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Spectrum of ichthyoses in an Austrian ichthyosis cohort from 2004 to 2017

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Summary

Background: Ichthyoses are a heterogeneous disease group, which makes clinical classification challenging. An ichthyosis cohort at a center for genodermatoses is presented in detail.

Patients and Methods: Patients with clinically and/or genetically confirmed ichthyosis seen from 2004 to 2017 and listed in a database were included. Disease onset, phenotype, histology, comorbidities and family history were described in detail. In genetically tested patients, the prevalence of various ARCI genes, ARCI phenotypes and syndromic ichthyoses, as well as genotype-phenotype correlation and year/method of genetic testing was assessed.

Results: Of all 198 patients who were included in the cohort, 151 were genetically tested. 81 had ichthyosis vulgaris, 43 X-linked ichthyosis, 38 autosomal recessive congenital ichthyosis (ARCI), 9 keratinopathic ichthyosis (KPI) and one exfoliative ichthyosis. 26 individuals suffered from syndromic ichthyoses. A good genotype-phenotype correlation was observed for common ichthyoses and KPI; the correlation was less good in syndromic ichthyoses. In 91 % of ARCI patients an accurate diagnosis was obtained by genetic testing. In only 33 % of syndromic ichthyoses was the definitive diagnosis suspected before genetic testing, which revealed a causative mutation in 86 % of cases.

Conclusion: This study describes the spectrum of ichthyoses in a center of expertise and shows that genetic testing should become a diagnostic standard for this disease group.

Introduction

Inherited ichthyoses belong to a heterogenous group of Mendelian disorders of cornification and are divided into nonsyndromic forms limited to the skin and syndromic forms with involvement of skin and other organs. Nonsyndromic forms include common ichthyoses such as ichthyosis vulgaris (IV) and X-linked ichthyosis (XLI), as well as rare forms such as autosomal recessive ichthyosis (ARCI), keratinopathic ichthyosis (KPI) and others [1].

Ichthyosis vulgaris is caused by loss-of-function mutations in the *FLG* (filaggrin) gene [2], resulting in an impaired epidermal barrier [3]. Histologically, the granular layer is absent or reduced. The phenotype appears within the first year of life and includes generalized fine scaling, palmoplantar hyperlinearity, and keratosis pilaris. There is a predisposition to atopic manifestations [4].

X-linked ichthyosis is caused by deletions of the *STS* gene, resulting in steroid sulfatase deficiency [5]. The phenotype manifests soon after birth and is characterized by generalized brownish scaling, accentuated on the extensor aspects. Interestingly, the prevalence of *FLG* mutations is increased in individuals with XLI [6].

The clinical presentation and severity of ARCI ranges from harlequin ichthyosis (HI) to lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), and pleomorphic ichthyosis (PI), the latter defined as spontaneous age-dependent phenotype improvement with mild residual scaling in adulthood [1, 7]. Most babies are born with a collodion membrane [1, 8]. Twelve causative genes for ARCI are known currently [7–22].

Keratinopathic ichthyosis is caused by mutations in keratin genes, resulting in epidermolysis of keratinocytes and impaired extracellular lipid membrane formation [23].

Mutations in *KRT1*, *KRT2*, and *KRT10* result in generalized phenotypes characterized by age-related and ichthyosis-type-specific erythroderma, blistering and hyperkeratosis. Keratinopathic ichthyosis mainly includes epidermolytic ichthyosis (EI), superficial epidermolytic ichthyosis (SEI), mosaic forms of EI, and ichthyosis with confetti (IWC) [8, 24–27].

Peeling skin syndrome (PSS) is characterized by superficial exfoliation of the epidermis. One subtype of PSS is autosomal recessive exfoliative ichthyosis (AREI) with mutations in *CSTA* [28, 29].

Syndromic ichthyoses present with generalized scaling of the skin and variable involvement of other tissues or systems [1, 30]. Our cohort included eight different subtypes:

Netherton syndrome (NS) [1] is caused by biallelic mutations in *SPINK5*, which encodes the serine protease inhibitor LEKTI. The stratum corneum thickness is reduced because of accelerated proteolysis of corneodesmosomes by kallikreins [31]. Netherton syndrome usually manifests at birth with CIE and later presents with ichthyosis linearis circumflexa, hair shaft abnormalities, failure to thrive, and atopy with high IgE-levels [32].

Neutral lipid storage disease with ichthyosis (NLSDI) encodes an acyltransferase involved in long-chain fatty-acid-oxidation and which deficiency results in an accumulation of triglycerides in leukocytes, muscle cells, hepatocytes and fibroblasts [33]. It is characterized by generalized ichthyosis, hepatosplenomegaly, myopathy and cataract [34–36].

Keratitis-ichthyosis-deafness (KID) syndrome is characterized by erythroderma, leathery skin, palmoplantar keratoderma, keratitis, and sensorineural deafness [37]. It is caused by mutations in *GJB2*, encoding the gap junction protein connexin-26 [38].

Autosomal recessive keratoderma ichthyosis deafness (ARKID) syndrome, characterized by palmoplantar keratoderma, generalized mild ichthyosis and sensorineural deafness was recently associated with mutations in *VPS33B*. The encoded class-C vacuolar protein is involved in sorting of intracellular molecules to late endosomes and lysosomes, and finally in collagen modification [39].

Ichthyosis prematurity syndrome (IPS), which is characterized by preterm birth and erythrodermic skin with thick vernix caseosa-like scales on the scalp, is caused by biallelic mutations in *SLC27A4*, encoding the fatty acid transporter protein 4 [40].

The common features of trichothiodystrophy (TTD) comprise sulfur-deficient brittle hair (tiger-tail-pattern in polarized light), dystrophic nails, and photosensitivity [41]. Trichothiodystrophy in association with ichthyosis is usually due to mutations in *ERCC2* or *ERCC3*, encoding helicase subunits of the DNA excision repair pathway [42–44].

Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome is caused by either biallelic mutations in *DSG1* or a specific heterozygous missense mutation in *DSP* [45, 46].

Sjögren-Larsson syndrome (SLS) presents mainly with congenital ichthyosis, spastic diplegia or tetraplegia and mild to moderate mental retardation. It is due to biallelic mutations in *ALDH3A2*, encoding the fatty aldehyde dehydrogenase, leading to accumulation of long-chain aliphatic alcohols [47, 48].

Classification of an ichthyosis patient to a distinct form of ichthyosis is challenging even for specialists. Clinically-based algorithms are instrumental in narrowing down the differential diagnosis [30]. As the genetic basis of most ichthyoses is now known, genetic testing becomes the standard procedure for confirmation of the clinical differential diagnosis in rare ichthyoses.

An ichthyosis cohort is analyzed in this retrospective study from a center of expertise.

Materials and Methods

Human subjects

This retrospective analysis included all individuals with clinically suspected or genetically confirmed ichthyoses who were seen in the outpatient department for genodermatoses in Innsbruck, Austria, between 2004 and 2017. Disease onset, phenotype, histology, comorbidities and family history were described in detail for all patients. Only data from genetically tested patients were used for relevant statistical analysis. The clinical diagnosis of ichthyosis was made by two experienced dermatologists (RG, MS) in accordance with the current disease classification [1]. The study was conducted according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients/parents.

Light microscopy and immunohistochemistry

We found histological results in our operating system for 79 of 198 patients. Punch biopsies were fixed in 4 % formaldehyde, paraffin-embedded, sectioned, and stained with hematoxylin-eosin stain. Semithin-sections for electron microscopy were stained with toluidine blue. For immunohistochemistry, paraffin-embedded sections were stained with monoclonal mouse/anti-human FLG-antibody (1 : 50; Novocastra Laboratories Ltd, UK), using the automated preparation system BenchMark XT (Ventana Medical Systems) and the high-temperature antigen unmasking technique according to the manufacturer's instructions.

Transmission electron microscopy

Transmission electron microscopy was used in 36 cases. Patient samples were analyzed after postfixation with reduced osmium tetroxide and ruthenium tetroxide [3, 49]. Ultrathin sections were mounted on Formvar-coated grids, counterstained with uranyl acetate and lead nitrate, and examined with a Jeol-JEM100CX electron microscope (80 kV) or a Philips CM120 (100 kV).

Genetic testing

Sanger sequencing, fluorescence *in situ* hybridization (FISH), and multiplex ligation-dependent probe amplification (MLPA) were performed according to standard protocols. After 2012 MLPA was preferred for diagnosis of XLI. Starting in 2012, panel sequencing was performed with next-generation sequencing (custom made panel or TruSight™ One Panel, Illumina®) after enrichment with the Nextera Rapid Capture Custom Enrichment Kit on a MiSeq or NextSeq 550 System (Illumina®). All known ichthyosis genes (up to 2017) were included in our gene panel. Transcript numbers are listed in online Supplementary Table 6. Data were analyzed with SeqNext software (JSI medical systems).

The common European *FLG* variants c.2282_2285del/p.(Ser761Cysfs*36), c.1501C>T/p.R501* and c.7339C>T/p.R2447* were analyzed with Sanger sequencing. These three mutations and c.9740C>A/p.S3247* were screened with allele-specific PCR in some of the patients, while the *FLG* variants c.3702delG/p.(Ser1235Hisfs*211) and c.6867delAG/p.(Ala2290Profs*129) were analyzed by sizing of fluorescently labeled PCR products [3, 50].

Statistics

Statistical analysis and graphics were performed using Microsoft Excel.

Results

Altogether the cohort included 198 patients, 172 with nonsyndromic and 26 with syndromic forms. The common ichthyoses IV (n = 81) and XLI (n = 43) were most frequently seen, followed by ARCI (n = 38) and KPI (n = 9). Overall 151 patients were genetically tested. Patients who were not genetically tested (mainly due to financial limitations and missing patients´ consent) are mentioned briefly at the beginning of each results section and are described in detail in online Supplementary Table 5, but were not included in relevant statistical analysis.

Nonsyndromic ichthyoses

Eighty-one patients with genetically confirmed or clinically suspected IV were included. A genetic analysis was performed in two thirds of cases (n = 54). In 50 of these patients a mutation in *FLG* was detected. In four patients no *FLG* mutation was detected, but full sequencing of *FLG* was not done. In three of these cases the diagnosis was supported by an absent or greatly reduced granular layer visualized with immunohistology (Table 1a). All except three patients showed palmoplantar hyperlinearity. Palmoplantar hyperlinearity was nondistinctive in two patients. In 44 patients (88 %) only IV was suspected before genetic testing was carried out (Table 3).

Table 1a Spectrum of ichthyoses in an Austrian ichthyosis cohort between 2004 and 2017.

Ichthyosis entity	Genetically confirmed (n)	Unsolved despite genetic testing (n)	Only clinically suspected (n)	Clinically suspected and histologically confirmed (n)	Total (n)
IV	50	4	25	30*	81
XLI	36	0	7	0	43
ARCI	30	3	5	0	38
Keratinopathic	6	0	3	2**	9
Syndromic	18	3	5	0	26
other (PSS)	1	0	0	0	1
in total	141	10	45	32***	198

*25 patients are also counted in “genetically confirmed” and 3 patients are also counted in “unsolved despite genetic testing”.
**Two patients are also counted in “genetically confirmed”.

Table 1b Genetic testing before and after 2012.

Ichthyosis entity	Before 2012 (n)	After 2012 (n)	Total (n)
IV	41	13	54
XLI	24	12	36
ARCI	6	27	33
Keratinopathic	2	4	6
Syndromic	2	19	21
other (PSS)	0	1	1
Total	75	76	151

Abbr.: IV, ichthyosis vulgaris; XLI, X-linked ichthyosis; ARCI, autosomal recessive congenital ichthyosis; PSS, peeling skin syndrome.

Table 2a ARCI – adult phenotype.

Genetic ARCI subtype	LI (n)	CIE (n)	PI (n)	HI (n)	Total (n)
TGM1	9	0	0	0	n = 9
ALOX12B	1	3	3	0	7
ALOXE3	0	2	4	0	6
CYP4F22	0	1	2	0	3
NIPAL4	0	0	2	0	2
SDR9C7	0	0	2	0	2
ABCA12	0	0	0	1	1
Total	10 (34 %)	6 (20 %)	13 (43 %)	1 (3 %)	30 (100 %)

Abbr.: LI, lamellar ichthyosis; CIE, congenital ichthyosiform erythroderma; PI, pleomorphic ichthyosis; HI, harlequin ichthyosis.

Overall 43 patients with genetically confirmed or clinically suspected XLI were included. In seven patients no mutation analysis was done (Table 1a, online Supplementary Table 1). In 83 % of cases XLI was suspected before genetic testing was carried out. In 50 % XLI was the only suspected diagnosis. In approximately 10 % XLI was not primarily suspected (Table 3). In these cases ARCI (one patient was born with a collodion membrane) and IV were suspected, respectively. Two thirds of the patients were genetically tested before 2012 (Table 1a). The genetic approach to diagnosis changed significantly during the period 2004–2017. Before 2012 genetic testing included FISH and serum protein electrophoresis, after 2012 it was done with MLPA. In addition, more histological analyses were done before 2012.

Thirty-eight patients with genetically confirmed or clinically suspected ARCI were included. In five patients no mutation analysis was done and in three patients the skin phenotype correlated with ARCI, but no corresponding mutation was detected (Tables 1a, 2a, b and online Supplementary Table 5). In most cases genetic analysis was performed after 2012 (Table 1b). In 30 patients mutations were detected in seven different ARCI genes, i.e. *TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4* and *SDR9C7*. Mutations in *TGM1* (28 %), *ALOX12B* (21 %) and *ALOXE3* (18 %) were the most frequent. Mutations in *CYP4F22* (9 %), *NIPAL4* (6 %), *SDR9C7* (6 %) and *ABCA12* (3 %) were less frequent (Figure 1a).

A sui generis correlation between genotype and phenotype was present in HI with compound heterozygous mutations in *ABCA12*, although there was only one patient with this most severe form of ARCI. The most frequent ARCI phenotype was PI (43 %), with mutations in *SDR9C7, NIPAL4, ALOX12B, ALOXE3* and *CYP4F22*. Lamellar ichthyosis was observed in 34 % with mutations in *TGM1* and *ALOX12B*. Congenital ichthyosiform erythroderma was seen in 20 % with mutations in *CYP4F22, ALOXE3*, and

Table 2b ARCI – presentation at birth.

Genetic ARCI subtype	Collodion baby (n)	Congenital erythroderma (n)	HI (n)	Dry skin (n)	Unremarkable (n)	Congenital; exact phenotype NA (n)	Total (n)
TGM1	7	0	0	0	0	2	n = 9
ALOX12B	5	1	0	0	0	1	7
ALOXE3	1	5	0	0	0	0	6
CYP4F22	1	0	0	1	0	1	3
NIPAL4	1	1	0	0	0	0	2
SDR9C7	0	0	0	0	2	0	2
ABCA12	0	0	1	0	0	0	1
Total	15 (50 %)	7 (23 %)	1 (3 %)	1 (3 %)	2 (7 %)	4 (14 %)	30 (100 %)

Abbr.: ARCI, autosomal recessive congenital ichthyosis; HI, harlequin ichthyosis; NA, not available.

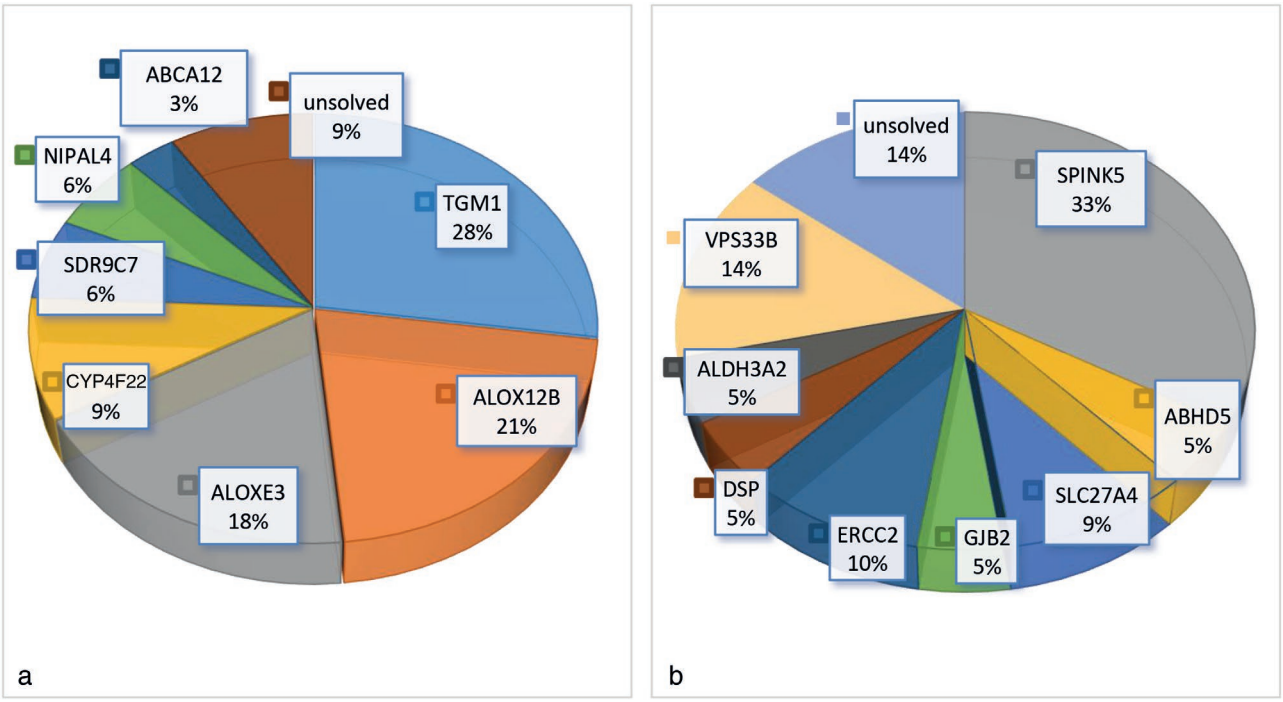

Figure 1 Percentage distribution of ARCI mutations (a). Percentage distribution of syndromic ichthyosis mutations.

ALOX12B (Table 2a). The most common presentation at birth was a collodion membrane (50 %), followed by congenital erythroderma (23 %). In two cases with *SDR9C7* mutations the phenotype at birth was unremarkable and disease onset occurred after two weeks of life (Table 2b). In almost all genetically confirmed cases (97 %) the diagnosis of ARCI was among the suspected differential diagnoses before genetic testing, in 83 % (n = 25) ARCI was the only suspected diagnosis (Table 2c). Nevertheless, clinical assessment rarely allowed for a precise prediction of a specific gene locus in ARCI.

Nine patients with genetically confirmed or clinically suspected KPI were included. In three cases no genetic testing was performed (Table 1a and online Supplementary Tables 3, 5). Two-thirds of the patients were tested after 2012 (Table 1b). The most frequent phenotype was EI, which was presented by two-thirds of the patients. Interestingly, only mutations in *KRT10* were detected in all of these patients. As described in the literature, the phenotype transformed from blisters, erosions, and erythroderma in the neonatal period to prominent hyperkeratosis and a cobblestone pattern

Table 2c ARCI – suspected diagnosis before genetic testing.

Genetic ARCI subtype	ARCI (n)	ARCI or others (n)	Other (n)	Total (n)
TGM1	9	0	0	9
ALOX12B	7	0	0	7
ALOXE3	5	0	1	6
CYP4F22	3	0	0	3
NIPAL4	0	2	0	2
SDR9C7	0	2	0	2
ABCA12	1	0	0	1
Total	25 (83 %)	4 (14 %)	1 (3 %)	30 (100 %)

Abbr.: ARCI, autosomal recessive congenital ichthyosis.

Table 3 Other ichthyoses – suspected diagnosis before genetic testing.

Ichthyosis entity	Only genetically confirmed diagnosis (n)	Genetically confirmed diagnosis or others (n)	Other (n)	NA (n)	Total (n)
IV	44 (88 %)	2 (4 %)	4 (8 %)	0	50
XLI	18 (50 %)	12 (33 %)	4 (11 %)	2	36
Keratinopathic	5 (83 %)	1 (17 %)	0 (0 %)	0	6
Syndromic	6 (33 %)	5 (28 %)	6 (33 %)	1	18

Abbr.: NA, not available; IV, ichthyosis vulgaris; XLI, X-linked ichthyosis.

during later life. All of the patients already had the hyperkeratotic phenotype before genetic testing. Together with a history of neonatal blistering, suspicion of KPI was obvious. One patient showed clear signs of SEI due to the characteristic Mauserung phenomenon on the extremities. Genetic testing revealed a mutation in *KRT2*. The differential diagnosis included PSS. The cohort included one patient with IWC who showed a characteristic phenotype of generalized erythroderma with patches of normal skin and palmoplantar keratoderma. Genetic testing was done at the age of 14 when the patient already showed the typical phenotype. Therefore, the clinical diagnosis was confirmed genetically by a mutation in *KRT10*. One patient with mosaic epidermolytic ichthyosis presented with the phenotype of epidermolytic epidermal nevus (mutation in *KRT1*). In summary there was a clear genotype-phenotype correlation in the patients with KPI (Table 3).

One patient presented with an AREI phenotype of palmoplantar hyperkeratosis, erythema and scaling on the dorsum of the feet and hands. Clinical diagnosis of PSS was confirmed by mutations in *CSTA*.

Syndromic ichthyoses

Twenty-six patients, including eight different disorders and three unsolved cases were seen (online Supplementary Tables 4a, b and 5). In four cases with clinically distinct phenotypes of NS (and in one case with suspected NLSDI and lacking the patient's consent) no genetic testing was done (online Supplementary Table 5). In 86 % of the 21 tested individuals a definitive diagnosis was obtained, but three cases remained unsolved (Figure 1b, online Supplementary Table 4a, b). Most patients were tested after 2012 (Table 1b). Each syndrome was allocated to a specific genotype, but the severity of the phenotype was variable.

The most frequent diagnosis was NS, which was seen in eleven patients and genetically confirmed in seven patients. In more than half of the tested individuals the characteristic phenotype strongly suggested NS prior to testing.

One patient with genetically confirmed NLSDI was included. In this case ARCI and XLI were suspected prior to testing. However, homozygous detection of a mutation in *ABHD5* together with lipid vacuoles in leukocytes and steatosis hepatis led to the correct diagnosis. There was also a second patient who presented a phenotype of congenital ichthyosis and lipid vacuoles in peripheral blood monocytes. This led to the suspicion of NLSDI, but genetic testing was not performed.

One patient had KID syndrome. She fulfilled all clinical criteria except for keratitis. She only suffered from sicca symptoms. The clinically suspected diagnosis was confirmed genetically by a heterozygous mutation in *GJB2*.

Three patients had ARKID syndrome. All of these presented with palmoplantar keratoderma, generalized ichthyosis and deafness. As this syndrome was previously unknown, the initial clinical suspicion was Vohwinkel syndrome. Histology was nonspecific. After the targeted mutation analysis of *GJB2* was found to be negative, whole exome sequencing (WES) revealed mutations in *VPS33B* in these patients [39].

Two patients suffered from IPS. Both were premature deliveries with neonatal asphyxia and congenital ichthyosis. In one patient the suspected diagnosis was ARCI, in the other patient IPS. In both patients a homozygous mutation in *SLC27A4* was detected.

Two patients suffered from TTD; one of them died at age three due to liver failure of unknown origin. Their symptoms included generalized ichthyosis, brittle hair, and developmental delay. Clinical differential diagnoses included trichorrhexis nodosa (NS), Menkes syndrome, ectodermal dysplasia, and TTD. In both cases the correct diagnosis was only confirmed by genetic testing, likely because of the complexity of the syndrome.

This cohort also included two patients with heterozygous mutations in *DSP*, which had been associated with SAM syndrome. One patient presented with palmoplantar keratoderma, onychodystrophy and missing teeth, and was initially thought to suffer from pachyonychia congenita. Since his mother, who carried the same mutation in *DSP*, was also

affected, the patient was diagnosed with SAM syndrome. The other patient presented with generalized scaling, brittle hair, missing eye lashes and recurrent bacterial skin superinfections. Genetic testing did not reveal a pathogenic variant, either by direct *DSP* testing or by panel analysis. The patient was therefore classified as an unsolved case (online Supplementary Table 4b).

One patient suffered from SLS. The onset of ichthyosis was during primary school. Further symptoms included mild spastic (diplegia) of the lower extremities, uveitis, and hypothyroidism. Because of relatively mild neurological symptoms and a lack of intellectual disability the initial clinical suspicion was KPI, EKV and (less likely) SLS. However, the correct diagnosis of SLS was confirmed by a known homozygous mutation in *ALDH3A2*.

These very rare cases show that in syndromic ichthyoses, due to the complex or atypical phenotypes in many cases a definite diagnosis is at least supported, but also made by genetic testing (Table 3). Rarely, even genetic testing is unable to achieve a definite diagnosis, as shown in the unsolved cases (Figure 1b and online Supplementary Table 4b).

Discussion

In most of the individuals with IV and XLI the diagnosis was suspected on clinical and histological grounds (Table 3). The characteristic phenotype with palmar hyperlinearity in IV, the family history and pathognomonic histological features with an absent/reduced granular layer were important clues for the diagnosis. In XLI the presence of brownish scales with a predilection for extensor aspects and the family history were indicative. For common ichthyoses it is possible to establish a distinct genotype-phenotype correlation in most cases.

In this cohort of ARCI, the different phenotypes were distinguished as LI, HI, CIE and PI. Pleomorphic ichthyosis was the most common phenotype with 43 % (Table 2a). This differs from published data from Scandinavian and Arabian ARCI cohorts, where PI was found in approximately 30 % and 2 %, respectively [7, 51, 52]. This can be explained by different relative distributions of the underlying mutations in this ARCI cohort (Figure 1a). Whereas in the Scandinavian cohort mutations in *TGM1* were detected in 42.4 % [51], in this cohort *TGM1* mutations were found in 28 % of all genetically tested ARCI patients. In the Arabian cohort, mutations in *ABCA12* were present in 25.9 % [52], but in this cohort these mutations were only detected in 3 %. However, the Scandinavian authors stated that the number of PI patients might be underestimated because of the transient nature of their skin problems [7].

When analyzing the neonatal phenotype of the ARCI patients, 23 % presented with erythroderma. In 10 % of the patients no skin phenotype or merely dry skin was documented at birth. 50 % of the ARCI patients presented with a collodion membrane, which is less than expected (Table 2b). One explanation for this low percentage is that the exact phenotype at birth was not known in 14 % of ARCI patients. In recently published literature most of the patients presenting as LI and HI, and half of the patients showing mature phenotypes CIE and PI were born with a collodion membrane [9, 51]. For this cohort, this would mean a proportion of collodion babies of about 65 %. The lower frequency of collodion babies in this cohort correlates perfectly with a lower frequency of LI and a higher proportion of subtypes with a mild phenotype.

In 91 % of all ARCI patients in whom a genetic analysis was performed, gene panel analysis uncovered the underlying gene mutation (Figure 1a). However, in 9 % (n = 3) of the patients no mutation was detected, suggesting novel genes or complex mutations as causal for ARCI.

Pigg et al. recently proposed to group IPS with ARCI instead of with the syndromic ichthyoses, since prematurity and its complications are only consequences of the cutaneous pathology which already manifests in utero [51]. Notably, one of our patients with IPS suffered not only from ichthyosis and prematurity, but also from sensorineural deafness, a feature not reported in the literature for IPS before.

Keratinopathic ichthyosis and its subtypes were always suspected correctly on clinical grounds before genetic testing (Table 3), most likely due to the characteristic phenotypic features. A distinct genotype-phenotype correlation was possible, in particular when patients were already presenting the mature phenotype.

In only 33 % of syndromic ichthyoses the definitive diagnosis was suspected before genetic testing was carried out (Table 3). Subsequently, genetic testing revealed a causative mutation in 86 % of cases (Figure 1b), confirming the importance of genetic testing in these rare ichthyoses. Despite genetic testing, it was not possible to establish a definitive diagnosis in 14 % (n = 3); in one of these cases even despite WES.

Fourteen percent of patients with syndromic ichthyoses were diagnosed as having ARKID syndrome, a recently described entity [39]. This might indicate that the phenotype was previously unrecognized. There is no reliable data about its prevalence. However, ARKID numbers from this cohort might be biased due to particular scientific interests in this center.

A precise diagnosis is a prerequisite for genetic counseling. Genetic testing guides the decision for further investigations in order to rule out systemic pathologies and to define the ichthyosis subtype as early as possible. Future clinical trials will depend on well-characterized patient cohorts. Genetic testing is therefore recommended, and it is advisable

to refer patients with ichthyosis to a center of expertise for diagnosis, genetic counseling, and initial treatment.

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