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Abstract (249 words):

Background: Inherited ichthyoses belong to a large, clinically and etiologically heterogeneous group of Mendelian disorders of cornification (MEDOC), typically involving the entire integument. Over the recent years, much 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 two years, eventually leading to the first Ichthyosis Consensus Conference held in Sorèze, France, 23.-24.1.2009, where subcommittees on different issues proposed terminology that was debated until consensus was reached.

Results: It was agreed that at present, the nosology should remain clinically-based. *Syndromic* vs. *non-syndromic* forms provide a useful major subdivision. Several clinical terms and controversial disease names have been redefined: e.g., the group due to keratin mutations is referred to by the umbrella term, *keratinopathic ichthyosis* (KPI) – under which are included *epidermolytic ichthyosis* (EI), *superficial epidermolytic ichthyosis* (SEI), and *ichthyosis Curth-Macklin* (ICM); *autosomal recessive congenital ichthyosis (ARCI)* 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.

Key words: autosomal recessive congenital ichthyosis; ARCI; epidermolytic ichthyosis; EI; genetics; histology; keratinopathic ichthyosis; KPI; Mendelian disorders of cornification; MEDOC; superficial epidermolytic ichthyosis; ultrastructure

Capsule summary (77 words):

- Inherited ichthyoses belong to a large and heterogeneous group of Mendelian disorders of cornification (MEDOC) and involve the entire integument.
- To reach a consensus on terminology and classification by a conference of experts and provide an internationally accepted frame of reference.
- The classification should remain clinically-based and distinguish between *syndromic* vs. *non-syndromic* ichthyosis forms.
- Bullous ichthyosis/EHK is redefined as *keratinopathic ichthyosis* (KPI). ARCI refers to harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosiform erythroderma.

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 many of those disorders, as well as in establishing genotype-phenotype correlations (reviewed in [4-11]). However, there is no universally accepted terminology and classification of the diseases considered under the umbrella term "ichthyosis". Hence, 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' (EHK), 'bullous congenital ichthyosiform erythroderma' 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 (ICC) on the terminology and classification of inherited ichthyoses, held in Sorèze, France (http://www.netzwerk-ichthyose.de/index.php?id=28&L=1). Subcommittees were formed to address controversial issues including both terminology and nosology. The consensus achieved is presented in Tables I-II. Tables III-VIII summarize the clinical and morphological findings of the inherited ichthyoses. Importantly, the clinical classification developed at the conference is consistent with current understanding of their molecular causes and pathophysiology as summarized in Table IX, and should be readily 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 for students. It should guide clinicians towards the correct genotyping of their patients and facilitate communications with investigators. The proposed classification (Table II.1-2) will need to be modified or expanded as new information accrues. A pathophysiologic classification of the ichthyoses and all the MEDOC should be initiated in the future (Table IX).

RECOMMENDED REVISION OF THE TERMINOLOGY AND CLASSIFICATION OF INHERITED ICHTHYOSIS

The generic term 'inherited ichthyosis' refers to all diseases that are *Mendelian disorders of cornification* (MEDOC) affecting all or most of the entire integument. The skin changes are clinically characterized by hyperkeratosis and/or scaling. Despite concerns of 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. Hence, inherited ichthyoses are regarded as one disease group within the greater group of MEDOC. For greater clarity, we redefined some important clinical and dermatological terms that are in common usage (Table I). Importantly, it is of note that the revised classification is based on a consented specific definition of the term *autosomal recessive congenital ichthyosis* (ARCI); and a major change has been achieved for the ichthyoses that are due to 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'), but decisions regarding further testing, i.e. molecular diagnostics, rest upon 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(s). Two principal groups are recognized: *non-syndromic* forms (Table II.1) and *syndromic* forms (Table II.2). This algorithms 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 and epidermolytic ichthyosis), or is it seen in the skin as well as in other organs (prototypes: Sjögren-Larsson syndrome and trichothiodystrophy)?

Noteworthy, *recessive X-linked ichthyosis* (RXLI) is regarded as syndromic, when accompanied by associated manifestations such as testicular maldescent, as well as non-syndromic, when ichthyosis occurs as an 'isolated type' [3] without any 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 of the diseases, e. g. hair abnormalities or neurologic signs (Table II.2).

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

Classification of ARCI

The acronym *ARCI* has been used as an umbrella term for non-syndromic disorders, e. g. *lamellar ichthyosis* (LI) and *congenital ichthyosiform erythroderma* (CIE), as well as for syndromic types of ichthyosis, such as *Netherton syndrome* (NS). We propose that ARCI should be used to exclusively refer to *harlequin ichthyosis* (HI) and disorders of the 'LI/CIE phenotypic spectrum' (Table IV). Harlequin ichthyosis (Figure 2a) was included, because functional null mutations in the *ABCA12* gene cause the disease [15, 16], whereas missense mutations in the same gene may be associated with a

81 milder phenotype that shows collodion membrane at birth and develops into LI [17, 18] or CIE [19, 20],
82 often with palmoplantar keratoderma. Those infants with *harlequin ichthyosis*, who survive the
83 perinatal period, go on to express a severe and very scaling erythroderma [21] (Figure 2b, c).

84 One difficulty of the ARCI classification is the limited genotype-phenotype correlation within the
85 'LI/CIE spectrum'. Mutations in six genes have been described in non-HI ARCI to date, including
86 *TGM1* the gene encoding transglutaminase-1 (TGase-1) [22, 23], the genes *ABCA12* [17] , *NIPAL4* (also
87 known as *ICHTHYIN*) [24], *CYP4F22* [25], and the lipoxygenase genes *ALOX12B* and *ALOXE3* [26]. The
88 report of a large cohort of 520 affected families showed a mutation distribution of 32% for *TGM1*,
89 16% for *NIPAL4*, 12% for *ALOX12B*, 8% for *CYP4F22*, 5% for *ALOXE3*, and 5% for *ABCA12* [27],
90 which approximately correlated with the recent report of 250 patients [28]. At least 22% of the cases
91 did not exhibit mutations in any of the known ARCI genes[27], implying that further loci must exist,
92 such as two loci on chromosome 12p11.2-q13 [29, 30]. A preliminary clinico-genetic correlation based
93 on the recent literature [17-20, 22-45] and our discussions at the consensus conference is given in Table
94 II.1.

95 LI is characterized by coarse and brown/dark scaling (Figure 2e-f). Affected individuals are often
96 born with collodion membrane and pronounced ectropion (Figure 2d). CIE is characterized by fine
97 and white scaling with varying degrees of erythema (Figure 2g,h). Individuals with CIE may also be
98 born with collodion membrane (often less severe), and then transit to generalized fine scaling and
99 pronounced erythroderma [31, 45]. The phenotypes can change over time and in response to treatment,
100 e. g. LI treated with oral retinoids can turn into an erythrodermic ichthyosis with a finer scale
101 pattern [46]. In a recent North American study of 104 patients with non-HI ARCI, mutations in *TGM1*
102 were significantly associated with collodion membrane, ectropion, plate-like scales, and alopecia.
103 Patients, who had at least one mutation predicted to truncate TGase-1, were more likely to have
104 severe hypohidrosis and overheating than those with *TGM1* missense mutations only [35].

105 Clinically other minor ARCI variants/subtypes can be distinguished: *Bathing suit ichthyosis* (BSI) [47]

106 has been attributed to particular *TGM1* mutations that render the enzyme sensitive to ambient
107 temperature (Figure 2i) [32, 42, 43, 48]. The *self-healing collodion baby* (SHCB) representing
108 approximately 10% of all ARCI cases [36, 49] has so far been associated with *TGM1* or *ALOX12B*
109 mutations [37, 44]. The recently described *acral self-healing collodion baby*, i.e. at birth collodion
110 membranes are strictly localized to the extremities and then heal, can also be due to *TGM1*
111 mutations [41].

112

113 **Classification of the keratinopathic ichthyoses (KPI)**

114 The term 'epidermolytic hyperkeratosis' (EHK) derives from the characteristic light microscopic
115 observation of intracellular vacuolisation, clumping of tonofilaments and formation of small
116 intraepidermal blisters as commonly seen in ichthyoses that are due to keratin mutations. Therefore
117 the term EHK is used (by some) as synonymous for 'bullous ichthyosis', 'ichthyosis exfoliativa',
118 'bullous congenital ichthyosiform erythroderma (of Brocq) (BCIE)' or 'ichthyosis bullosa of
119 Siemens'[50-55]. However, the light microscopic features of the cytoskeletal abnormalities due to
120 keratin mutations may not be observed in all instances [56-59]. To replace the long list of various
121 names, which have been used for these ichthyoses - those that are all due to keratin mutations - we
122 propose the novel umbrella term and definition *keratinopathic ichthyosis* (KPI) (Table I). In analogy
123 to the prevalent morphological key features, we then suggest the term *epidermolytic ichthyosis* (EI)
124 as a novel name for the specific disease spectrum that is accompanied by EHK at the ultrastructural
125 level. The term *epidermolytic hyperkeratosis* (EHK) should be used exclusively as an ultrastructural
126 or histopathological descriptor. We propose the novel disease name *superficial epidermolytic*
127 *ichthyosis* (SEI) for the well defined entity 'ichthyosis bullosa Siemens', which in contrast to EI
128 shows a more superficial pattern of epidermolysis, and is caused by mutations in keratin 2, rather
129 than in keratins 1 or 10, as in EI.

130 Clinically, *keratinopathic ichthyoses* show a broad spectrum of skin manifestations and severity

131 (Table V). Widespread skin blistering is characteristic of neonates with EI (Figure 3a), not seen
132 thereafter except for focal blisters. The blistering phenotype present at birth, which is due to loss of
133 mechanical resilience in the upper epidermis, evolves into a hyperkeratotic one ("phenotypic shift")
134 (Figure 3c), which is suggested to be influenced primarily by the abnormal lamellar body (LB)
135 secretion, rather than corneocyte fragility [60]. SEI (Figure 3d) has a milder phenotype than EI and
136 can be distinguished by the lack of erythroderma and by a characteristic "moulting" phenomenon
137 (Figure 3f). Here, light microscopy and ultrastructure reveal cytolysis that correlates with the
138 distinctive expression pattern of keratin 2 in the stratum granulosum or upper stratum spinosum [61].
139 Different features such as distribution, erythema or blistering were used for separating patients with
140 EI into six clinical groups, but the most distinctive characteristic was the involvement of palms and
141 soles (PS 1-3 vs. NPS 1-3) [62]. Palmoplantar keratoderma (PPK) is usually predictive of a *KRT1*
142 mutation (Figure 3e). One explanation is that keratin 9, which is expressed in palms and soles, may
143 compensate for keratin 10 defect, whereas keratin 1 is the only type II keratin expressed in
144 palmoplantar skin [63-65]. However, PPK may occur with *KRT10* mutations as well [66].

145 Hence, similar to pachyonychia congenita or the epidermolysis bullosa simplex group, the vast
146 majority of the KPI arises from autosomal dominant mutations. The resulting mutant keratin is
147 normally expressed but interferes with the assembly and/or function of keratin intermediate
148 filaments (KIF), often leading to KIF aggregation and cytolysis. However, *KRT10* nonsense
149 mutations have been observed that do not lead to the usual "dominant negative effect" and cause an
150 autosomal recessive KPI form [67]. Therefore, *autosomal recessive EI* (AREI) is listed as new
151 separate KPI. For *ichthyosis Curth Macklin* (ICM) [57-59, 68], which represents a very rare form of KPI
152 and shows a unique ultrastructure (described in Table V), we propose to omit the adjective "hystrix"
153 and retain the eponym Curth Macklin. Hystrix skin changes can be observed in other ichthyoses, e.
154 g. KID syndrome (Figure 5c), or in particular types of *ectodermal dysplasia* (ED) [69]. The *annular*
155 *EI* (AEI) (Figure 3e), which is due to *KRT1* or *KRT10* mutations [70, 71], is classified as a clinical
156 variant of EI.

Importantly, linear *epidermolytic nevi*, i.e. those epidermal nevi exhibiting the histopathology of EHK, 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 (Figure 3g, a) [72-74]. Because recognition of this risk is important for genetic counseling, epidermolytic nevi have been shown here (in brackets) in the classification of KPI (Table I.1).

Other diseases considered in the classification of inherited ichthyoses

The inclusion of the disease entities into this classification of inherited ichthyosis rests upon an appropriate clinical disease description and our definition of inherited ichthyosis (see Table I). A detailed consented overview of the disease onset, initial clinical presentation, disease course, cutaneous and extracutaneous findings as well as of the skin ultrastructure is given for each entity: common forms of ichthyosis (Table III), autosomal recessive congenital ichthyoses (Table IV), keratinopathic ichthyoses and *congenital reticular ichthyosiform erythroderma* (CRIE) (Table V), other non-syndromic ichthyosis forms (Table VI), X-linked ichthyosis syndromes (Table VII), and autosomal ichthyosis syndromes with 'prominent hair abnormalities' (Table VIII.1), 'prominent neurological signs' (Table VIII.2), 'fatal disease course' (Table VIII.3) and 'other associated signs' (Table VIII.4).

Diseases that are classically regarded as ichthyosis in the previously published scientific literature and that will continue in the list of ichthyoses are: *Sjögren-Larsson syndrome* [75, 76] (Figure 5b), *Refsum syndrome* [77, 78], *neutral lipid storage disease with ichthyosis* (also referred to as *Chanarin Dorfman syndrome*) (Figure 5g) [40, 79, 80], *ichthyosis follicularis-atrichia-photophobia* (IFAP) *syndrome* (Figure 5d) [81, 82], *Conradi-Hünermann-Happle syndrome* (CDPX2) (Figure 5f)[83, 84], *multiple sulfatase deficiency* (MSD) [85, 86], *congenital reticular ichthyosiform erythroderma* (CRIE) also referred to as ichthyosis variegata [87] (and ichthyosis 'en confettis' [88]) (Figure 4e), and *ichthyosis prematurity syndrome* (IPS) [89, 90] (Figure 5e). In IPS affected pregnancies exhibit

abnormal amniotic fluid both on ultrasound and clinically [91]. It has to be distinguished from the *self-healing collodion baby* (SHCB), because in both diseases the skin heals almost completely soon after birth [89]. Many advances in the heterogeneous field of *trichothiodystrophies* (TTDs) (Figure 5a) 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 (LK) also referred to as *'Camisa variant of Vohwinkel keratoderma'* (Figure 4c) [95-97], the *cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma* (CEDNIK) *syndrome* [98], the *arthrogryposis renal dysfunction cholestasis* (ARC) *syndrome* [99-101], the *mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratoderm* (MEDNIK) *syndrome* [102], the *ichthyosis-hypotrichosis-sclerosing cholangitis* (IHSC) *syndrome* (also known as NISCH syndrome) [103-105], the *ichthyosis hypotrichosis syndrome* (IHS) (Figure 5i) [106] and its allelic variant *congenital ichthyosis-follicular atrophoderma-hypotrichosis-hypohidrosis syndrome* [107, 108], and the *keratosis linearis-ichthyosis-congenital sclerosing keratoderma* (KLICK) (Figure 4f) [109, 110].

Erythrokeratoderma variabilis (EKV) [111-113], which is characterized by migratory erythematous patches and more fixed, symmetric hyperkeratotic plaques often with palmoplantar involvement (Figure 4b), is genetically heterogeneous and can in 50-65% [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 *progressive symmetric erythrokeratodermia* (PSEK) [111, 112] that has a considerable clinical overlap with EKV [113] harbors a distinct MEDOC form, is debated and depends on future genetic data. At present, it is known that PSEK is heterogeneous; and patients of two families diagnosed with PSEK 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 felt that the inclusion of EKV into this

207 classification is appropriate and useful – in accordance with *keratitis ichthyosis deafness* (KID)
208 *syndrome* [118, 119] (Figure 5c) that is identical to ichthyosis hystrix type Rheydt [120] or hystrix-like
209 ichthyosis deafness syndrome [3]. KID syndrome is due to heterozygous mutations in *GJB2*
210 (connexin 26) [121]. Especially patients with congenital presentation have generalized skin
211 involvement. In special cases it may overlap with *Clouston syndrome* that is caused by mutations in
212 *GJB6* (connexin 30) [69, 122].

213 One could argue that *Netherton syndrome* (NS) [123] (Figure 5h) should not be classified with the
214 ichthyoses, since it is characterized by premature desquamation and a thinner rather than thicker
215 SC. However, the clinical features often overlap with the CIE phenotype, and scaling is a common
216 clinical feature. Hence, the consensus was to retain the disorder in the classification. The *peeling*
217 *skin disease* (PSD) (Figure 4d) [124] has to be differentiated from *Netherton syndrome* (NS). Unlike
218 NS, the disease does not show hair anomalies, is not due to *SPINK5* mutations [125], and shows
219 different immunochemical features [126]. It may also be accompanied by atopic diathesis [3, 124], but
220 despite the name we tend to classify the disorder as non-syndromic form.

221

222 **Diseases related to inherited ichthyoses**

223 A certain number of MEDOC forms can be regarded as phenotypically and/or etiologically related
224 to ichthyosis, or have to be considered as differential diagnoses. Examples are palmoplantar
225 keratoderma, which sometimes show non-acral involvement, e. g. *Vohwinkel keratoderma* [127] also
226 caused by a particular dominant *GJB2* mutations (connexin 26) [128], *Mal de Meleda* [129] caused by
227 recessive *SLURP1* mutations [130], and *Papillon-Lefèvre syndrome* [131] caused by recessive *CTSC*
228 mutations encoding cathepsin C [132]. Mutations in keratin 5 or 14 cause *epidermolysis bullosa*
229 *simplex* (EBS) [133, 134], which can initially present with severe neonatal blistering clinically
230 indistinguishable from *epidermolytic ichthyosis* [62, 65, 135]. Importantly, hypohidrosis - a common
231 symptom in ichthyoses, especially ARCI [136] - represents one main criterion for the heterogeneous

group of ED [137, 138]. Generalized erythroderma with scaling, and even collodion membranes, have been described in single cases of *hypohidrotic ectodermal dysplasia* (ED) [139, 140]. One important differential diagnosis of *harlequin ichthyosis* (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 CNS anomalies [144]. *Congenital hemidysplasia-ichthyosiform nevus-limb defect* (CHILD) syndrome [145] that is strictly limited to one half of the body does not fulfill the ichthyosis criterion of a *generalized* cornification disorder and 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 due to X-linked dominant mutations in the *EBP* (CDPX2) and *NSDHL* gene (CHILD), respectively [84, 146]. CDPX2 may present with severe CIE or collodion membrane and is therefore regarded as an ichthyosis (Figure 4f) [147]. *Darier disease* [148, 149] and *Hailey–Hailey disease* [150] are autosomal dominant common genodermatoses often referred to as 'acantholytic disorders'. They represent MEDOC forms, in which the formation and/or stability of the keratinocytic desmosomal adhesion is altered by a defect of a sarco(endo)plasmic reticulum Ca^{2+}-ATPase pump (Darier: *ATP2A2* gene) or a secretory Ca^{2+}/Mn^{2+}-ATPase pump of the Golgi apparatus (Hailey-Hailey: *ATP2C1* gene) [151, 152]. The typical lesions of *Darier disease* - usually beginning in adolescence - are tiny keratotic papules, have a firmly adherent keratin cap, and are most often found in the seborrheic areas (nape), scalp and extremities, but generalized involvement is very rare.