Pierre Fabre
DERMATOLOGIE

NIRK
NETWORK FOR ICHTHYOSES AND RELATED KERATINIZATION DISORDERS

Ichthyosis Consensus Conference

January 23.-24.01.2009

Point d'accueil de l'Abbaye-école
rue Saint-Martin, 81540 Sorèze
France

… all these approaches start with
a somewhat 'provisional' aspect,
but will be gaining ground the more
experts work together.

– Ingrid Hausser,
to Vinzenz Oji, 01/2008

Ichthyosis Consensus Conference

Program for Sorèze 2009

Friday 23. January 2009

11:30 h **Welcome and Opening** (Gianluca Tadini)

Pierre Fabre group presentation and welcome (Director Manager of Pierre Fabre Dermatology Pascal Lefrancois & International Manager Philippe Coudiere)

11:45-13:15 h **Introduction** (Chairs: Gianluca Tadini and Heiko Traupe)

- Heiko Traupe (15' + 5' discussion): History of ichthyoses: Classification – Why it is so painful?
- Takashi Hashimoto (10' + 5' discussion): Structures in Japan of providing care for ichthyosis
- Didier Coustou (10' + 5' discussion): Effectiveness and safety of Dexeryl® cream in the treatment of ichtyosis in children: Results of an international multicentric randomised controlled double blind study
- Mary Williams (30' + 10' discussion): Biologic aspects of cornification disorders

13:15-15:00 h *lunch break*

15:00-16:30 h **Update on ichthyosis genetics** (Chairs: Gabriele Richard & Alain Hovnanian)

- Daniel Hohl (20' + 10' discussion): Ichthyosis and keratin disorders
- Judith Fischer (20' + 10' discussion): Gene mapping of ARCI
- Hans Christian Hennies (20' + 10' discussion): The molecular diagnosis of congenital ichthyosis

16:30-17:00 h *coffee break*

17:00-18:00 h **Update on ichthyosis ultrastructure** (Chairs: Hiroshi Shimizu & Mary Williams)

- Ingrid Hausser (10'): The German experience on ichthyosis ultrastructure
- Akemi Ishida-Yamamoto (10'): The Japanese experience on ichthyosis ultrastructure
- Peter Elias (10'): The American experience on ichthyosis ultrastructure
- 30 min for open discussion

18:00-19:15 h **Special disorders and clinical presentations** (Chairs: Blanchet Bardon & Leonard Milstone) (presentations à 8' + 4' discussion):

- Philip Fleckman (8' + 4' discussion) : Update on ichthyosis vulgaris
- Masashi Akiyama (8' + 4' discussion) : Genotype/phenotype correlation and ABCA12
- Christine Bodemer (8' + 4' discussion) : Update on Netherton syndrome
- John DiGiovanna (8' + 4' discussion) : Trichothiodystrophy – the American experience
- Alain Taieb (8' + 4' discussion): Trichothiodystrophy – the European experience
- Pierre Vabres ((8' + 4' discussion) : Clinical presentation of NISCH syndrome
- Sancy Leachman (8' + 4' discussion): Gentherapy of keratin disorders

19:15-19:30 h **Comments on the protocol of the Ichthyosis Consensus Conference and assignment of subcommittee 1 – 6** (Moderation: Juliette Mazereeuw-Hautier & Vinzenz Oji)

19:30 h *Social evening (Transfer to the restaurant of the site of Le Carla)*

Saturday 24. January 2009

09:00-11:00 h **Plenum: Discussion basic module** (Chairs: Anders Vahlquist & Eli Sprecher)

- Vinzenz Oji (30'): Update of the moderation process of the ichthyosis classification
- Maurice von Steensel (30'): The pros of a genetic classification approach
- Hiroshi Shimizu (30'): The pros of a clinical classification approach
- 30 min for open discussion

11:00-11:30 h *coffee break*

11:30-13:00 h **Subcommittee work (issue 1 - 6)**

- Elaboration of proposals, which should find a consensus after latter presentation and discussion in the plenum or which can then be modified to find a consensus

13:00-15:00 h *lunch break*

Optional time for subcommittee work

15:00-16:30 h **Plenum: Report, discussion and consensus of issue 1 - 3:**
(chairs: Amy Paller & John Harper)

- Subcommittee 1 (speakers/reporters: Mary Williams & Hiroshi Shimizu):
  "Definitions and clinical terms"
- Subcommittee 2 (speakers/reporters: Akemi Ishida-Yamamoto & Alain Taieb):
  "What is the correct and best name for bullous ichthyosis?"
- Subcommittee 3 (speakers/reporters: Irene Leigh & John DiGiovanna):
  "Disorders, which should be considered in the classification"

16:30-17:00 h *coffee break*

17:00-18:30 h **Plenum: Report, discussion and consensus of issue 4 - 6:**
(Chairs: Irene Leigh and Alain Taieb)

- Subcommittee 4 (speakers/reporters: Gabriele Richard & Maurice von Steensel):
  "Disorders, which should be related to ichthyosis"
- Subcommittee 5 (speakers/reporters: Judith Fischer & Anders Vahlquist):
  "How to classify ARCI?"
- Subcommittee 6 (speakers/reporters: Ingrid Hausser & Eli Sprecher):
  "How to classify ichthyoses due to keratin mutations?"

18:30 h Concluding remarks (Mary Williams and Heiko Traupe)

19:00 h Acknowledgements and end of the meeting

Abstract

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Author(s):	Masashi **Akiyama**
Title:	**Genotype/phenotype correlation and ABCA12**
	Among autosomal recessive congenital ichthyoses (ARCI), harlequin ichthyosis (HI) shows apparently the most severe phenotype. The nature of scaling and intensity of erythroderma are important clinical features to distinguish between non-bullous congenital ichthyosiform erythroderma (NBCIE) and lamellar ichthyosis (LI). ABCA12 belongs to a large superfamily of the ATP-binding cassette (ABC) transporters, which aid in the transport of various biomolecules across the limiting membrane. The ABCA subfamily, of which the ABCA12 is a member, works in lipid transport. ABCA12 has been shown to be a keratinocyte lipid transporter associated with lipid transport in lamellar granules and loss of ABCA12 function leads to a defective lipid barrier in the stratum corneum, resulting in the HI or LI/NBCIE phenotype. Several genotype/phenotype correlations with *ABCA12* mutations have now come to light. Combinations of missense mutations resulting in only one amino acid alteration in the first ATP-binding cassette of the ABCA12 peptide underlie the LI phenotype. In NBCIE families harboring *ABCA12* mutations, at least one mutation on each allele is to be a missense mutation leading to only one amino acid alteration. In contrast, most mutations in HI are truncation mutations which lead to loss-of-function of ABCA12 peptide, although various kinds of mutations including splice site mutations, missense mutations, small deletions and exon deletions were also reported in HI families. Recently, we generated ABCA12-deficient mice by disrupting *Abca12*. This *Abca12*$^{-/-}$ mice showed complete ABCA12 deficiency and closely reproduced the human HI phenotype. Thus far, it is apparent that complete loss of ABCA12 function due to homozygous or compound heterozygous truncation mutations always results in HI phenotype. To better elucidate genotype/phenotype correlations between *ABCA12* mutations and ARCI phenotypes, further accumulation of data on *ABCA12* mutations and their effects on the transporter function are needed.

Abstract

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Author(s):	Christine **Bodemer,** MD, PHD Service de Dermatologie, Hôpital Necker Enfants Malades, Université Descartes Paris V. INSERM U 781. Centre de reference *MA*ladies *Gé*nétiques à *E*xpression *C*utanée (*MAGEC) christine.bodemer@nck.aphp.fr*
Title:	**Netherton Syndrome**
	Netherton syndrome (NS) is a life-threatening autosomal recessive disorder of the newborn and children. It has been defined clinically by severe ichtyosis (Ichtyosis lnearis circumflexa and/or congenital ichtyosiform erythroderma, trichorrhexis invaginata and atopic manifestations with high IgE levels. Hypernatremic dehydratation is frequent in neonates and other neonatal morbidities are related to sepsis and weight loss. The gene has recently been identified: *SPINK5*, encoding LEKTI, a serine protease inhibitor of the Kazal type with anti-trypsin activity. Defective expression of LEKTI in skin sections could be a constant feature in NS patients, whilst an extended reactivity pattern is observed in samples from other keratinizing disorders, demonstrating that loss of LEKTI expression in the epidermis is a diagnostic feature of NS (immunohistochemy (IHC)). Kallikrein 7 (KLK)7 (stratum corneum chymotryptic enzyme) and KLK5 (stratum corneum tryptic enzyme), involved in desquamation through the proteolysis of intercellular adhesion molecules (such as desmoglein), are targets of specific LEKTI short fragments. The clinical diagnosis of NS can be now rapidly confirmed by skin biopsy and IHC. A clinical heterogeneity, previously underlined (persistent desquamative erythroderma, through the life, or mild and even localized ILC, …) is now confirmed. More than 37 mutations in SPINK5 have been identified since the report of the first mutations. The majority of mutations lead to premature codon termination resulting in reduced expression of mutated SPINK5 alleles. Mild patients could have downstream mutations near 3' end and severe erythrodermic patients early truncation of LEKTI because of premature termination mutations. We follow now a large series of NS (more than 30 patients), most of them from the birth. Genotype/phenotype correlations are under-investigations. I would like to underline: the great clinical heterogeneity (and even intrafamilial heterogeneity), suggesting the role of modulator genes, and/or modulator factors; the possibility of collodion baby syndrome in NS; and the possibility of other causal genes as some patients with Netherton syndrome-like are not related to loss of LEKTI expression.

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Author(s):	J J **DiGiovanna**[a,b], S Faghri[a,b], D Tamura[b], K H Kraemer[b] [a] The Warren Alpert Medical School of Brown University, Providence, RI and [b] National Cancer Institute, NIH, Bethesda, MD
Title:	**Trichothiodystrophy: the American experience**
	Trichothiodystrophy (TTD) is a rare, autosomal recessive disease, characterized by brittle, sulphur deficient hair and multisystem abnormalities. A systematic literature review[1] identified 112 patients ranging from 12 weeks to 47 years of age (median 6 years). In addition to hair abnormalities, common features reported were developmental delay/intellectual impairment (86%), short stature (73%), ichthyosis (65%), abnormal characteristics at birth (55%), ocular abnormalities (51%), infections (46%), photosensitivity (42%), maternal pregnancy complications (28%) and defective DNA repair (37%). There was high mortality, with 19 deaths under the age of 10 years (13 infection related), which is 20-fold higher compared to the US population. The spectrum of clinical features varied from mild disease with only hair involvement to severe disease with profound developmental defects, recurrent infections and a high mortality at a young age. The most frequently reported skin finding was ichthyosis, and of the 73 patients with ichthyosis, 29 had collodion presentation at birth. Ten patients were reported to have lamellar ichthyosis and 6 of these had collodion presentation. We evaluated patients with TTD and related disorders and found a similar spectrum of abnormalities in 20 TTD patients clinically examined. The clinical features of ichthyosis in our patients was extremely variable. If suspected, a rapid diagnosis of TTD can be made by simple microscopic examination of hair shafts and supported by finding low sufur (cystine) content. The constellation of tiger-tail banding under polarizing light microscopy in association with specific hair shaft abnormalities is diagnostic for TTD was not found in other disorders including a variety of disorders of cornification.[2] There are important clinical implications of making a diagnosis of TTD. Newborns diagnosed with TTD can be carefully monitored for infection, which can be aggressively managed, and ocular problems such as cataract. Mothers who have complications during a pregnancy carrying a TTD affected fetus can be monitored during future pregnancies. Abnormal characteristics at birth and pregnancy complications, unrecognized but common features of TTD, suggest a role for DNA repair genes in normal fetal development. [1] Faghri S, Tamura D, Kraemer KH, DiGiovanna JJ. Trichothiodystrophy: a systematic review of 112 published cases characterizes a wide spectrum of clinical manifestations. J Med Genet 2008 Oct;45(10):609-21 [2] Liang C, Kraemer KH, Morris A, Schiffmann R, Price VH, Menefee E, DiGiovanna JJ. Characterization of tiger tail banding and hair shaft abnormalities in trichothiodystrophy. J Amer Acad Dermatol 2005; 52(2):224-232.

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Author(s):	Peter **Elias**, Matthias Schmuth, and Debra Crumrine
Title:	**Utility of Ultrastructure in the Diagnosis of the Ichthyoses**
	Electron microscopy can provide important clues as to the clinical diagnosis of the ichthyoses, allowing clinicians to narrow genetic testing among a limited number of possible disease entities. However, ruthenium tetroxide post-fixation, which allows visualization of extracellular alterations in the stratum corneum, is required to distinguish among many, if not most of the ichthjyoses. Ultrastructure also provides invaluable information about disease pathogenesis, allowing assessment of genotype-phenotype relationships, and the identification of homeostatic responses that mitigate disease severity. Finally, awareness of compensatory responses to the permeability barrier abnormality in the ichthyoses can alert clinicians about therapies that could aggravate, rather help patients.

Abstract

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Author(s):	**Fischer**, Judith
Title:	**Gene mapping of ARCI**
	Autosomal recessive congenital ichthyosis (ARCI) is a clinically and genetically heterogeneous group of disorders of keratinisation characterized by skin desquamation over the whole body, often associated with erythema (Williams *et al.* 1985, Traupe *et al.* 1989). It is a severe condition with an estimated prevalence of 1 in 300,000 newborns and most of the patients are born as collodion babies. To date, six genes for ARCI have been identified, *TGM1* (MIM 242300) on chromosome 14q11 (Huber *et al.* 1995, Russell *et al.* 1995), *ABCA12* (MIM 601277) on chromosome 2q34-q35 (Lefèvre *et al.* 2003), *ichthyin* on chromosome 5q33 (Lefèvre *et al.* 2004), *ALOXE3* and *ALOX12B* (MIM242100) on chromosome 17p13 (Jobard *et al.* 2002) and *CYP4F22* on chromosome 19p12-q12 (MIM 604777) (Fischer *et al.* 2000, Lefèvre *et al*. 2006). I will give an overview of : i) the genetic approaches which have led to the identification of these genes, ii) the distribution of mutations in the causative genes and their consequences, iii) a few examples of genotype-phenotype correlations, iv) our plans to identify new localizations and genes in ACRI families.

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Author(s):	Philip **Fleckman**
Title:	**Ichthyosis Vulgaris**
	Ichthyosis vulgaris is an autosomal semidominant disorder with underlying null mutations in the profilaggrin gene, *FLG*. Fine, white scale accentuated on the extensor surfaces of extremities, and hyperlinear palms and soles are seen in homozygotes and compound heterozygotes; similar but more subtle findings are seen in ~60% of heterozygotes. Profilaggrin constitutes most of the keratohyalin granule in human interfollicular skin. The >400 kDa protein is synthesized in the granular layer and undergoes extensive post-translational modification before it is metabolized to filaggrin, which aggregates keratin filaments in the lower stratum corneum and is then broken down to hygroscopic compounds. Profilaggrin contains 10 to 12 ~37 kDa filaggrin repeats sandwiched between unique N- and C-terminal peptides and partial filaggrin repeats. At least 24 mutations have been described and an additional dozen detected throughout the filaggrin repeats, resulting in little to no profilaggrin expression, a reduced to absent granular layer, and no processing to filaggrin. Barrier defects result from the lack of filaggrin. Common and rare mutations appear to differ between ethnic populations. Null alleles are seen in ~9% of the eurocaucasian population. *FLG* null alleles strongly predispose to eczema at all ages, persistent eczema, asthma in association with eczema, and atopic sensitization to common allergens. Approximately 42 to 47 per cent of individuals with eczema have *FLG* null alleles; the penetrance of *FLG* null alleles in eczema is ~38.5-42%. *FLG* null alleles may modify other cutaneous disorders.

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Author(s):	Takashi **Hashimoto** (Department of Dermatology, Kurume University School of Medicine, Kurume, Japan)
Title:	**Structures in Japan of providing care for ichthyosis**
	The Japanese Society of Ichthyosis Families was first founded by a family with two siblings with relatively severe ichthyosis in Kurume on 1996. These patients were only recently diagnosed as ichthyosis vulgaris by finding of two heterozygous mutations in filagrin gene. On 1998, the head of the society changed to the mother of a patient with severe bullous congenital ichthyosiform erythroderma (BCIE), who has been cared by me and was found to have p.L486P mutation in Keratin 1 gene. The society has expanded and now has 35 family members. The types of ichthyosis in these families include 11 cases of NBCIE, 7 cases of ichthyosis vulgaris, 4 cases of BCIE, 3 cases of Harlequin ichthyosis and other types. Once a year, all the family members get together in Kyushu area and enjoy the reunion. This is supported by many volunteers including the medical doctors from Department of Dermatology of Kurume University. The family members can exchange their information for the care and treatment for ichthyosis patients and hear the lecture of the expert for research and treatment for ichthyosis. The society has been continuously working to show the presence of such a rare and severe hereditary skin disease, ichthyosis, to the publics. The society prepared and distributed booklets for ichthyosis to many schools and hospitals, organized many seminars to mass-communications, and participated in various television programs. These actions were published in many newspapers and journals. Then, the society gathered courteous signatures from about 150.000 publics for supporting the activity of the society, and handed them to the Ministry of Health, Labour and Welfare. As a result of the activity of the society, last year, both BCIE and NBCIE were selected as the intractable disease, the investigation for which is supported financially by the Ministry of Health, Labour and Welfare (Research on Intractable Diseases) of Japanese Government. Now, the research group for the intractable skin diseases in the Ministry of Health, Labour and Welfare is actively working to collect the information for all the patients with BCIE and NBCIE in Japan and to establish the method for the correct diagnosis of ichthyosis including genetic studies and the proper treatments for ichthyosis.

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Author(s):	**Hausser**, Ingrid, ScD. Dermatology Department, Electron Microscopic Laboratory, University Clinic Heidelberg, Germany
Title:	**The German Experience on Ichthyosis Ultrastructure**
	Thorough studies on ultrastructural identification of basic abnormalities as clues to genetic disorders of the epidermis and especially on criteria for the distinction of different types of keratinization disorders have been performed in our lab since the 1970ies. In the meanwhile, including results of other groups and confirmed by various international labs, a series of entities can be delineated based on their specific ultrastructural markers. The comparison of normal and specifically altered structures and organelles may also serve as a hint to underlying pathophysiological and/or molecular mechanisms and enhance our knowledge on normal terminal differentiation. Examples include ichthyosis vulgaris with abnormal keratohyaline and corresponding filaggrin mutations; subgroups of autosomal recessive lamellar ichthyosis/ichthyosis congenita characterized by polygonal cholesterol clefts and transglutaminase-1-deficiency or aberrant vesicular structures and ichthyin mutations, respectively; harlekin ichthyosis with specific lamellar body defect and ABCA12 mutations; peculiar keratin cytoskeleton aberrations in epidermolytic hyperkeratosis and other conditions with underlying mutations in differentiation specific keratins. Overall, over the last 35 years, in biopsies of more than 1700 patients with suspicion on keratinization disorders, about 600 could be classified by morphological criteria. Within the last five years, 235 cases were recruited within the German NIRK (Network for Ichthyoses and Related Keratinization Disorders); about 50% (116) revealed diagnostic ultrastructural markers, while in the other cases the respective conditions could be ruled out. The systematic investigations also revealed a bulk of conditions without any specific morphological alterations as well as some unequivocal situations.

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Author(s):	Hans Christian **Hennies**, Katja-Martina Eckl, Aysel Önal-Akan, Marc Nätebus, Janine Kurtenbach
Title:	**The molecular diagnosis of congenital ichthyosis**
	Autosomal recessive congenital ichthyosis (ARCI) represents a group of severe keratinization disorders characterized by both clinical and genetic heterogeneity. It is therefore imperative to characterize the mutation spectrum for ARCI and to facilitate a flexible and instrumental regime for the molecular diagnosis of ARCI. Mutations in several genes have been described in ARCI cases, including TGM1, ABCA12, ichthyin, CYP4F22, and the lipoxygenase genes ALOX12B and ALOXE3. Moreover, further loci must exist, such as a locus on chromosome 12q13. In a recent study of a series of 250 unrelated ARCI patients, we have found mutations in TGM1 in 38% of the cases. We have identified a total of 11 different novel mutations in ALOX12B and ALOXE3 and demonstrated that mutations in the two lipoxygenase genes are the second most common cause for ARCI, each representing 6.8% of the cases. All three genes TGM1, ALOX12B, and ALOXE3 showed extended allelelic heterogeneity. The total number of known mutations in ALOX12B has now increased to 32; several mutations were private ones, and none of them was seen on more than four chromosomes. In contrast, only nine different mutations are known in ALOXE3. Two of these, p.Arg234X and p.Pro630Leu, were found on 11 and 15 different chromosomes, respectively, in our study. Haplotype analysis pointed out that the mutations occurred on different genetic backgrounds and identified them as mutational hotspots. Functional analysis of all missense and splice site mutations found demonstrated that complete loss of function of the enzymes, which are subsequent members of the 12-lipoxygenase pathway metabolizing arachidonic acid in epidermal keratinocytes, underlies the phenotype.

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Author(s):	Akemi **Ishida-Yamamoto** MD, Mari Kishibe MD
Title:	**The Japanese experience on ichthyosis ultrastructure**
	In my opinion, the ichthyosis ultrastructure is an “ultra complicated structure”. Not many people want to know about it, because it is too complicated to understand. To better understand ultrastructure, we need to sort it out in terms of structural-functional relationships. In the process of desquamation of cornified cells, you have six players; corneodesmosomes, cornified cells, membrane traffic, proteases, protease inhibitors, and lamellar granules. We will see the following. 1. What happens when the membrane traffic is abnormal? 2. What happens if there are no protease inhibitors? 3. What will happen if proteases are abnormal in the skin? 4. What if there is no corneodesmosomes?

Abstract

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Author(s):	Vinzenz **Oji**, MD
Title:	**Update of the Moderation Process of the Ichthyosis Classification**
(page 1/2)	The ichthyoses form a clinical and etiologically heterogeneous group of genetic cornification disorders. Popular classification schemes and terminology of these diseases continue to vary greatly between Europe, America/United States and Asian countries. For instance, the same entity may be referred to as "epidermolytic hyperkeratosis", as "bullous congenital ichthyosiform erythroderma" or as "bullous ichthyosis", depending on the continent where it is diagnosed. The initial idea for a Consensus Classification crystallized at the First World Conference on Ichthyosis (August 31 – September 2, 2007) in Münster, which was organized by the German network for ichthyosis and related keratinization disorders (NIRK). Heiko Traupe and I - together with Anders Vahlquist - presented the preliminary draft and ideas of a classification, which were thought to serve as a starting point for a future consensus debate. The proposed preliminary classification is hierarchically structured and based on the four clinical main criteria **non-congenital**, **congenital**, **non-syndromal**, and **syndromal**. Each resulting column can then be classified accordingly to special clinico-genetic aspects, e. g. non-syndromal congenital ichthyoses start with the group of autosomal recessive congenital ichthyosis (ARCI). The term ARCI as such is proposed as an umbrella term for Harlequin ichthyosis, lamellar ichthyosis, congenital ichthyosiform erythroderma, and "congenital ichthyosis with fine/focal scaling" (CIFS as proposed by Anders Vahlquist), etc.. Moreover, it has been suggested that the umbrella term "bullous ichthyosis" is inappropriate for the ichthyotic disorders, which are due to keratin mutations. Expressions like "LI type 1, 2, 3, etc." should be omitted. The key question of the discussion in Münster was: What comes first - the clinical name of the diseases, the genetic diagnosis or the pathophysiologic group? After the conference 2007 a new draft of the classification has been proposed and sent to all colleagues. This manuscript followed the wish of the majority of the participants of the Münster conference, and other colleagues, and proposed that the individual disorders should be referenced with their molecular cause(s), but that the clinical diagnosis remains the guiding principle. The review process of this manuscript (January-March 2008, ~15 reviewers involved) helped to update the classification. The resulting manuscript from March 2008 addresses the following issues (listed in tables):

(page 2/2)	(Update of the Moderation Process of the Ichthyosis Classification)
	1.) Aims of the classification 2.) Definitions and important clinical terms 3.) Proposal for new terms and definitions 4.) Proposed classification of autosomal recessive congenital ichthyoses 5.) Proposed classification of "hyperkeratotic keratinopathies (?)" 6.) Cornification disorders, which can be considered "ichthyosis" (giving an overview on the disease onset, initial clinical presentation, disease course, morphological key features and pathophysiology) 7.) Cornification disorders related to ichthyosis 8.) Proposed overview on the classification of ichthyosis The proposal suggested that "ichthyosis" is a clinical disease concept that is firmly entrenched in the minds of dermatologists, paediatricians and other specialities, which could be still justified. A broad classification of all disorders of ceratinization (DOC) was beyond the scope of the consensus project. One key question concerned the "keratinopathies". Colleagues proposed the names "bullous ichthyosis", or "epidermolytic hyperkeratosis", or suggested novel terms such as "keratinopathy" (E. Sprecher, I. Hausser), or "hyperkeratotic keratinopathy" (A. Taeib), or "keratinopathic ichthyosis" (A. Ishida-Yamamoto). The ongoing second review process (starting in March 2008, ~20 reviewers involved) suggested some modifications, e. g. the exclusion of HID syndrome as separate entity, but also demonstrated controversial aspects, e. g. how to categorize X-linked recessive ichthyosis. Not surprisingly, it appeared increasingly difficult to reach a consensus for the "bullous ichthyoses". New terms being proposed are "keratin hyperkeratosis" (G. Richard) and "congenital keratinopathic ichthyosis" (V. Oji). Because of this debate and in order to "bridge the oceans" (especially with the colleagues in the US) the group felt the need for a consensus conference. It was already at the end of 2007, that Gianluca Tadini in conjunction with the Pierre Fabre company offered to organize a meeting devoted to the discussion of the ichthyosis classification. This very generous offer has now been realized with the first *Ichthyosis Consensus Conference in Sorèze, France, 23.-24.01.2009*. This conference certainly represents a unique event in the history of ichthyosis. Thus, we hope to achieve a consented scheme for the classification of ichthyoses and related diseases that should be useful for clinicians, skin morphologists and molecular biologists alike, and may serve as a reference point for future clinical and molecular research bridging the continents worldwide.

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Author(s):	Hiroshi **Shimizu**, Masashi Akiyama Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
Title:	**The proposal of a clinical classification approach of ichthyosis**
	We would like to discuss the following matters. The Classification of ichthyosis should be: 1) useful for clinicians 2) useful for patients 3) logical and scientific 4) used globally 5) clear cut Points for discussion 1) Keratinopathic ichthyosis: Is this better than hyperkeratotic keratinopathy? 2) What is NBCIE? 3) Hystrix type of Curth Macklin: Is this a good name? 4) Is congenital ichthyosis with fine/focal scaling a distinct phenotype?

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Author(s):	F Morice-Picard (1,2), M Cario-André (1,3), D Lacombe (2), A. Sarasin (4), Alain **Taïeb** (1,3) National reference centres for rare skin disorders (1) and genetic developmental disorders (2); Inserm U 876 (3); Inst G Roussy, CNRS FRE 2839.
Title:	**Genotype-phenotype correlations in trichothiodystrophy**
	Trichothiodystrophy (TTD) is a congenital hair dysplasia with autosomal recessive transmission. Cross banding pattern under polarized light plus trichoschisis and a low sulfur content of hair shafts define the disorder, which is associated with variable and heterogeneous neuroectodermal symptoms. So-called photosensitive forms of TTD (with *in vitro* abnormal DNA repair) are caused by mutations in genes encoding subunits of the transcription factor TFIIH. 10% of non photosensitive patients are known to have *TTDN1* mutations, the specific role of which is unknown. We studied 9 patients recruited at our institution and reviewed 65 cases reported in literature with the aim to collect systematically the clinical features of TTD patients and establish genotype-phenotype correlations. The frequency of congenital ichthyosis, collodion baby type, was significantly higher in the TFIIH mutated group. Hypogonadism was significantly more frequent in the non photosensitive group. There was no statistical difference regarding osseous anomalies. Mutations in TFIIH sub-units leading to abnormal expression in genes involved in epidermal differentiation could explain the particular dermatological features seen in photosensitive cases of TTD. We suggest a new clinico-genetic classification of TTD which may help clinicians confused by the current acronyms used (IBIDS, PIBIDS…). Understanding the TTD ichthyotic phenotype could lead to therapeutic advances in the management of TTD and other types of ichthyoses.

Abstract

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Author(s):	Heiko **Traupe**, Münster, Germany
Title:	**History of the ichthyoses: why is the classification so painful?**
	The recorded history of ichthyosis begins on March 16, 1731, when the English astronomer John Machin presents a member of the Lambert family to the Royal Society of London. In 1808 Roberrt Willan publishes one of the first textbooks of dermatology. He devotes a whole chapter to the description of the Lambert family and uses for their disease the term “ichthyosis”. In 1899 Peukert from Germany redefines “ichthyosis” and restricts its use to those keratinization disorders where the entire skin is affected thus excluding palmoplantar keratoderma and erythrokeratoderma. Around 1900 Riecke classifies ichthyosis into 3 groups and Brocq calls attention to blistering and erythroderma. Around 1929 Siemens contributes greatly to a genetic concept of different types of ichthyosis and from 1953 to 1974 great advances in histological and ultrastructural understanding are made by French and German groups. In 1966 the Americans Frost, Weinstein and van Scott perform sophisticated cellkinetic studies, developing the concept of retention hyperkeratosis for ichthyosis vulgaris and of hyperproliferation hyperkeratosis for congenital ichthyoses. Moreover, they create a complete new nomenclature and coin terms like “lamellar ichthyosis” replacing “ichthyosis congenita” and epidermolytic hyperkeratosis” replacing “bullous congenital ichthyosiform erythroderma”. Nomenclature becomes deeply divided between the continents. In 1983 Williams and Elias propose to classify ichthyoses either as abnormalities of bricks (proteins) or of mortar (lipids). In 1989 Traupe publishes a comprehensive textbook on ichthyoses and proposes a new classification algorithm distinguishing a) isolated vulgar ichthyoses, b) associated (syndromic) vulgar ichthyoses, c) isolated congenital ichthyoses and d) associated (syndromic) congenital ichthyoses. The molecular age of ichthyosis research starts in 1992 when keratin 1 and 10 mutations are identified in bullous congenital ichthyosiform erythroderma.

Abstract

Ichthyosis Consensus Conference

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Author(s):	Maurice A.M. **van Steensel**
Title:	**Why we should want a biological classification of the ichthyoses**
(page 1/2)	For a long time, medicine has sought to understand disease through phenomenology. In the eighteenth and nineteenth centuries, scientists were obsessed with classifying nature and all that is in it, from humans to flowers, in their attempts to understand Nature. Diseases were no exception and this was nowhere more in evidence than in dermatology, where phenomenological cladistics flowered into the “arbre des dermatoses” of d’Alibré. This first ordering of skin disorders has been of tremendous help in laying the foundations for modern skin biology. Its usefulness is amply illustrated by the success of modern genetics in defining the genetic basis of inherited disease. However, the old clinical classification schemes are coming apart at the seams. We need something more comprehensive, flexible and extensible. I argue that a biological classification, complementing the clinical one, will be more useful to us in the years to come. The skin has a limited number of responses available to insults, be they intrinsic or extrinsic. As a result, different biological processes may give rise to similar disease phenotypes. The ichthyoses are a prime example. Classified as scaling skin disorders, they are very heterogeneous and their clinical heterogeneity only partly reflects their genetic diversity. Partly - as exemplified by the group of diseases known as lamellar ichtyosis. Here, several sometimes quite different molecular defects converge onto a single phenotypic spectrum. The clinical classification does not do justice to the molecular diversity because its resolution simply is not high enough. The term “scaling” simply does not do justice to myriad of ways that can lead to the phenomenon. Why is this a problem? Most importantly because it will sooner or later affect the patient. Sooner or later, we will have targeted therapies. If we are to optimally treat our patients, we will have to know their genetic defect. Clinical classification may help to guide molecular diagnosis, but it falls short of providing the fine-grained detail that we will need. It is of note in this context that a biological classification goes beyond a genetic one. Ultrastructural data and functional analyses may also be used. As an example in point, patients with Lelis syndrome look like they have an epidermolytic hyperkeratosis. Clinically they would be classified as having BCIE/EHK. Electron microscopic analysis however shows abnormalities that are also seen in patients with ABCA12 mutations. (...)

(page 2/2)	Why we should want a biological classification of the ichthyoses)
	(…) Why is this a problem? Most importantly because it will sooner or later affect the patient. Sooner or later, we will have targeted therapies. If we are to optimally treat our patients, we will have to know their genetic defect. Clinical classification may help to guide molecular diagnosis, but it falls short of providing the fine-grained detail that we will need. It is of note in this context that a biological classification goes beyond a genetic one. Ultrastructural data and functional analyses may also be used. As an example in point, patients with Lelis syndrome look like they have an epidermolytic hyperkeratosis. Clinically they would be classified as having BCIE/EHK. Electron microscopic analysis however shows abnormalities that are also seen in patients with ABCA12 mutations. Our understanding of skin biology will also benefit from insisting on a molecular classification. Seeing that clinically distinct disorders have a common biological basis can shed new light on hitherto unexplained findings or can lead to novel insights in seemingly unrelated processes. From this it will be evident that I do not propose doing away with clinical observation. Shared phenotypic characteristics point to shared functions for proteins. As an example, Sjögren-Larsson and Chanarin-Dorfman syndromes are both caused by disturbances in lipid metabolism and they therefore share some features. I will not need to dwell on the tremendous gains in knowledge that genetics has given us in such a short time. Focusing on biology rather than on clinical appearances does mean that we will have to agree on definitions because biology allows us to look beyond the surface. Is BCIE of Brocq an ichthyosis or should it be classified as a form of epidermolysis bullosa? Is the scaling that results from a transglutaminase 1 mutation perhaps also due to an adhesion defect, like acral peeling skin syndrome? Or should the latter be reclassified as an ichthyosis? What then to make of Netherton's? I think that it is quite clear that some dramatically different entities are now lumped in one group. We will always need phenomenology to guide us in the clinic, but it must give way to fundamentals if we are to improve treatment for our patients.

Addresses of Participants

Masashi Akiyama

Masashi Akiyama, M.D., Ph.D.
Associate Professor
Department of Dermatology
Hokkaido University Graduate School of Medicine
North 15, West 7, Sapporo 060-8638, Japan
Ph: 81-(0)11-716-1161 ext. 5962
Fax 81-(0)11-706-7820
Email: akiyama@med.hokudai.ac.jp
http://www.med.hokudai.ac.jp/~derma-w/

Blanchet Bardon

Prof. Blanchet Bardon
Department of Dermatology
Saint Louis Hospital
1, Avenue Claude-Vellefaux, 75010 Paris, France
Ph: +33 (0) 1 42 49 99 61
claudine.blanchet-bardon@sls.ap-hop-paris.fr

Christine Bodemer

Prof. Christine Bodemer
Assistance Publique - Hopitaux de Paris
Hopital Necker Enfants Malades - Service de Dermatologie
149 rue de Sevres, 75743 Paris, Cedex 15, France
Ph: +33 144494672
Fax: +33 144494660
Email: Christine.Bodemer@nck.aphp.fr

Philippe Coudiere

Philippe Coudiere, MD
Pierre Fabre Dermatologie
Les Cauquillous, 81500 LAVAUR, France
Ph: +33 (5) 6 268 43779
Fax: +33 (0) 5 63 58 86 63
Email: philippe.coudiere@pierre-fabre.com

Didier Coustou

Didier Coustou, MD
Pierre Fabre Dermatologie
Les Cauquillous, 81500 LAVAUR, France
Ph: +33 (5) 63 58 97 31
Fax: +33 (5) 63 58 86 63
Email: didier.coustou@pierre-fabre.com

John DiGiovanna

John J. DiGiovanna, MD
Professor, Dept. Dermatology
Director, Division Dermatopharmacology
The Warren Alpert Medical School of Brown University and Rhode Island Hospital
JBS-1, 593 Eddy St, Providence, RI 02903, USA
Ph: +1-401-444-7858
Fax: +1-401-444-7439
Email: jdg@brown.edu

Peter Elias

Peter M. Elias, MD
Dermatology (190)
VA Medical Center
4150 Clement Street, San Francisco, CA 94121, USA
Ph: +1-415-750-2091
Fax:+1- 415-750-2106
Email: eliasp@derm.ucsf.edu

Judith Fischer

Judith Fischer, MD, PhD
Directeur de recherche Inserm
CEA, Institut de Génomique
Centre National de Génotypage
Laboratoire Maladies Dermatologiques
2, rue Gaston Crémieux, 91057 Evry, France
Ph: +33 (1) 60878357
Fax: +33 (1) 60878383
Email: fischer@cng.fr

Philip Fleckman

Philip Fleckman, MD
University of Washington, Dept. of Dermatology
Box 356524, Seattle, WA 98195-6524, USA
Ph: +1-206 543-7490
Fax: +1-206 543-2489
Email: fleck@u.washington.edu

Michal Gina

Michal Gina
Universitaire Vaudois
Service de Dermatologie des Hospices
Av de Beaumont 29, 1011 Lausanne, Switzerland
Email: michal.gina@gmx.at

Takashi Hashimoto

Takashi Hashimoto, M.D.
Department of Dermatology
Kurume University School of Medicine
67 Asahimachi, Kurume, Fukuoka 830-0011, Japan
Ph: +81-942-31-7571
Fax: +81-942-34-2620
Email:hashimot@med.kurume-u.ac.jp

John Harper

Prof. Dr. John I. Harper
Great Ormond Street Children's Hospital
Great Ormond Street, London WC1N 3JH, UK
Ph: +44-20-7405 9200
Email: harpej@gosh.nhs.uk

Ingrid Hausser

Dr. Ingrid Haußer
Hautklinik des Universitätsklinikum Heidelberg
Elektronenmikroskopisches Labor
Vossstr. 2, 69115 Heidelberg, Germany
Ph: +49 (06221) 5638591
Fax: +49 (06221) 564481
Email: ingrid_hausser@med.uni-heidelberg.de

Hans Christian Hennies

Dr. Hans Christian Hennies
Cologne Center for Genomics
Abt. für Dermatogenetik, Universität zu Köln
Zülpicher Str. 47, 50674 Köln, Germany
Ph: +49 (221) 4706911
Fax: +49 (221) 4701595
Email: h.hennies@uni-koeln.de

Daniel Hohl

Prof. Daniel Hohl
Hospices Cantonaux - Centre Hospitalier Universitaire Vaudois
Service de Dermatologie des Hospices
Av de Beaumont 29, 1011 Lausanne, Switzerland
Ph: +41 213140350
Fax: +41 213140382
Email: daniel.hohl@hospvd.ch

Alain Hovnanian

Alain Hovnanian, MD, PhD
Professor of Genetics
Coordinator of the Reference Centre for rare skin diseases
Department of Medical Genetics
Director of Department of Genetics
INSERM U563, Pavillon Lefebvre
Purpan hospital BP 3028 31024 Toulouse cedex 03, FRANCE
Ph: (33) 562 74 45 00
fax: (33) 562 74 45 58
Email: alain.hovnanian@inserm.fr

Akemi Ishida-Yamamoto

Dr. Akemi Ishida-Yamamoto
Department of Dermatology
Asahikawa Medical College
Midorigaoka-Higashi 2-1-1-1, Asahikawa 078-8510, Japan
Email: akemi@asahikawa-med.ac.jp
Ph: +81 166 68 2523
Fax: +81 166 68 2529

Sancy Leachman

Sancy Leachman, MD, PhD
University of Utah
Huntsman Cancer Institute
2000 Circle of Hope; Rm 5242, Salt Lake City, UT 84112, USA
Phone: 801-585-9427
Fax: 801-585-7477
Email: sancy.leachman@hci.utah.edu

Pascal Lefrancois

Pascal Lefrancois
Pierre Fabre Dermatologie
Les Cauquillous, 81500 LAVAUR, France

Irene Leigh

Professor Irene Leigh OBE DSc FRCP FMedSci
University of Dundee
College of Medicine, Dentistry and Nursing
Ninewells Hospital
Dundee DD1 95Y
Scotland, UK
Phone: +44 (1382) 632763
Fax: +44 (1382) 644267
Email: i.m.leigh@dundee.ac.uk

Juliette Mazereeuw-Hautier

Dr. Juliette Mazereeuw-Hautier
Dermatology Department
Reference Centre for rare skin diseases
CNRS-UPS UMR 5165, « Différenciation épidermique et autoimmunité rhumatoïde »
CHU Purpan, Place du Dr Baylac TSA40031,
31059 Toulouse, Cedex 9, France
Ph: (33) 561 77 25 40 ou 05 61 32 26 29
fax: (33) 561 77 76 72
Email: mazereeuw-hautier.j@chu-toulouse.fr

Leonard Milstone

Leonard Milstone, MD
Yale University
P.O. Box 208059, 333 Cedar Street, New Haven, CT 06520, USA
PH: +1-203-785-3646
Email: Leonard.Milstone@yale.edu

Vinzenz Oji

Vinzenz Oji, MD
University Hospital Münster
Department of Dermatology
Von-Esmarch-Str. 58
48149 Münster
Germany
Ph: +49-251-8356501
Fax: +49-251-8357279
Email: vinzenz.oji@ukmuenster.de; ojiv@uni-muenster.de

Amy Paller

Paller, Amy, M.D.
Walter J. Hamlin, Professor and Chair of Dermatology
Professor of Pediatrics
Northwestern University
Feinberg School of Medicine
Department of Dermatology
676 N. St. Clair, Suite 1600, Chicago, IL 60611, USA
Ph +1-312-695-3721
Fax +1-312-695-0664
Email: apaller@northwestern.edu

Gabriele Richard

Gabriele Richard, MD, FACMG
Medical Director
GeneDx
207 Perry Parkway, Gaithersburg, MD 20877
Ph: +1-301-519-2100 ext 6122
Fax: +1-301-519-2892
Email: gabi@genedx.com

Matthias Schmuth

Matthias Schmuth, MD
UCSF
4150 Clement St 111F, San Francisco, CA 94121, USA
Email: Matthias.schmuth@i-med.ac.at

Hiroshi Shimizu

Hiroshi Shimizu, MD, PhD.
Professor and Chairman
Department of Dermatology
Hokkaido University Graduate School of Medicine
North 15, West 7, Kita-ku, Sapporo 060-8638, Japan
Ph : +81-11-706-7387
Fax +81-11-706-7820
Email: shimizu@med.hokudai.ac.jp
http://www.derm-hokudai.jp/

Eli Sprecher

Eli Sprecher MD PhD
Department of Dermatology
Tel Aviv Sourasky Medical Center
6, Weizmann Street, Tel Aviv 64239, ISRAEL
Office: +972-3-6974287
Fax: +972-3-6974810
Mobile: +972-52-7360032
Email: elisp@tasmc.health.gov.il

Gianluca Tadini

Dr. Gianluca Tadini
Centro Malattie Cutanee Ereditarie
Istituto di Scienze Dermatologiche
IRCCS Ospedale Maggiore
Via Pace 9, 20122 Milano, Italy
Ph: +39 (02) 55035355
Fax: +39 (02) 55035118
Email: gtadinicmce@unimi.it

Alain Taïeb

Prof Alain Taïeb
Dept of Dermatology & Ped Dermatology
National Reference Center for Rare Skin Diseases
Hôpital St André
1, rue Jean Burguet, 33075 Bordeaux cedex, France
Ph: +33 556794705
Fax: +33 556794975
Email: alain.taieb@chu-bordeaux.fr

Jorge Toro

Jorge R. Toro, M.D.
Genetics Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
6120 Executive Boulevard
Executive Plaza South, Room 7012
Rockville, MD 20892-4562, USA
Ph: +1-301-451-4562
Fax: +1-301-402-4489
Email: toroj@mail.nih.gov

Heiko Traupe

Prof. Dr. Heiko Traupe
Department of Dermatology
University Hospital Muenster
Von-Esmarch-Str. 58, 48149 Muenster, Germany
Ph: +49-251-83-56588
fax: +49-251-83-57279
email: traupeh@mednet.uni-muenster.de

Pierre Vabres

Dr. Pierre VABRES
Dermatologie
Hôpital du Bocage
BP 77908, 21079 DIJON Cedex, FRANCE
Email: pierre.vabres@chu-dijon.fr

Anders Vahlquist

Prof. Anders Vahlquist, MD, PhD
Department of Medical Sciences /Dermatology and Venereology/
Hudkliniken, University Hospital
Akademiska sjukhuset, S-751 85 Uppsala, Sweden
Ph: +46 186112676
Fax: +46 186112680
Email: anders.vahlquist@medsci.uu.se

Maurice Van Steensel

Maurice A.M. van Steensel MD PhD
Maastricht University Center for Molecular Dermatology
Department of Dermatology
University Hospital Maastricht
PO Box 5800, 6202 AZ Maastricht, The Netherlands
Ph: +31433871641
Email: mauricevsteensel@vodafone.nl

Mary Williams

Mary Williams M.D.
Department of Dermatology
UC San Franscisco
Box 0316
1701 Divisadero
San Francisco
CA 94143-0316
Ph: +4153537800
Fax: +4153537850
Email: peteandmarysf@yahoo.com

Brigitte Willis

Brigitte Willis
Department of Dermatology
University Hospital Muenster
Von-Esmarch-Str. 58, 48149 Muenster, Germany
Ph: +49-251-83-57278
fax: +49-251-83-57279
email: brigitte.willis@ukmuenster.de

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