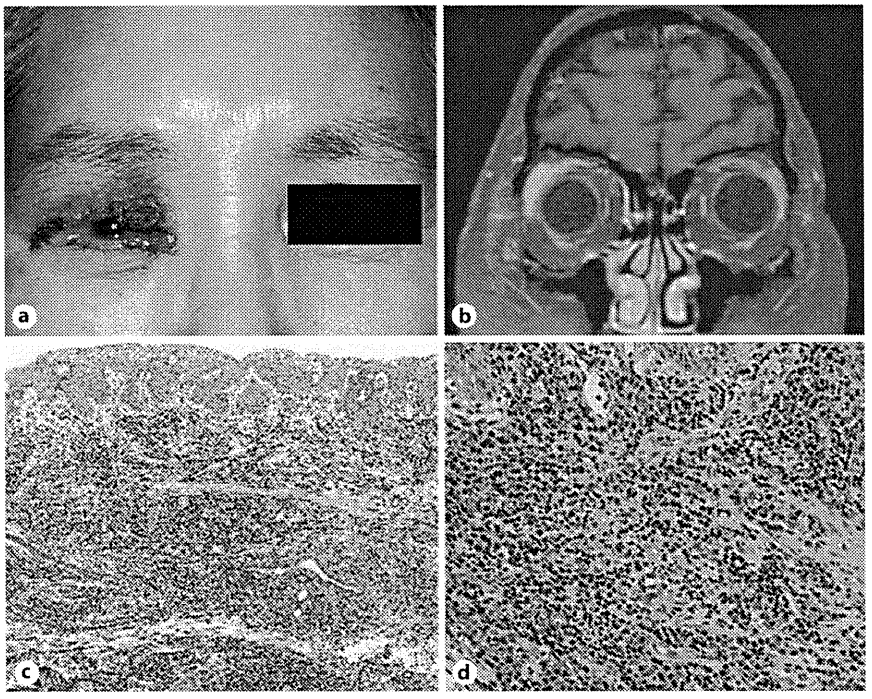

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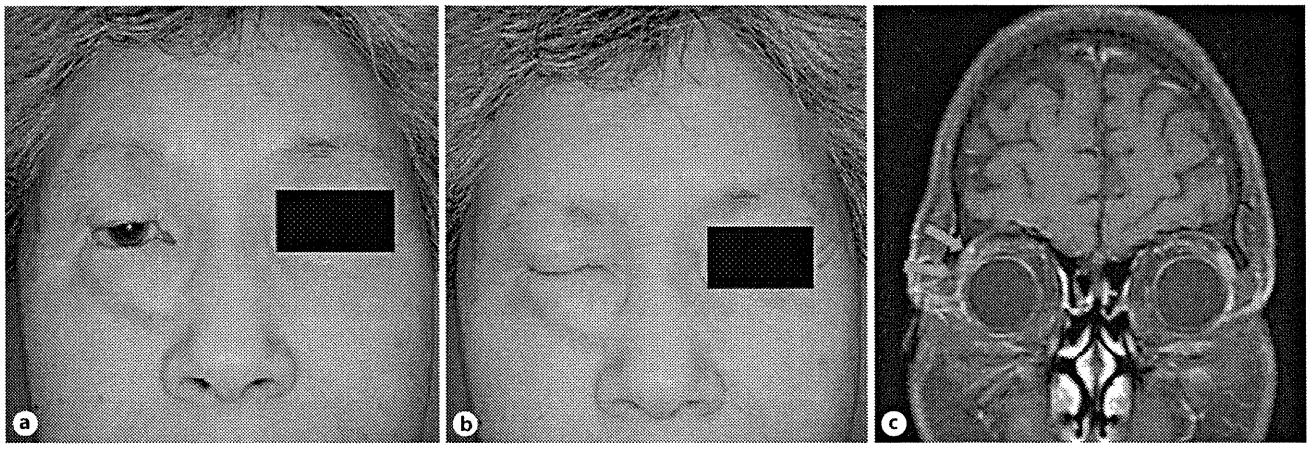
Fig. 3. Clinical, histopathological and MRI features of case 2. **a** An ulcer with surrounding erythema on the right upper eyelid. **b** Orbital MRI showing area of hyperintensity on T_1-weighted image in the right lachrymal gland and upper eyelid. **c**, **d** Skin biopsy specimens showing dermal abscesses with dense aggregates of plasma cells. HE. Original magnifications: ×20 (**c**), ×60 (**d**).

Fig. 4. Clinical and MRI features of case 2 two years after the eyelid repair operation. She was able to open (**a**) and close her eyes (**b**). **c** Orbital fat-saturated T_1-weighted image after immunosuppressive therapy revealing the area of hyperintensity had diminished (red arrows).



4

ical disorders or rheumatoid arthritis. Orbital MRI showed homogeneous hyperintensity areas on fat-saturated T_2-weighted image, and hypointensity areas on T_1-weighted image in the right lachrymal gland and upper eyelid (fig. 1e, f), suggesting an acute inflammation of the extracutaneous areas. An initial combined therapy with prednisolone (1 mg/kg/day) and cyclosporin A (5 mg/kg/day) improved the skin lesions as well as intraorbital involvement (fig. 2a, b). PG disease activity was controlled and the eroding ulcer on the upper portion of the right eyelid and cheek healed with scarring. However, the destruction of the right eyelid led to poor eye closure and continuous corneal exposure to air. Two months after the remission of the cutaneous lesions of PG, perforation of the right cornea occurred and the right eye had to be enucleated. Treatment with prednisolone and cyclosporin A was continued and no recurrence was observed for 4 months after the enucleation of the eye.

Case 2

A 65-year-old Japanese woman was referred to our department with a 9-month history of a facial ulcer. A painful erythema and ulcer appeared on her right upper eyelid without any preceding episodes. At first, the patient visited an ophthalmology clinic. The lesion was initially diagnosed as

Table 1. Summary of the clinical information on reported cases with PG of the eyelid

Patient No.	Age, years	Sex	Distribution of PG	Initial diagnosis	Initial treatment	Duration from onset to diagnosis	Treatment	Outcome and prognosis	Complications	Ref.
1	64	male	left temple, scleral conjunctivitis, anterior uveitis, corneal opacity	N/A	antibiotics	N/A	PSL, azathioprine	recurrence	arthritis	Happle et al. [2]
2	62	male	left upper eyelid	N/A	N/A	14 days	chlorhexidine gluconate	recurrence	none	Browning et al. [3]
3	63	male	left eye	N/A	N/A	25 years	clofazimine	recurrence	N/A	Mensing [4]
4	67	female	right lower eyelid	N/A	antibiotics	60 days	PSL	recurrence, corneal perforation, evisceration of the eye	diabetic	Newman and Frank [5]
5	80	female	bilateral eyelids	N/A	antibiotics	N/A	PSL	no recurrence	ulcerative colitis	Tirpitz et al. [6]
6	47	female	right lower eyelid, left eyelid	N/A	N/A	8 days	mPSL (500 mg) 3 days, PSL	no recurrence	rhinosinusitis	Sidwell et al. [7]
7	28	female	left upper eyelid, right eye, left orbit, liver, spleen	nodular scleritis, orbital inflammation	N/A	3 years	PSL, cyclosporin	defective ocular motility	arthritis	Miserocchi et al. [8]
8	61	female	right upper eyelid, right necrotising scleritis	chalazia	antibiotics	30 days	PSL, cyclophosphamide	no recurrence	none	Rose et al. [9]
9	56	male	left upper eyelid, ischemic sclerokeratitis, corneal perforation	bacterial infection	antibiotics	14 days	immunosuppressive therapy	eyelid construction, keratoplasty	rheumatoid arthritis	Rose et al. [9]
10	75	female	left upper eyelid	N/A	N/A	a few weeks	PSL	eyelid construction	interstitial pneumonia	Rose et al. [9]
11	67	N/A	lower eyelid, lateral canthus, lateral orbit	N/A	antibiotics	N/A	PSL, clofazimine	corneal perforation, subtotal orbital exenteration	none	Rose et al. [9]
12	82	male	left lower eyelid, left cheek	chronic wound	antibiotics, surgical operation	2.5 years	PSL, cyclosporin	recurrence (after operation)	none	Lindberg-Larsen and Fogh [10]
13	19	female	right lower eyelid	N/A	N/A	N/A	PSL, dapsone	eyelid construction	none	Procianoy et al. [11]
14	75	male	right upper eyelid, lachrymal gland	adnexal tumour	surgical operation	1.8 years	PSL, cyclosporin	corneal perforation, subtotal orbital exenteration	none	present case 1
15	65	female	right upper eyelid, lachrymal gland	chalazia	antibiotics	180 days	PSL	eyelid construction	none	present case 2

N/A = Not available; PSL = prednisolone.

a chalazion although neither several incisions nor antibiotics improved it. The initial skin biopsy was performed at the ophthalmology clinic, and the lesion was diagnosed as PG from the histopathological findings. Systemic prednisolone (initial dose: 1 mg/kg/day) improved the lesion; however, the skin lesion recurred when the prednisolone dose was reduced to 0.2 mg/kg/day. The patient was referred to our department for further consultation.

At the initial examination, an ulcer with surrounding erythema was observed (fig. 3a). Skin biopsy specimens showed a dermal abscess containing dense aggregates of plasma cells (fig. 3c, d). Light microscopic observations did not show giant cells, ballooning degeneration or reticular degeneration. Gram, PAS, Grocott and Ziehl-Neelsen stains, and culture of skin tissue failed to identify infectious diseases due to bacteria, mycobacteria, atypical mycobacteria and fungi. Using a laboratory examination and endoscopy, no systemic complications were detected. Anti-proteinase 3, anti-myeloperoxidase antibodies or atypical anti-neutrophil cytoplasmic antibodies were not detected. Orbital MRI showed hypointensity areas on T_2-weighted image and hyperintensity areas on T_1-weighted image, suggesting fibrosis in the right lachrymal gland and eyelid (fig. 3b). From the clinical features and histopathological findings, the lesion was also diagnosed as PG in our department. We started high-dose systemic prednisolone (1.2 mg/kg/day), and it improved not only the lesion of the eyelid but also the intraorbital involvement (fig. 4c). The systemic prednisolone was then gradually tapered for 15 months. In order to obtain adequate ocular surface protection, an eyelid repair was performed 12 months after the cessation of systemic prednisolone (fig. 4a, b). No recurrence of skin ulcers or ocular involvement was observed without systemic steroid administration for 5 years.

Discussion

Here, we report 2 cases with PG of the eyelid and review well-documented reports from the literature [2–11]. We summarise the clinical information of the 15 PG cases of the eyelid including the present 2 patients in table 1. It seems to be difficult to make an early diagnosis of PG of the eyelid. In fact, 5 cases (33%) out of 15 were initially misdiagnosed as bacterial infections, chalazia or adnexal tumours (table 1). In 7 cases (47%) it took more than 1 month to be diagnosed as PG. Two cases (13%) were treated by surgical operation, resulting in enlargement of the PG lesions. Seven cases (47%) showed extracutaneous PG lesions including the lachrymal gland, orbit, sclera and uvea as well as internal organ involvement [2, 8, 9]. The eyelids are indispensable for protection of the eye, especially the cornea. Destruction of the eyelid often leads to serious visual disability. Eyelid defects due to PG caused corneal perforation in 4 cases (27%) including the present case 1 [5, 9]. In 3 patients (20%), the affected eyes were required to be enucleated [5, 9]. One patient had defective ocular motility due to severe fibrosis involving the orbital cavity [8].

In the present case 1, surgical intervention made the skin lesion worse. A new distinct PG lesion appeared along the postoperative wounds, affecting the right upper eyelid and cheek. Despite the systemic treatment with immunosuppressive agents, the defect in the right upper eyelid remained, leading to a continuous corneal exposure and perforation of the cornea. Eventually, the right eye had to be enucleated. In contrast, the visual function in case 2 was preserved owing to early diagnosis and immunosuppressive therapy.

Although there has been no report which described the usefulness of MRI, our 2 cases suggest that MRI is effective in detecting PG lesions within intraorbital tissues. In case 1, MRI showed marked homogeneous hyperintensity on fat-saturated T_2-weighted image and hypointensity on T_1-weighted image in the right lachrymal gland, indicating acute inflammation. In case 2, MRI revealed marked hypointensity on T_2-weighted image and hyperintensity on T_1-weighted image in the right lachrymal gland, suggesting the presence of fibrosis. MRI also demonstrated improvements after immunosuppressive therapy in both cases. The present 2 cases suggest that MRI is a powerful tool for evaluating the extent of subcutaneous PG lesion involvement.

In conclusion, our cases and the review of the literature indicate that successful management of PG and the preservation of visual acuity depend on early diagnosis and the induction of an adequate immunosuppressive therapy.

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Letter to the Editor

A founder effect of c.1938delC in *ITGB4* underlies junctional epidermolysis bullosa and its application for prenatal testing

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Abstract: Junctional epidermolysis bullosa associated with pyloric atresia (JEB-PA) is one of the most severe inherited skin diseases, characterized by generalized blister formation and occlusion of the pylorus at birth. Most JEB-PA patients have mutations in the gene encoding β4 integrin (*ITGB4*). No recurrent mutations in *ITGB4* have been described as having founder effects. We collected three JEB-PA families with c.1938delC in *ITGB4*. Haplotype analysis using single nucleotide polymorphism markers throughout *ITGB4* suggested one rare haplotype (2.8% of the Han Chinese and ethnic Japanese populations) in all alleles with c.1938delC. The parents of one of the three families sought prenatal diagnosis for a subsequent pregnancy. We succeeded in performing prenatal exclusion of JEB-PA using the foetal genomic DNA. Our study clearly demonstrated that recurrent c.1938delC in *ITGB4* is a founder mutation in JEB-PA patients, and that genotyping of the mutation can be utilized for prenatal diagnosis of JEB-PA.

Key words: basement membrane zone – haplotype analysis – single nucleotide polymorphism

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Background

Recurrent mutations in a population might be explained by founder effects, in which the mutant alleles of a few ancestors spread in the population because of limited gene pool, genetic drift and healthy carrier migration (1).

Epidermolysis bullosa (EB) comprises a group of disorders characterized by congenital skin fragility. EB has been classified into EB simplex, junctional epidermolysis bullosa (JEB), dystrophic EB and Kindler syndrome (2–4). JEB is subclassified into three clinical subtypes: Herlitz JEB, non-Herlitz JEB and JEB with pyloric atresia (JEB-PA). JEB-PA is characterized by generalized blistering and occlusion of the pylorus at birth, which usually leads to early demise (5). Mutations in the gene encoding α6 (*ITGA6*) or the β4 integrin subunit (*ITGB4*) are responsible for JEB-PA (6,7). Most patients with JEB-PA have mutations in *ITGB4* (8). No frequent prevalent mutations have been noted, except in the Hispanic population, where c.1802G>A (p.Cys601Tyr) is present on five of 10 alleles of JEB-PA patients (9).

Here, we have collected three JEB-PA families, in which c.1938delC in *ITGB4* is present. Haplotype analysis revealed c.1938delC as a founder mutation in JEB patients. Based on these data, we successfully performed prenatal exclusion of JEB-PA with this mutation.

Experimental design

Patients

Three unrelated non-consanguineous Japanese families (A, B and C) with JEB-PA in this study are summarized in Fig. S1a. Family A and B originate from Shikoku Island in Japan and family C is from other part of the country. A-1 and B-1 are newly identified JEB-PA patients. They died of disseminated intravascular coagulation 1 and 2 months after birth, respectively. Immunofluorescence study of skin specimens from both of the patients showed the absence of β4 integrin and weak expression of α6 integrin subunits (data not shown). Immunostaining for laminin 332, type IV collagen, type VII collagen, type XVII collagen, plectin and BP230 revealed normal linear labelling patterns (data not shown). C-2 is a patient with non-lethal variant of JEB-PA. The case description and mutational data of C-2 have been reported previously (10).

Mutation detection

Genomic DNA (gDNA) was extracted from blood cells of the probands and their parents. Mutation detection was performed after polymerase chain reaction (PCR) amplification of all exons and intron–exon borders of *ITGB4*, followed by direct sequencing using an ABI Prism 3100 genetic analyzer (Advanced Biotechnologies Inc., Columbia, MD, USA) (11–13). The genomic DNA nucleotides, the complementary DNA nucleotides and the amino

acids of the protein were numbered based on the following sequence information (GenBank accession No. NM_000213).

Haplotype analysis

To determine whether c.1938delC is a founder mutation, we performed haplotype analysis of three JEB-PA families. We constructed linkage disequilibrium (LD) blocks containing *ITGB4* using genotype data from the HapMap database (International HapMap Consortium, 2005). The haplotype structure with its tag-single nucleotide polymorphisms (SNPs) was determined using Haploview (14). We genotyped 15 tag-SNPs (Fig. S1b) using the ABI Prism 3100 genetic analyzer (Advanced Biotechnologies Inc.).

Prenatal diagnosis

We performed prenatal diagnosis of a foetus (A-2) at risk for JEB-PA from family A. A total of 30 ml of amniotic fluid was obtained under ultrasound guidance at 16 weeks' gestation. Foetal DNA was extracted from fresh cells from 10 ml of amniotic fluid. Genomic DNA isolated from amniotic fluid cells was subjected to polymerase chain reaction (PCR) amplification, followed by direct automated sequencing as described. The mutation site was sequenced using both forward and reverse strands and verified by *PmlI* (New England Biolabs Inc., Beverly, MA, USA) enzyme digestion of the PCR products.

The medical ethical committee of Hokkaido University and National Center for Child Health and Development approved all described studies. The study was conducted according to Declaration of Helsinki Principles. Participants gave their written informed consent.

Results

Recurrent c.1938delC in *ITGB4*

ITGB4 mutation analysis revealed that A-1 was homozygous for c.1938delC (Fig. 1c). The father and mother of A-1 were heterozygous for c.1938delC (Fig. 1a, b). B-1 was heterozygous for paternal c.1938delC and maternal c.4050_4057del (data not shown). c.1938delC was previously described in a patient with non-lethal variant of JEB-PA who is compound heterozygous for c.1938delC and c.2168C>G (p.Pro723Arg) (C-2) (10). c.4050_4057del was also reported in a JEB-PA patient who is compound heterozygous for c.4050_4057del and c.3434delT (12).

Founder effects of c.1938delC

The haplotype structure containing *ITGB4* was constructed using genotype data from the HapMap database (Fig. S1b, c). The haplotype block was represented by 16 haplotypes with >2% frequency (Fig. S1b, c). The chromosome containing c.1938delC in A-1 and B-1 had haplotype XI (GGGACGGGCGTCACC), which is seen in 2.8% of the Han Chinese and ethnic Japanese populations. The chromosome containing c.1938delC in C-2 might have had this haplotype although the phase was not determined.

Prenatal exclusion of JEB-PA

Direct sequencing of PCR products from the foetal gDNA (A-2) revealed the presence of c.1938delC in one allele and wild-type sequence in another allele (Fig. 1d). To confirm the results of direct sequencing, we performed restriction enzyme analysis. c.1938delC was found to result in the loss of a restriction enzyme for *PmlI*. The PCR product from the proband (A-1) after *PmlI* digestion revealed a 285-bp band, which indicated that she was homozygous for c.1938delC (Fig. 1f). In contrast, the PCR product from the parents and the foetus (A-2) after *PmlI* digestion showed 285-, 195- and 90-bp bands, which indicated that they were heterozygous for c.1938delC (Fig. 1f). Haplotype analysis of this family using microsatellite markers excluded maternal contamination of foetal cells (data not shown). These results predicted that the foetus would not be affected, and the pregnancy was continued. A neonate was born at full term in good health with completely normal skin.

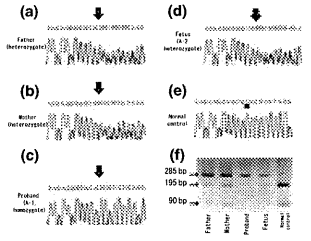

Figure 1. Prenatal diagnosis of junctional epidermolysis bullosa with pyloric atresia (family A). (a–e) Direct sequencing of *ITGB4*. The parents were heterozygous for c.1938delC in *ITGB4* (a, b). A-1, the proband, was homozygous for that mutation (c). A-2, the foetus, was found to be a heterozygous carrier (d). A cytosine at cDNA position 1938 in normal control is underlined (e). Arrows indicate a deleted cytosine in *ITGB4* sequence. (f) *PmlI* restriction enzyme digestion of the PCR products from the family members' genomic DNA. c.1938delC results in the loss of a site for *PmlI*. *PmlI* restriction enzyme digestion of the PCR products from normal control reveals 195- and 90-bp bands. Only a 285-bp band is observed in A-1 (the proband), who is homozygous for c.1938delC. In contrast, 285-, 195- and 90-bp bands are detected in the father, mother and A-2, suggesting that they are heterozygous for c.1938delC.

Conclusions

There are no recurrent *ITGB4* mutations that have been demonstrated to have founder effects in JEB-PA patients. Our study detected recurrent c.1938delC in *ITGB4* and revealed this to be a founder mutation in JEB-PA patients.

DNA-based prenatal testing of JEB-PA has been described (15–18). Our study has demonstrated the successful prenatal exclusion of JEB-PA with c.1938delC through mutation analysis of the foetal genomic DNA.

In summary, our study identified a founder c.1938delC in *ITGB4* and showed that this mutation can be applied for prenatal diagnosis of JEB-PA.

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Conflicts of interest

The authors declare no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Haplotype analysis of the junctional epidermolysis bullosa families.

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Letter to the Editor

IL-1 signalling is dispensable for protective immunity in *Leishmania*-resistant mice

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Abstract: Leishmaniasis is a parasitic disease affecting ~12 million people. Control of infection (e.g. in C57BL/6 mice) results from IL-12-dependent production of IFNγ by Th1/Tc1 cells. In contrast, BALB/c mice succumb to infection because of preferential Th2-type cytokine induction. Infected dendritic cells (DC) represent important sources of IL-12. Genetically determined differences in DC IL-1α/β production contribute to disease outcome. Whereas the course of disease was not dramatically altered in IL-1RI$^{-/-}$ mice, local administration of IL-1α to infected C57BL/6 mice improved disease outcome. To definitively elucidate the involvement of IL-1 in immunity against leishmaniasis, we now utilized IL-1α/β-double-deficient C57BL/6 mice. C57BL/6 mice are believed to be a good surrogate model for human, self limited cutaneous leishmaniasis (CL). *Leishmania major*-infected IL-1α/β$^{-/-}$ mice were resistant to experimental CL comparable to controls. In addition, DC-based vaccination against leishmaniasis in C57BL/6 mice was independent of IL-1. Thus, in *Leishmania*-resistant C57BL/6 mice, IL-1 signalling is dispensable for protection.

Key words: IL-1 – dendritic cells – *L. major*

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Background

Leishmaniasis is a parasitic disease transmitted by the bite of a sand fly. The disease ranges from cutaneous leishmaniasis (CL) to visceral leishmaniasis and ~12 million people are affected worldwide (1). In murine experimental leishmaniasis, control of infection results from IL-12-dependent production of Th1/Tc1-derived IFNγ that activates infected macrophages (MΦ) to eliminate parasites (2–5). In disease-resistant C57BL/6 mice, skin DC infected with *Leishmania major* represent important sources of IL-12 (6). In contrast, BALB/c mice respond to infection with preferential Th2-type cytokine production, which is associated with disease progression.

Abbreviations: CL, cutaneous leishmaniasis; DC, dendritic cells; MΦ, macrophages.

Genetically determined DC-derived factors that influence disease susceptibility of BALB/c mice include elevated levels of inhibitory IL-12p80 (7) and decreased release of IL-1α/β (8,9). Previously, we demonstrated that IL-1α/β facilitates Th1 induction in several inflammatory disease models (9–11). Treatment of BALB/c mice with IL-1 during T cell priming inhibited progressive disease by shifting the immune response towards Th1 (9). However, prolonged administration of IL-1α promoted Th2 expansion in already established infections and worsened disease outcome (11).

Question addressed

IL-1 is a key mediator of inflammation (12,13). IL-1α and IL-1β exert similar biological functions by binding to the IL-1 type I receptor (IL-1RI) (14). To definitively elucidate the involvement of IL-1 in immune responses in CL, we utilized IL-1α/β-double

Medical genetics

An Indian family with Sjögren-Larsson syndrome caused by a novel *ALDH3A2* mutation

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Abstract

Sjögren-Larsson syndrome is an autosomal-recessive hereditary disorder characterized by congenital ichthyosis, mental retardation and spastic diplegia or tetraplegia. It is known that mutations in the fatty aldehyde dehydrogenase (FALDH) gene (*ALDH3A2*) underlie SLS. We report two Indian sisters showing typical clinical features of SLS. Direct sequencing of the entire coding region of *ALDH3A2* revealed a novel homozygous mutation, c.142G>T (p.Asp48Tyr) in exon 1, in both patients. Their parents harbored the mutation heterozygously. Mutant-allele-specific amplification analysis using PCR products as a template verified the mutation in the patients. The aspartic acid residue at the mutation site is located in the C-terminal portion of the second a-helix strand, a2, of N-terminal four helices of FALDH and the FALDH amino-acid sequence alignment shows that this aspartic acid residue is conserved among several diverse species. Until now, a number of mutations in *ALDH3A2* have been shown to be responsible for SLS in Europe, the Middle East, Africa, and North and South America. However, in Asian populations, *ALDH3A2* mutations have been identified only in Japanese SLS patients. Here we report an *ALDH3A2* mutation for the first time in SLS patients in the Asian country other than Japan. The present results suggest that *ALDH3A2* is a gene responsible for SLS in Asian populations. We hope *ALDH3A2* mutation search will be globally available including many Asian countries in the future.

Case

Two sisters were born in an Indian nonconsanguineous family. The patient was a 1.5-year-old girl. She had had severe ichthyosis on the entire body since birth, especially prominent on the bilateral lower limbs (Fig. 1a–c). She showed mental retardation and spastic tetraplegia. Ocular fundus evaluation revealed white dots in the maculae. The elder sister also had icthyotic lesions all over the body at birth and had global developmental delay. She had had seizures since 2.5 years of age that had been controlled with multiple antiepileptic medications. At the age of four, severe hyperkeratosis appeared on the chest, back, axillae and predominantly over the limbs (Fig. 1d,e). She has hypertelorism, dolichocephalic head, large low-set ears, long eyelashes and short 3rd, 4th, and 5th metatarsals. Neurological evaluations revealed severe spastic tetraplegia with persistent ankle clonus and complete head lag. She showed serious mental retardation. She had severe photophobia, and ocular fundus evaluation showed white glistening dots in the maculae bilaterally. Severe auditory startle reaction was a characteristic feature. Magnetic resonance imaging of the brain showed bilateral symmetrical diffuse white matter at high intensity in T2-weighted images in the frontal, temporal, and parietal regions. Both sisters were diagnosed with Sjögren-Larsson syndrome (SLS) from these clinical features and laboratory data.

Fatty aldehyde dehydrogenase (FALDH) gene (*ALDH3A2*) mutational analysis was performed on the affected girls and their parents, as previously described.[1,2] In the patients, a novel homozygous mutation, c.142G>T (p.Asp48Tyr) in exon 1, was identified. Their parents harbored the mutation heterozygously (Fig. 2a). This mutation was not found in 200 normal unrelated alleles (100 individuals) by direct sequence analysis. Mutant-allele-specific amplification (MASA) analysis verified the mutation in this family (Fig. 2b).

Discussion

Sjögren-Larsson syndrome (MIM# 270200) is an autosomal-recessive hereditary disorder characterized by congenital ichthyosis, mental retardation and spastic diplegia or

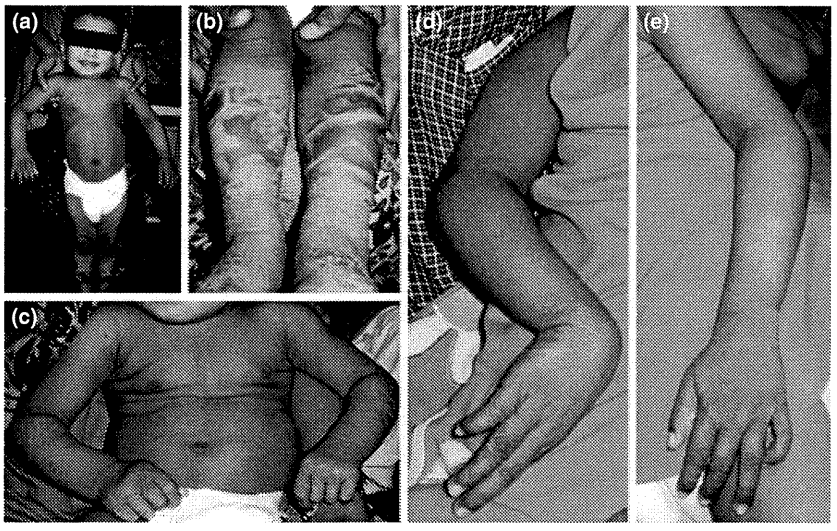

Figure 1 Clinical features of the Indian sisters with SLS. (a–c) The younger sister. Hyperkeratosis and scales cover whole body surface at 1.5 years of age (a). Dark brown scales are seen on the bilateral legs (b), the arms and the trunk (c). (d, e) The elder sister shows hyperkeratosis and brown scales on the bilateral arms at 4 years of age

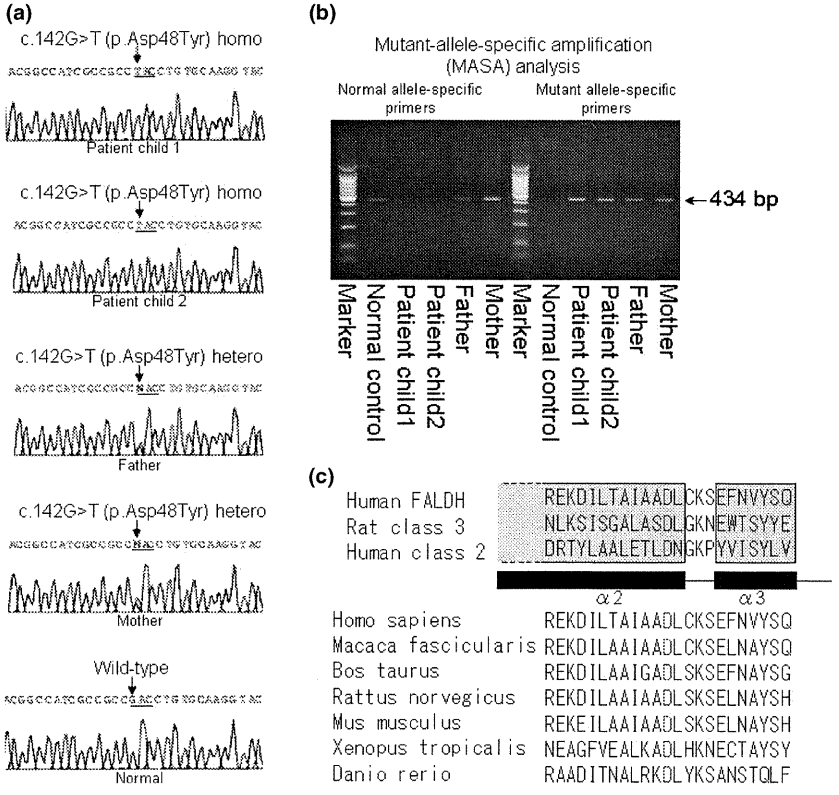

Figure 2 *ALDH3A2* mutation in the present SLS patients, and sequence alignments around the missense mutation. (a) Sequence analysis of *ALDH3A2*. In both patients, the younger sister (child 1) and the elder sister (child 2), a homozygous missense mutation c.142G>T (p.Asp48Tyr) in exon 1 derived from their parents was detected. The parents were heterozygous for the mutation. (b) Mutant allele-specific amplification analysis. With normal allele-specific primers, no amplification band is seen in the PCR products from the patients' DNA samples, suggesting that they have no normal allele. With mutant allele specific primers, the amplification band from the mutant alleles is detected as a 434-bp fragment in the PCR products from the DNA samples from the patients and their parents, and not in the PCR products from control DNA samples. This confirms the presence of the mutation c.142G>T in the patients. (c) Top: a sequence alignment between FALDH, rat class 3 and human class 2 ALDHs. Aspartic acid residue at codon 48 of FALDH is conserved. Secondary structure components found in the class 3 rat ALDH structure by Liu *et al.*[6] are presented with bars representing α-helices. Bottom: FALDH amino acid sequence alignment shows the level of conservation in diverse species of aspartic acid residue at codon 48 (D48) (red characters), which was altered by the missense mutation in the present family

tetraplegia.[3] In 1996, De Laurenzi *et al.*[4] reported that mutations in *ALDH3A2* underlie SLS. The present study reports a novel homozygous mutation in *ALDH3A2* in an Indian family with SLS.

The FALDH amino-acid sequence alignment shows that this aspartic acid residue at codon 48 is conserved among several diverse species. Compared with other aldehyde dehydrogenase (ALDH)-related sequences identified by Perozich *et al.*,[5] this aspartic acid is highly conserved among many members of the ALDH family (Fig. 2c). Analysis of the crystallized 3-D structure of the related class 3 rat cytosolic ALDH revealed that this aspartic acid is located in the C-terminal portion of the second α-helix strand, α2, of N-terminal four helices (Fig. 2c).[6] These findings strongly suggest that this aspartic acid residue is essential for the normal function of the FALDH. In the literature, missense mutation p.Ile45Phe in the α2 helix, three codons upstream of the present mutation site, was reported and the mutant enzyme was revealed to have only 9% residual enzyme activity compared with the wild-type enzyme.[7]

Until now, a number of mutations in *ALDH3A2* have been shown to be responsible for SLS in Europe, the Middle East, Africa, and North and South America.[1,7] However, in Asian populations, *ALDH3A2* mutations have been identified only in Japanese SLS patients.[1,2,8–10] Here, we report an *ALDH3A2* mutation for the first time in SLS patients in the Asian country other than Japan. The present results suggest that *ALDH3A2* is a gene responsible for SLS in Asian populations. Mutation analysis of the *ALDH3A2* gene is a highly sensitive method of confirming a diagnosis of SLS. It does not require a skin biopsy or FALDH enzymatic assays. We hope *ALDH3A2* mutation search will be globally available including many Asian countries in the future.

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SPECIAL REPORT

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

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Münster, Heidelberg, and Cologne, Germany; Milano, Italy; Sapporo, Fukuoka, and Asahikawa, Japan; Paris, Lavaur, Evry, Toulouse, Bordeaux, and Dijon, France; Providence, Rhode Island; San Francisco, California; Seattle, Washington; Lausanne, Switzerland; London, United Kingdom; Pretoria, South Africa; Salt Lake City, Utah; New Haven, Connecticut; Chicago, Illinois; Gaithersburg and Rockville, Maryland; Innsbruck, Austria; Tel Aviv, Israel; Maastricht, The Netherlands; and Uppsala, Sweden

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

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

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

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

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

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

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

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

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

Abbreviations used:

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

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

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

AIMS AND LIMITATIONS OF THE CONSENSUS REPORT

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

CAPSULE SUMMARY

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

RECOMMENDED REVISION OF THE TERMINOLOGY AND CLASSIFICATION OF INHERITED ICHTHYOSIS

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

General framework for the revised classification system

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

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

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

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

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

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

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

*Previously termed LI/nonbullous ichthyosiform erythroderma.

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

Classification of ARCI

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

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

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

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

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

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

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

[‡]Also known as *ICHTHYIN* gene.

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

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

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

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

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

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

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

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

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

†In context of contiguous gene syndrome.

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

§Also known as neonatal ichthyosis sclerosing cholangitis syndrome.

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

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

Classification of the keratinopathic ichthyoses

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

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

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

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

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

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

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

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

AR, Autosomal recessive; *BSI*, bathing suit ichthyosis; *CE*, cornified cell envelope; *CIE*, congenital ichthyosiform erythroderma; *HI*, harlequin ichthyosis; *IV*, ichthyosis vulgaris; *LB*, lamellar body; *LI*, lamellar ichthyosis; *SC*, stratum corneum; *SG*, stratum granulosum; *SHCB*, self-healing collodion baby; *TGase*, transglutaminase.
**NIPAL4* also known as *ICHTHYIN*.

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

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

Continued

Table VI. Cont'd

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

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

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

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

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

Other diseases considered in the classification of inherited ichthyoses

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

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

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

Continued