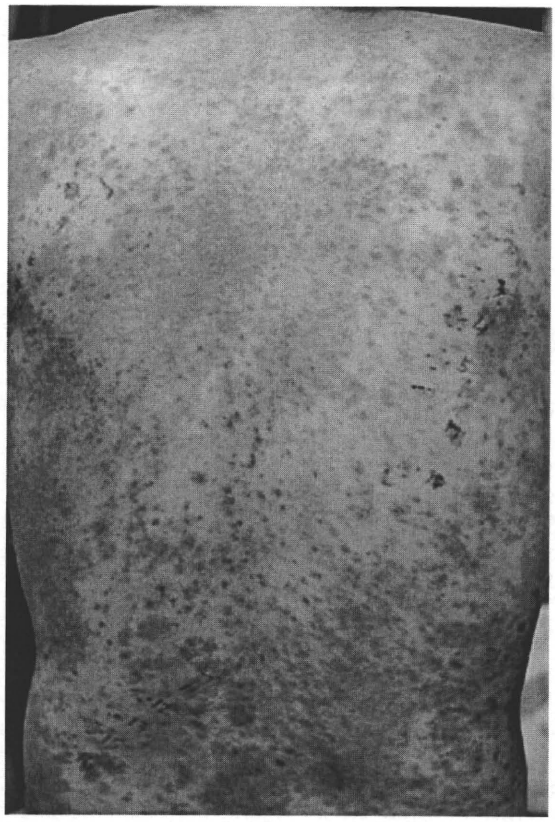

Fig. 1. Flare-up reaction is observed on the trunk after the patch test on D3. Diffuse oedematous erythema and pigmentation developed on the previous lesion.

procedure, a severe flare-up reaction has been observed. Oral corticosteroid at 10 mg/day has proved necessary prior to the removal of each zinc filling. Most of the zinc fillings have now been replaced and the patient's skin eruption has improved.

Discussion

Zinc is widely used in dental restoration. However, it is rare for zinc to cause systemic allergic dermatitis. Previously reported dental metal eruptions caused by zinc have been oral lichen planus (2, 3), palmoplantar pustulosis (4), and a maculopapular rash (5). Our case of generalized flare-up reactions to a zinc patch test and dental treatments suggests that systemic allergic dermatitis from this dental material is caused by the absorption of the metal through the skin or oral mucosa. However, one may suspect the amount of zinc that can be absorbed through the skin or oral mucosa compared with that obtained through dietary zinc intake to be small.

In conclusion, even widely used dental metals such as zinc may cause systemic allergic dermatitis that may flare-up by a patch test and metal removal treatments. Our case suggests that we should suspect systemic allergic dermatitis and take a detailed medical history when patients present with diffuse pruritic eruptions that fail to respond to conventional therapy.

References

1. Raap U, Stiesch M, Reh H, Kappo A, Werfel T. Investigation of contact allergy to dental metal in 206 patients. *Contact Dermatitis* 2009: 60: 339–343.
2. Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R. Oral symptoms due to zinc as a minor component of dental amalgam. *Contact Dermatitis* 2001: 44: 252–253.
3. Ido T, Kumakiri M, Kiyohara T, Sawai T, Hasegawa Y. Oral lichen planus due to zinc in dental restorations. *Contact Dermatitis* 2002: 47: 51.
4. Yanagi T, Shimizu T, Abe R, Shimizu H. Zinc dental fillings and palmoplantar pustulosis. *Lancet* 2005: 366: 1050.
5. Shimizu T, Kobayashi S, Tanaka M. Systemic contact dermatitis to zinc in dental fillings. *Clin Exp Dermatol* 2003: 28: 675–676.

Address:
Naoko Yamane, MD, PhD
Department of Dermatology
Hokkaido University Graduate School of Medicine
N15 W7, Sapporo 060–8638
Japan
Tel: +81 11 716 1160
Fax: +81 11 706 7820
e-mail: nayamane@med.hokudai.ac.jp

Japanese-Specific Filaggrin Gene Mutations in Japanese Patients Suffering from Atopic Eczema and Asthma

Journal of Investigative Dermatology (2010) **130,** 2834–2836; doi:10.1038/jid.2010.218; published online 5 August 2010

TO THE EDITOR

Mutations in *FLG*, the gene encoding profilaggrin/filaggrin, are the underlying cause of ichthyosis vulgaris (OMIM 146700) and an important predisposing factor for atopic eczema (AE) (Sandilands *et al.*, 2007). *FLG* mutations are also significantly associated with asthma with AE mainly in the European population (Rodríguez *et al.*, 2009; van den Oord and Sheikh, 2010). The presence of population-specific *FLG* mutations has been reported in both the European and Asian races (Nomura *et al.*, 2007; Sandilands *et al.*, 2007). To clarify whether *FLG* mutations are a predisposing factor for asthma in the non-European population, we initially studied 172 Japanese AE patients (mean age, 24.8 ± 9.1 years) and 134 unrelated Japanese control individuals (healthy volunteers; mean age, 27.9 ± 6.0 years). All AE patients had been diagnosed based on widely recognized diagnostic criteria (Hanifin and Rajka, 1980). The majority of AE patients and control individuals were identical to those in a previous study (Nemoto-Hasebe *et al.*, 2010). In this AE cohort, 73 AE patients (mean age, 25.4 ± 8.9 years) experienced complications with asthma. Furthermore, we studied another Japanese asthma cohort (137 patients; mean age, 58.2 ± 16.9 years). Patients were considered asthmatic based on the presence of recurrent episodes of ≥2 of the three symptoms (coughing, wheezing, or dyspnea) associated with demonstrable reversible airflow limitation, either spontaneously or with an inhaled short-acting β2-agonist and/or increased airway responsiveness to methacholine (Isada *et al.*, 2010). Fully informed consent was obtained from the participants or their legal guardians for this study. This study had been approved by the Ethical Committee at Hokkaido University Graduate School of Medicine and was conducted according to the Declaration of Helsinki Principles.

FLG mutation screening revealed that 27.4% of patients in our Japanese AE complicated with asthma case series carried one or more of the eight *FLG* mutations (combined minor allele frequency of 0.151, $n=146$) (Table 1). Conversely, 26.3% of Japanese AE patients without asthma carried one or more of the eight *FLG* mutations (combined minor allele frequency of 0.147, $n=198$). The *FLG* variants are also carried by 3.7% of Japanese control individuals (combined minor allele frequency of 0.019, $n=268$). We found that all compound heterozygous mutations were present in *trans* by observing transmission or haplotype analysis (Nomura *et al.*, 2007, 2008). There is a statistically significant association between the eight *FLG* mutations and AE with asthma, and between the eight *FLG* mutations and AE without asthma (Table 1). Moreover, AE complicated with asthma manifested in heterozygous carriers of *FLG* mutations with an odds ratio for AE and asthma of 9.74 (95% confidence interval 3.47–27.32), suggesting a relationship between *FLG* mutations and AE with asthma.

In the Japanese general asthma cohort, 8.0% of the asthma patients carried one or more of the eight *FLG* mutations (combined minor allele frequency of 0.04, $n=274$) (Table 2). Whereas, of the Japanese patients with asthma complicated by AE, 22.2% carried one or more of the *FLG* mutations (combined minor allele frequency of 0.11, $n=36$). In contrast, 5.9% of asthma patients without AE carried one or more of the *FLG* mutations (combined minor allele frequency of 0.03, $n=238$). There was a statistically significant association between the eight *FLG* mutations and asthma with AE (Table 2). There was no statistically significant association between the *FLG* mutations and entire asthma patients, nor between *FLG* mutations and asthma without AE. We cannot exclude the possibility that this lack of significant association is due to the small number of the patients included in this study. We used the same control set for both case-controlled studies. Thus, strictly speaking, there is no independent replication for the control group.

Recent meta-analysis revealed that *FLG* mutations are significantly associated with asthma in the European population and there are especially, strong effects observed for *FLG* mutations for the compound phenotype, asthma in addition to eczema (Rodríguez *et al.*, 2009; van den Oord and Sheikh, 2010). In contrast, there appeared to be no association of *FLG* mutations with asthma in the absence of eczema (Rodríguez *et al.*, 2009; van den Oord and Sheikh, 2010).

This Japanese cohort has a completely different *FLG* mutation spectrum from those in the European and the North American populations. However, our results clearly confirm the strong association of *FLG* mutations with our Japanese cohort of AE patients with asthma complications, and the association of *FLG* mutations and asthma patients with AE complications, for the first time outside Europe or North America. Conversely, this study showed no significant correlation between general asthma patients and *FLG* mutations, suggesting that atopic asthma patients associated with *FLG* mutations are a minority among general asthma patients. The frequency of heterozygous, compound heterozygous, and homozygous *FLG* mutation carriers

Abbreviation: AE, atopic eczema

Table 1. Atopic eczema case–control association analysis for *FLG* null variants in Japan

	R501X		3321delA		S1695X		Q1701X		S2554X		S2889X		S3296X		K4022X		Combined			
Genotype	Con	AE	Con	AE	Con	AE	Con	AE	Con	AE	Con	AE	Con	AE	Con	AE	Con	AE (total)	AE (asthma+)	AE (asthma−)
AA	134	172	133	163	133	172	134	169	133	162	132	152	134	166	134	169	129	126	53	73
Aa	0	0	1	9	1	0	0	3	1	10	2	20	0	6	0	3	5	41	18	23
aa	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5[1]	2	3
Total	134	172	134	172	134	172	134	172	134	172	134	172	134	172	134	172	134	172	73	99

Abbreviations: AE, atopic eczema; CI, confidence interval; Con, healthy control; OR, odds ratio.
For combined genotype: AE+asthma, exact *P*-value of Pearson χ^2-test=1.909×10^{-6}, OR and 95% CI for dominant models (AA vs aX)=9.737 (3.473–27.322); AE−asthma, exact *P*-value of Pearson χ^2-test=7.189×10^{-7}, OR and 95% CI for dominant models (AA vs aX)=9.191 (3.383–24.938); all AE, exact *P*-value of Pearson χ^2-test=1.189×10^{-7}, OR and 95% CI for dominant models (AA vs aX)=9.416 (3.625–24.450).
[1]All the five patients were compound heterozygotes for minor alleles.

Table 2. Asthma case–control association analysis for *FLG* null variants in Japan

	R501X		3321delA		S1695X		Q1701X		S2554X		S2889X		S3296X		K4022X		Combined			
Genotype	Con	Asthma	Con	Asthma	Con	Asthma	Con	Asthma	Con	Asthma	Con	Asthma	Con	Asthma	Con	Asthma	Con	Asthma (total)	Asthma (AE+)	Asthma (AE−)
AA	134	137	133	137	133	137	134	137	133	133	132	132	134	136	134	136	129	126	14	112
Aa	0	0	1	0	1	0	0	0	1	4	2	5	0	1	0	1	5	11	4	7
aa	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	134	137	134	137	134	137	134	137	134	137	134	137	134	137	134	137	134	137	18	119

Abbreviations: AE, atopic eczema; CI, confidence interval; Con, healthy control; OR, odds ratio.
For combined genotype: asthma+AE, exact *P*-value of Pearson χ^2-test=0.0122, OR and 95% CI for dominant models (AA vs aX)=7.3692 (1.7715–30.6748); asthma−AE, exact *P*-value of Pearson χ^2-test=0.5563, OR and 95% CI for dominant models (AA vs aX)=1.6124 (0.4979–5.2219); all asthma, exact *P*-value of Pearson χ^2-test=0.1968, OR and 95% CI for dominant models (AA vs aX)=2.2523 (0.7609–6.6667).

observed in our Japanese controls was only 3.7%, which was much lower than that seen in European general population, where it is approximately 7.5%. This suggested that there may be further mutations yet to be discovered in the Japanese. As we have sequenced more than 40 Japanese families with ichthyosis vulgaris, there is now little possibility that further highly prevalent mutations will be found in the Japanese population. However, it is still possible that there might be multiple, further low-frequency *FLG* mutations discovered in the Japanese population. In addition, because of the relatively small sample size of this genetic study, further replication in association studies will be required for *FLG* mutations and asthma in Japan.

In our cohorts, serum IgE levels were extremely high (median, 3141.9 IU ml^{-1}; 25th–75th percentiles, 1276.0–9753.0 IU ml^{-1}) in AE patients with asthma ($n=73$) in the AE cohort, compared with that in total asthma patients (median, 156.0 IU ml^{-1}; 25th–75th percentiles, 71.05–441.45 IU ml^{-1}, $n=137$) in the asthma cohort. These findings suggest that extrinsic allergic sensitization might have an important role in atopic asthma pathogenesis. Recent studies hypothesized skin barrier defects caused by *FLG* mutation(s) allow allergens to penetrate the skin, resulting in initiation of further immune response and leading to the development of systemic allergies, including atopic asthma (Fallon *et al.*, 2009). In patients with asthma that also harbor *FLG* mutations, we could not exclude the possibility that the systemic effects of early eczema might simply influence airway responsiveness (Henderson *et al.*, 2008).

CONFLICT OF INTEREST

Irwin McLean has filed patents relating to genetic testing and therapy development aimed at the filaggrin gene.

ACKNOWLEDGMENTS

We thank the patients and their families for their participation. We also thank Kaori Sakai for fine technical assistance and Dr James McMillan for proofreading and comments concerning this paper. This work was supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan to M Akiyama (Kiban B 20390304) and by the Health and Labour Sciences Research Grant (Research on Allergic Diseases and Immunology; H21-Meneki-Ippan-003) to H Shimizu. Filaggrin research in the McLean laboratory was supported by grants from The British Skin Foundation; The National Eczema Society; The Medical Research Council (Reference number G0700314); A*STAR, Singapore, and donations from anonymous families affected by eczema in the Tayside region of Scotland.

Rinko Osawa[1], Satoshi Konno[2], Masashi Akiyama[1], Ikue Nemoto-Hasebe[1], Toshifumi Nomura[1,3], Yukiko Nomura[1], Riichiro Abe[1], Aileen Sandilands[3], W.H. Irwin McLean[3], Nobuyuki Hizawa[4,5], Masaharu Nishimura[2] and Hiroshi Shimizu[1]

[1]Department of Dermatology, Hokkaido University School of Medicine, Sapporo, Japan; [2]First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan; [3]Epithelial Genetics Group, Division of Molecular Medicine, University of Dundee, Colleges of Life Sciences and Medicine, Dentistry & Nursing, Dundee, UK;

[4]*Department of Pulmonary Medicine, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan and* [5]*University Hospital, University of Tsukuba, Tsukuba, Ibaraki, Japan*
E-mail: akiyama@med.hokudai.ac.jp

REFERENCES

Fallon PG, Sasaki T, Sandilands A *et al.* (2009) A homozygous frameshift mutation in the mouse *Flg* gene facilitates enhanced percutaneous allergen priming. *Nat Genet* 41: 602–8

Hanifin JM, Rajka G (1980) Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 92:44–7

Henderson J, Northstone K, Lee SP *et al.* (2008) The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 121:872–7

Isada A, Konno S, Hizawa N *et al.* (2010) A functional polymorphism (-603A —> G) in the tissue factor gene promoter is associated with adult-onset asthma. *J Hum Genet* 55: 167–74

Nemoto-Hasebe I, Akiyama M, Nomura T *et al.* (2010) *FLG* mutation p.Lys4021X in the C-terminal imperfect filaggrin repeat in Japanese atopic eczema patients. *Br J Dermatol* 161:1387–90

Nomura T, Akiyama M, Sandilands A *et al.* (2008) Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol* 128:1436–41

Nomura T, Sandilands A, Akiyama M *et al.* (2007) Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol* 119:434–40

Rodríguez E, Baurecht H, Herberich E *et al.* (2009) Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 123:1361–70

Sandilands A, Terron-Kwiatkowski A, Hull PR *et al.* (2007) Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 39:650–4

van den Oord RA, Sheikh A (2010) Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 339:b2433

See related commentary on pg 2703

RNase 7 Protects Healthy Skin from *Staphylococcus aureus* Colonization

Journal of Investigative Dermatology (2010) **130,** 2836–2838; doi:10.1038/jid.2010.217; published online 29 July 2010

TO THE EDITOR

The Gram-positive bacterium *Staphylococcus aureus* is an important pathogen that causes various skin infections (Miller and Kaplan, 2009). However, healthy skin is usually not infected by *S. aureus,* despite the high carrier rates in the normal population (Noble, 1998). This suggests that the cutaneous defense system has the capacity to effectively control the growth of *S. aureus.* There is increasing evidence that antimicrobial proteins are important effectors of the cutaneous defense system (Harder *et al.*, 2007). A recent study reported that keratinocytes contribute to cutaneous innate defense against *S. aureus* through the production of human β-defensin-3 (Kisich *et al.*, 2007). In addition to human β-defensin-3,, other antimicrobial proteins may also participate in cutaneous defense against *S. aureus.* One candidate is RNase 7, a potent antimicrobial ribonuclease that is highly expressed in healthy skin (Harder and Schröder, 2002; Köten *et al.*, 2009).

To investigate the hypothesis that RNase 7 may contribute to protect healthy skin from *S. aureus* colonization, we first incubated natural RNase 7 isolated from stratum corneum skin extracts (Harder and Schröder, 2002) with *S. aureus* (ATCC 6538). In concordance with our initial report about RNase 7 (Harder and Schröder, 2002), we verified that RNase 7 exhibited a high killing activity against *S. aureus* (lethal dose of 90% $=3$–$6\,\mu g\,ml^{-1}$).

Recently, we reported a moderate induction of RNase 7 mRNA expression in primary keratinocytes treated with heat-killed *S. aureus* (Harder and Schröder, 2002). To assess the induction of RNase 7 by *S. aureus* in the

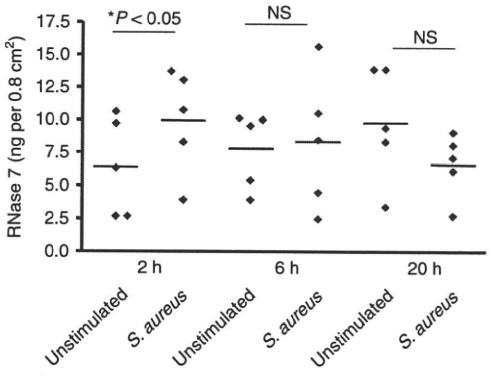

Figure 1. Induced secretion of RNase 7 on the skin surface on treatment with living *S. aureus*. Defined areas (0.8 cm^2) of skin explants derived from plastic surgery were incubated with or without approximately 1,000 colony-forming units of *S. aureus* (ATCC 6538) in 100 µl of sodium phosphate buffer. After 2, 6, and 20 hours, the concentration of secreted RNase 7 was determined by ELISA. Stimulation with *S. aureus* for 2 hours revealed a significant induction as compared with the unstimulated control after 2 hours (*$P<0.05$, Student's *t*-test; n.s. = not significant). Data shown are means of triplicates of five skin explants derived from five donors.

ORIGINAL ARTICLE

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

Vinzenz Oji, MD,[a] Gianluca Tadini, MD,[b] Masashi Akiyama, MD, PhD,[c] Claudine Blanchet Bardon, MD,[d] Christine Bodemer, MD, PhD,[e] Emmanuelle Bourrat, MD,[d] Philippe Coudiere, PharmD,[f] John J. DiGiovanna, MD,[g] Peter Elias, MD,[h] Judith Fischer, MD, PhD,[i] Philip Fleckman, MD,[j] Michal Gina, MD,[k] John Harper, MD, FCRCP, FRCPCH,[l] Takashi Hashimoto, MD,[m] Ingrid Hausser, PhD,[n] Hans Christian Hennies, PhD,[o] Daniel Hohl, MD, PhD,[k] Alain Hovnanian, MD, PhD,[p,q] Akemi Ishida-Yamamoto, MD, PhD,[r] Witold K. Jacyk, MD,[s] Sancy Leachman, MD, PhD,[t] Irene Leigh, MD, FRCP, FMedSci,[u] Juliette Mazereeuw-Hautier, MD, PhD,[v] Leonard Milstone, MD,[w] Fanny Morice-Picard, MD,[x] Amy S. Paller, MS, MD,[y] Gabriele Richard, MD, FACMG,[z] Matthias Schmuth, MD,[aa,bb] Hiroshi Shimizu, MD, PhD,[c] Eli Sprecher, MD, PhD,[cc] Maurice Van Steensel, MD, PhD,[dd] Alain Taïeb, MD,[x] Jorge R. Toro, MD,[ee] Pierre Vabres, MD,[ff] Anders Vahlquist, MD, PhD,[gg] Mary Williams, MD,[aa] and Heiko Traupe, MD[a]

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

From the Department of Dermatology, University Hospital Münster[a]; Centro Malattie Cutanee Ereditarie, Istituto di Scienze Dermatologiche, Istituto Di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore, Milano[b]; Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo[c]; Department of Dermatology, Saint-Louis Hospital, Paris[d]; Department of Dermatology, Necker Enfants Malades Hospital (Assistance Publique Hopitaux de Paris [APHP])—University Paris V, National Reference Centre for Genodermatoseis Centre de reference sur les Maladies Génétiques à Expression Cutanée[e]; Pierre Fabre Dermatologie, Lavaur[f]; Division of Dermatopharmacology, Department of Dermatology, The Warren Alpert School of Medicine of Brown University, Providence[g]; Dermatology, Department of Veterans Affairs Medical Center, San Francisco[h]; Centre National de Génotypage, Evry[i]; Division of Dermatology, University of Washington[j]; Hospices Cantonaux—Centre Hospitalier, Universitaire Vaudois, Service de Dermatologie des Hospices, Lausanne[k]; Great Ormond Street Children's Hospital, London[l]; Department of Dermatology, Kurume University School of Medicine, Fukuoka[m]; Department of Dermatology, University Hospital Heidelberg[n]; Cologne Center for Genomics, Division of Dermatogenetics, University of Cologne[o]; Departments of Genetics and Dermatology, Necker Enfants Malades Hospital (APHP)—University Paris V[p]; Institut national de la santé et de la recherche médicale U781[q]; Department of Dermatology, Asahikawa Medical College[r]; Department of Dermatology, University of Pretoria[s]; University of Utah Health Sciences Center[t]; Queen Mary and Westfield College, Centre for Cutaneous Research, Institute of Cell and Molecular Science, Barts and the London Medical School Queen Mary[u]; Reference Center for Rare Skin Diseases, Department of Dermatology, Purpan Hospital, Toulouse[v]; Yale University, New Haven[w]; Department of Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin Diseases, Hôpital St André, Bordeaux[x]; Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago[y]; GeneDx, Gaithersburg[z]; University of California San Francisco[aa]; Department of Dermatology, Innsbruck Medical University[bb]; Department of Dermatology, Tel Aviv Sourasky Medical Center[cc]; Department of Dermatology, Maastricht University Medical Center and GROW Research School for Oncology and Developmental Biology, University of Maastricht[dd]; Genetics Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville[ee]; Université de Bourgogne, Department of Dermatology, Hôpital du Bocage, Dijon[ff]; and Department of Medical Sciences, Dermatology and Venereology, Uppsala University.[gg]

The accommodation and travel costs of the participants and the conference rooms of the Ichthyosis Consensus Conference were sponsored by the Laboratories Pierre Fabre, Castres, France. Moreover, our work is supported by the Network for Ichthyoses and Related Keratinization Disorders (Bundesministerium für Bildung und Forschung, GFGM01143901), the Foundation for Ichthyosis and Related Skin Types (United States), and the Ichthyosis Patient Organization of Germany (Selbsthilfe Ichthyose e. V.).

Conflicts of interest: None declared.

Accepted for publication November 17, 2009.

Reprint requests: Vinzenz Oji, MD, Department of Dermatology, University Hospital Münster, Von-Esmarch-Str. 58, 48149 Münster, Germany. E-mail: ojiv@uni-muenster.de.

Published online July 17, 2010.

0190-9622/$36.00

doi:10.1016/j.jaad.2009.11.020

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 10.1016/j.jaad.2009.11.020.)

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

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

Abbreviations used:

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

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

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

AIMS AND LIMITATIONS OF THE CONSENSUS REPORT

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

CAPSULE SUMMARY

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

RECOMMENDED REVISION OF THE TERMINOLOGY AND CLASSIFICATION OF INHERITED ICHTHYOSIS

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

General framework for the revised classification system

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

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

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

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

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

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

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

*Previously termed LI/nonbullous ichthyosiform erythroderma.

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

Classification of ARCI

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

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

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

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

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

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

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

[‡]Also known as *ICHTHYIN* gene.

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

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

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

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

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

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

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

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

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

[†]In context of contiguous gene syndrome.

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

[§]Also known as neonatal ichthyosis sclerosing cholangitis syndrome.

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

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

Classification of the keratinopathic ichthyoses

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

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

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

FISH, Fluorescent in situ hybridization; *IV*, ichthyosis vulgaris; *KG*, keratohyaline granules; *RXLI*, recessive X-linked ichthyosis; *SC*, stratum corneum; *SG*, stratum granulosum; *XR*, X-linked recessive.

*RXLI within context of contiguous gene syndrome (Table III), eg, in Kallmann syndrome, chondrodysplasia punctata (brachytelephalangic type), or ocular albinism type 1.

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

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

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

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

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

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

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

Continued

Table VI. Cont'd

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

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

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

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

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

Other diseases considered in the classification of inherited ichthyoses

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

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

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

Continued

Table VII. Cont'd

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

Acral PSS, Acral peeling skin syndrome; *AD*, autosomal dominant; *AR*, autosomal recessive; *CE*, cornified cell envelope; *CIE*, congenital ichthyosiform erythroderma; *EKV*, erythrokeratodermia variabilis; *IE*, ichthyosiform erythroderma; *KG*, keratohyaline granules; *KLICK*, keratosis linearis–ichthyosis congenita–keratoderma; *LB*, lamellar body; *LK*, loricrin keratoderma; *PPK*, palmoplantar keratoderma; *PSD*, peeling skin disease; *SC*, stratum corneum; *SG*, stratum granulosum.

*We propose to classify disorder as nonsyndromic form and therefore modified name "peeling skin syndrome (PSS)" into "peeling skin disease."

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Continued

Table X. Cont'd

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

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

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

Diseases related to inherited ichthyoses

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