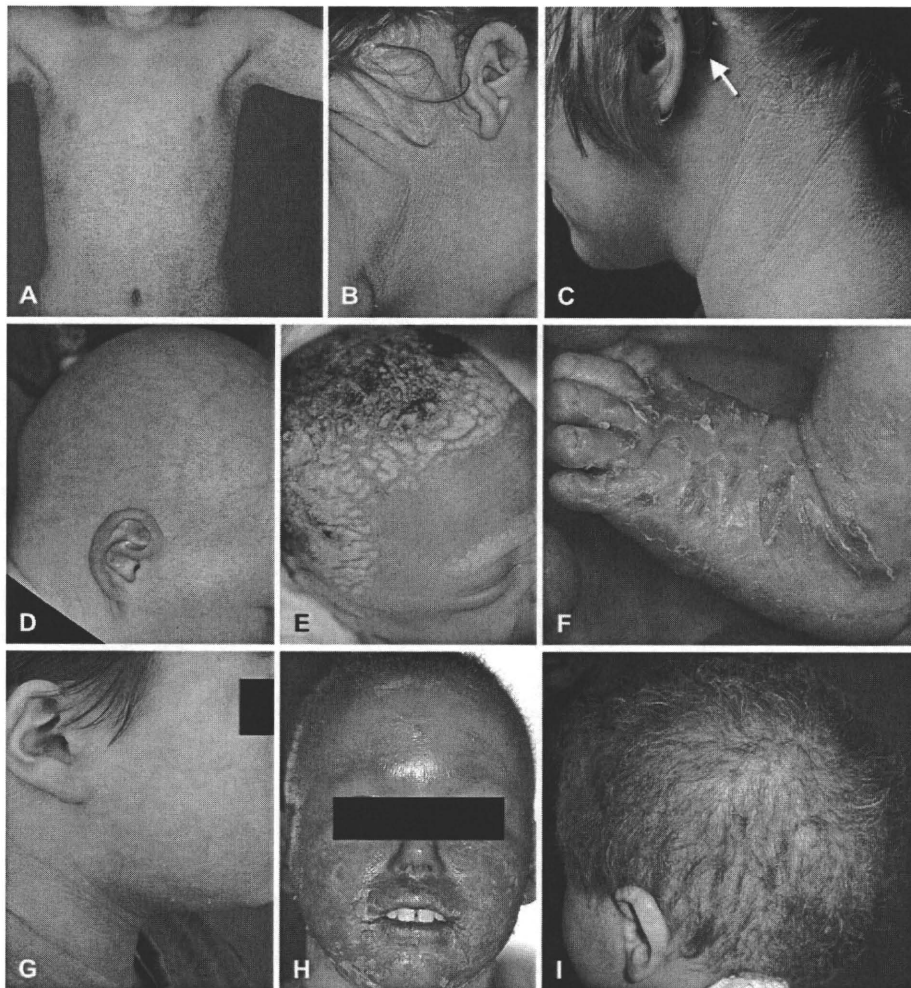
Fig 5. Clinical examples of syndromic forms of ichthyosis: trichothiodystrophy (**A**); Sjögren-Larsson syndrome (**B**); KID syndrome (**C**); ichthyosis follicularis—atrichia—photophobia syndrome (**D**); ichthyosis prematurity syndrome (**E**); Conradi-Hünermann-Happle syndrome (**F**); neutral lipid 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
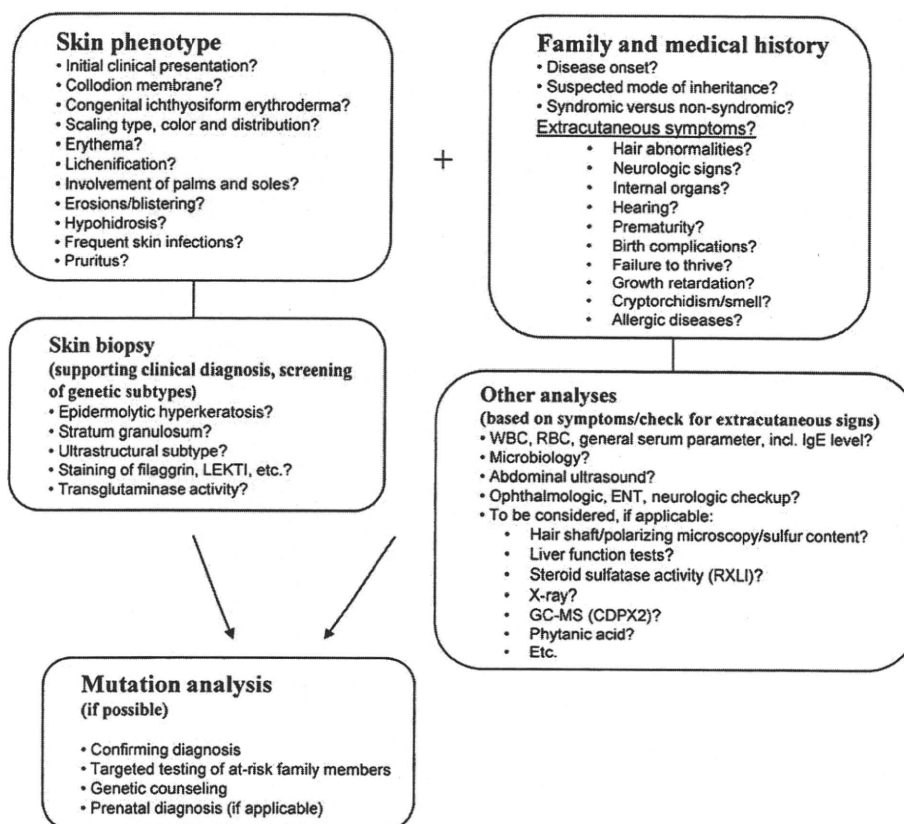
Fig 6. Concept for diagnostic approach. Diagnosis is based on dermatologic evaluation, careful family and medical history, and can be strongly supported by directed morphologic examinations and other special analyses. If available, molecular analyses are suggested to confirm diagnosis, allow for testing 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 ortho-hyperkeratosis. 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).

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coexistent proliferative epidermal lesions, such as condyloma acuminatum, Bowen's disease, and squamous cell carcinoma, but not in adjacent EMPD areas [3,9,10]. Therefore, HPV infection in these cases is more likely coincidental than causal in the pathogenesis of EMPD, although the precise relationship still needs to be elucidated.

Our findings provide further evidence that HPV infection is unlikely to contribute to the carcinogenesis of EMPD. However, further investigation is required to determine whether or not there is an association between EMPD and other types of HPV that were not detected by the methods used in this study.

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30 March 2010

Letter to the Editor

Chromosome 11q13.5 variant: No association with atopic eczema in the Japanese population

Dear Sir,

A single nucleotide polymorphism (SNP) on chromosome 11q13.5 [rs7927894] has been attracting great attention since Esparza-Gordillo et al. [1] reported highly significant association of a common variant of rs7927894 with atopic eczema (AE) in the German population. In the report, approximately 13% of individuals are homozygous for the SNP and their risk of developing AE is 1.47 times that of noncarriers. Very recently, O'Regan et al. [2] further published interesting results on the association between rs7927894 and AE in a collection of Irish children with moderate-to-severe AE and Irish controls. The association between rs7927894 and AE was replicated in the Irish population (p = 0.0025, Chi-square test; odds ratio (OR) = 1.27, 95% confidence interval (CI) 1.09–1.49). Additional analyses performed to test the statistical significance of the rs7927894 SNP having controlled for the presence/absence of the strongly significant *FLG* null genotype indicated that rs7927894 still shows a statistically significant effect (p = 0.0025) with an OR of 1.22 (95% CI 1.02–1.26) [2]. Tests for interaction between each of the *FLG* and rs7927894 risk alleles showed no evidence of statistically significant epistatic effects [2]. The rs7927894 association was independent of the well-established *FLG* risk alleles and may be multiplicative in its effects.

In order to clarify whether this common variant is associated with AE also in the Japanese population or not, we evaluated the association between rs7927894 and AE in an cohort of 194 Japanese AE patients we had collected to date and 113 unrelated Japanese control individuals. All the AE patients had been diagnosed with AE based on widely recognized diagnostic criteria [3] or their parents reported a dermatologist's diagnosis of AE (at least once). Majority of AE patients and control individuals were identical to those in a previous study [4]. Using genomic DNA, AE patients and control individuals were screened for the variant allele of rs7927894 on chromosome 11q13, by direct DNA sequencing. In addition, the AE patients and the control individuals were screened for eight *FLG* mutations previously identified in the Japanese population, by restriction enzyme digestion, fluorescent PCR and/or direct DNA sequencing as described previously [4,5].

Case–control association analyses were performed for the variant using Fisher's exact test. In addition, we performed case–control statistical analysis for the common variant allele of rs7927894 after stratification for *FLG* mutations. The rs7927894 on chromosome 11q13 genotype data in the Japanese AE case series and ethnically matched population control series are summarized in Table 1. All alleles were observed to be in normal Hardy–Weinberg equilibrium.

Here we demonstrate that 22.7% and 1.5% of the patients in our Japanese AE case series are heterozygous and homozygous for rs7927894[T], respectively (combined rs7927894[T] allele frequency = 0.129, n = 388) (Table 1). rs7927894[T] is also carried by 23.0% of the Japanese control individuals (combined minor allele frequency = 0.115, n = 226). There is no statistically significant association between the rs7927894[T] and AE.

After stratification for *FLG* mutations previously identified in the Japanese population, 26.0% and 4.0% of our Japanese AE case series with *FLG* mutations are heterozygous and homozygous for rs7927894[T] (combined rs7927894[T] allele frequency = 0.17, n = 100). 21.5% and 0.7% of the Japanese AE patients without *FLG* mutations are heterozygous and homozygous for rs7927894[T] (combined rs7927894[T] allele frequency = 0.11, n = 288). There is no statistically significant association between the rs7927894[T] and AE without *FLG* mutations or rs7927894[T] and AE with *FLG* mutations (Fisher's exact test p = 0.338). Furthermore, interaction