ORIGINAL REPORT

The Clinical Spectrum of Rare Inherited Ichthyosis in China: A Review of Thirty-five Cases

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Inherited ichthyosis comprises a spectrum of genetic disorders related to over 50 pathogenic genes. However, there are limited data summarizing the clinical and molecular characteristics of Chinese patients. To broaden the knowledge of clinical and genetic characteristics of inherited ichthyosis and to optimize disease diagnosis and therapies, cases diagnosed with inherited ichthyosis in 1 tertiary centre from 2019 to 2023 were collected, excluding ichthyosis vulgaris and X-linked recessive ichthyosis, genomic sequencing was then performed, and clinical details of the patients were assessed. A total of 35 patients from Jiangsu and Anhui provinces of China were enrolled, 31 of whom were diagnosed with non-syndromic ichthyosis. Within this group, there were cases of autosomal recessive congenital ichthyosis (18/31), epidermolytic ichthyosis (9/31), and superficial epidermolytic ichthyosis (4/31). Additionally, 4 patients were diagnosed with syndromic ichthyosis, comprising 1 case of Chanarin–Dorfman syndrome and 3 cases of Netherton syndrome. The genetic analysis revealed a total of 47 variants across 13 genes, of which 19 were identified as novel variants. This study describes the clinical spectrum of rare inherited ichthyosis in the Jiangsu-Anhui region of China and further expands the genetic characteristics of the disease.

Key words: congenital ichthyosiform erythroderma; epidermolytic ichthyosis; ichthyosis; Netherton syndrome.

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Inherited ichthyosis constitutes a group of genodermatoses characterized by widespread dry skin, scaling, and hyperkeratosis. Clinical manifestations may extend to abnormalities in skin appendages and other organ systems (1). Timely diagnosis of inherited ichthyosis is imperative due to the diverse prognoses associated with different subtypes. Ichthyosis vulgaris (2) and X-linked ichthyosis (3) are the most common subtypes of ichthyosis. However, it is challenging to diagnose numerous rare inherited ichthyoses primarily based on clinical features (4). In recent years, advancements in genetic testing technology have helped to identify over 50 genes causing inherited ichthyosis (5). Identifying the genotype of inherited ichthyosis is crucial for advancing clinicians' comprehension of the condition, facilitating early diagnosis, and enabling effective intervention for associated complications. Furthermore, it can offer evidence-based recommendations for the daily management of patients with inherited ichthyosis (6, 7).

To enhance our understanding of the genomic characteristics of inherited ichthyosis, we conducted an analysis of 35 patients diagnosed with inherited ichthyosis from Jiangsu and Anhui provinces of China, excluding ichthyosis vulgaris and X-linked ichthyosis. Our study expanded the spectrum of pathogenic variants associated with inherited ichthyosis in this distinct region.

SIGNIFICANCE

Inherited ichthyosis is a group of rare inherited skin disorders with multiple types. Among them, ichthyosis vulgaris and X-linked recessive ichthyosis have a high prevalence and are relatively easy to diagnose, while the diagnosis of rare ichthyoses remains challenging. This study enrolled 35 cases with rare ichthyosis and analysed their clinical and genetic characteristics and heterogeneity. Our genetic analysis revealed a total of 47 variants across 13 genes, of which 19 new variants are first reported here. Thus, this work further expands the clinical and genetic spectrum of ichthyosis and provides more information for dermatologists to help diagnose rare ichthyosis.

MATERIALS AND METHODS

Subjects

From October 2019 to October 2023, we enrolled 35 clinically diagnosed patients with various inherited ichthyosis subtypes (excluding ichthyosis vulgaris and X-linked recessive ichthyosis), recruited from the Genetic Skin Disease Center, Institute of Dermatology, Chinese Academy of Medical Sciences, and Peking Union Medical College. These individuals mainly originated from the Jiangsu–Anhui region in China.

Ethics

The research was approved by the Ethics Committee of the Institute of Dermatology of the Chinese Academy of Medical Sciences and Peking Union Medical College (2019-Clinic-005). The study adhered to the principles and guidelines in the Declaration of Helsinki.

Sample preparation, DNA sequencing, and bioinformatics analyses

Blood samples were collected from all patients and DNA extraction was carried out using a Genomic DNA Kit (Tsingke, Beijing, China). Sanger sequencing was employed for DNA samples from 5 patients (P21, P23, P29, P30, P33), while whole-exome sequencing was performed on DNA samples from an additional 5 patients (P4, P9, P17, P18, P33). The remaining 25 patients underwent testing using a skin next-generation sequencing (NGS) panel comprising 723 target genes (MyGenostics, Beijing, China) (8). Candidate variants identified through next-generation sequencing and family segregation were subsequently validated using Sanger sequencing. Pathogenic variants were determined using pathogenicity prediction tools including REVEL, SIFT, PolyPhen-2, GERP^{++}, and MutationTaster (9).

RESULTS

In our clinic, a comprehensive cohort of 35 patients was evaluated by the same experienced dermatologist. The group comprised 17 males and 18 females, spanning ages from 1 month to 43 years, with 18 individuals below 18 years old. All patients belonged to the Han ethnicity. Genetic testing was performed for all 35 patients, and family members of 19 patients underwent subsequent verification. Initial diagnoses before genetic testing were diverse: 15 patients were diagnosed with congenital ichthyosiform erythroderma (CIE), 3 with lamellar ichthyosis (LI), 9 with epidermolytic ichthyosis (EI), 3 with superficial epidermolytic ichthyosis (SEI), 3 with erythrokeratodermia variabilis (EKV), and 2 with Netherton syndrome. Ultimately, a definitive genetic diagnosis was established for all cases, encompassing 19 novel variants and 10 variants previously reported by our team. Additionally, diagnoses included 18 patients with autosomal recessive congenital ichthyosis (ARCI), 9 with epidermolytic ichthyosis (EI), 4 with SEI, 3 with Netherton syndrome, and 1 with Chanarin–Dorfman syndrome. Detailed patient characteristics and molecular data are summarized in **Table I**.

Autosomal recessive congenital ichthyosis

Among the 18 patients diagnosed with ARCI, various genes were implicated, including *ALOX12B* (3/18), *NIPAL4* (1/18), *CERS3*(1/18), *PNPLA1* (5/18), *SDR9C7* (1/18), *TGM1*(1/18), *ABCA12* (5/18), and *ALOXE3* (1/18). This involved the identification of 13 novel variants and 9 variants previously reported by our team. For patients P1–P3, presenting with either LI or CIE, variants in the *ALOX12B* gene were identified. P1 was born with collodion and diagnosed with CIE, carrying a novel deletion mutation c.488delG and a novel missense mutation c.1876T>C. P2, diagnosed with LI, harboured a novel missense mutation c.1317C>A. P4, also diagnosed with LI, had a novel missense mutation c.500G>C and a novel deletion mutation c.741delC in the *NIPAL4* gene. Patients P6–P10 harboured variants in the *PNPLA1* gene. P6 and P7 (**Fig. 1**A), initially suspected of EKV due to map-like erythroderma and desquamation with seasonal changes, were ultimately found to have mutations in the *PNPLA1* gene. P7 had a novel deletion of exons 3–8. P8–P10 were diagnosed with CIE, including P10 with a novel missense mutation c.106C>T, and P8, who also had a deletion mutation c.3321del in the *FLG* gene. P11, presenting with LI and onychomycosis, which was confirmed by fungal fluorescent staining (Fig. 1B), had variants in the *SDR9C7* gene. P13–P17 had *ABCA12* gene variants characterized by at least 1 heterozygous missense mutation. They did not exhibit the characteristic armour-like thick scales encasement, ectropion, and eclabium at birth that is pathognomonic for harlequin ichthyosis (HI), which typically requires biallelic truncating mutations in *ABCA12* as established by previous genotype–phenotype correlation studies (10). The observed missense variants in these patients may represent a milder allelic variant of *ABCA12*-related ichthyosis. P13–P16 displayed CIE, while P17 (11) showed EKV. P13 had a novel deletion mutation c.7526del and a novel missense mutation c.6233G>C. P14 had a novel missense mutation c.3830-5T>G in intron 26 and a missense mutation c.12064A>T in *FLG*. P15 had novel missense mutations c.2984C>A and c.3304A>G in *ABCA12*. P18, diagnosed with CIE, had a novel missense mutation c.1317C>A in *ALOXE3*.

Keratinopathic ichthyosis (KPI)

Among the 13 patients diagnosed with KPI, 3 genes were implicated: *KRT1* (3/13), *KRT10* (6/13), and *KRT2* (4/13), with a total of 4 novel variants identified in this group. P19–P21 exhibited frameshift mutations in either *KRT1* or *KRT10*. P19 presented with dryness of the entire skin and hyperkeratosis in the palmoplantar, knee, groin, and elbow regions (Fig. 1C), carrying a novel insertion mutation c.1617_1618dupTG in *KRT1*. P20, diagnosed with EI, displayed palmoplantar hyperkeratosis and harboured a novel deletion mutation c.1870_1874del in *KRT1*. P21, presenting with diffuse erythroderma, desquamation, and itching, was found to have a novel insertion mutation c.1636dupA in *KRT10*. In other patients with KPI, P24 exhibited marble-like hyperkeratosis in the lower limbs due to inappropriate care, with a mutation in *KRT10* (Fig. 1D). P26, initially diagnosed as SEI, had a novel

Table I. Clinical and molecular findings in 35 patients with inherited ichthyosis.

Patient code	Gender	Age	Clinical diagnosis	Final diagnosis	Gene	Inheri-tance	Exon	Zygosity	Mutations (cDNA level)	Mutations (protein level)	Type	ACMG
1	M	22m	CIE	ARCI	ALOX12B	AR	exon4	Compound heterozygous	c.488delG[a]	p.R163Pfs*34	Deletion	Likely pathogenic
							exon14		c.1876T>C[a]	p.C626R	Missense	Uncertain
2	M	3 y	LI	ARCI	ALOX12B	AR	exon10	Compound heterozygous	c.1317C>A[a]	p.S439R	Missense	Uncertain
							exon10		c.1350dup	p.L451Afs*27	Insertion	Pathogenic
3	F	10 y	CIE	ARCI	ALOX12B	AR	exon13	Compound heterozygous	c.1694G>C	p.R565P	Missense	Likely pathogenic
							exon11		c.1496G>A	p.R499H	Missense	Uncertain
4	F	6 y	LI	ARCI	NIPAL4	AR	exon3	Compound heterozygous	c.500G>C[a]	p.W167S	Missense	Uncertain
							exon4		c.741delC[a]	p.T248Pfs*138	Deletion	Uncertain
										138		
5	F	21 y	CIE	ARCI	CERS3	AR	exon12	Compound heterozygous	exon12 deletion[b]	/	Deletion	Likely pathogenic
							exon11		c.746A>G[b]	p.K249R	Missense	Uncertain
6	F	30 y	EKV	ARCI	PNPLA1	AR	exon6	Homozygous	c.1300delG[b]	p.A434Hfs*22	Deletion	Pathogenic
7	M	5 y	EKV	ARCI	PANLA1	AR	exon1	Compound heterozygous	c.100G>A	p.A34T	Missense	Pathogenic
							exon3-8		exon3-8 deletion[a]	/	Deletion	Likely pathogenic
8	F	7 m	CIE	ARCI	PNPLA1	AR	exon2	Compound heterozygous	c.434T>C[b]	p.I145T	Missense	Likely pathogenic
							exon2		c.320T>A[b]	p.V107D	Missense	Uncertain
9	F	16m	CIE	ARCI	PNPLA1	AR	exon2	Compound heterozygous	c.377G>A[b]	p.R126H	Missense	Uncertain
							exon1		c.100G>A[b]	p.A34T	Missense	Likely pathogenic
10	M	29 y	CIE	ARCI	PANLA1	AR	exon1	Compound heterozygous	c.106C>T[a]	p.R36W	Missense	Uncertain
							exon1		c.100G>A	p.A34T	Missense	Pathogenic
11	F	23 y	LI	ARCI	SDR9C7	AR	exon1	Homozygous	c.187C>T	p.Q63*	Nonsense	Pathogenic
12	F	13 y	CIE	ARCI	TGM1	AR	exon3	Compound heterozygous	c.463C>T	p.R155W	Missense	Likely pathogenic
							exon5		c.856C>T	p.R286W	Missense	Pathogenic
13	M	32 m	CIE	ARCI	ABCA12	AR	exon51	Compound heterozygous	c.7526del[a]	p.P2509Qfs*5	Deletion	Likely pathogenic
							exon42		c.6233G>C[a]	p.G2078A	Missense	Uncertain
14	F	2 y	CIE	ARCI	ABCA12	AR	exon27	Compound heterozygous	c.3889C>T	p.R1297*	Missense	Pathogenic
							intron26		c.3830-5T>G[a]	/	Splicing	Uncertain
15	F	20 y	CIE	ARCI	ABCA12	AR	exon22	Compound heterozygous	c.2984C>A[a]	p.T995K	Missense	Uncertain
							exon24		c.3304A>G[a]	p.M1102V	Missense	Uncertain
16	F	20 y	CIE	ARCI	ABCA12	AR	exon2	Homozygous	c.130C>T	p.R44W	Missense	Likely pathogenic
17	M	23 y	EKV	ARCI	ABCA12	AR	exon49	Compound heterozygous	c.7247C>T[b]	p.P2416L	Missense	Pathogenic
							exon25		c.3653A>G[b]	p.Y1218C	Missense	Uncertain
18	F	24 y	CIE	ARCI	ALOXE3	AR	exon10	Compound heterozygous	c.1235C>A	p.T412K	Missense	Uncertain
							exon10		c.1189_1209dup[a]	p.N397_H403dup	Insertion	Uncertain
									up	s403dup		
										s403dup		
19	M	3 y	EI	EI	KRT1	AD	exon9	Heterozygous	c.1617_1618dupTG[a]	p.G540Vfs*75	Insertion	Likely pathogenic
20	F	22 y	EI	EI	KRT1	AD	exon9	Heterozygous	c.1870_1874del[a]	p.K624Lfs*28	Deletion	Uncertain
21	M	4 y	EI	EI	KRT10	AD	exon7	Heterozygous	c.1636dupA[a]	p.S546Kfs*35	Insertion	Uncertain
22	F	43 y	EI	EI	KRT10	AD	exon1	Heterozygous	c.467G>A	p.R156H	Missense	Pathogenic
23	F	5 y	EI	EI	KRT10	AD	exon1	Heterozygous	c.467G>A	p.R156H	Missense	Pathogenic
24	F	21 y	EI	EI	KRT10	AD	exon1	Heterozygous	c.466C>T	p.R156C	Missense	Pathogenic
25	F	2 y	EI	EI	KRT10	AD	exon6	Heterozygous	c.1346A>G	p.Y449C	Missense	Pathogenic
26	M	22 y	SEI	EI	KRT10	AD	exon4	Heterozygous	c.911_922delTGGA AATGAATG[a]	p.V304_N307del	Deletion	Uncertain
27	F	6 y	EI	EI	KRT1	AD	exon2	Heterozygous	c.623T>C	p.L208P	Missense	Pathogenic
28	M	25 y	EI	SEI	KRT2	AD	exon7	Heterozygous	c.1459G>A	p.E487K	Missense	Pathogenic
29	M	33 y	SEI	SEI	KRT2	AD	exon7	Heterozygous	c.1459G>A	p.E487K	Missense	Pathogenic
30	M	1 m	SEI	SEI	KRT2	AD	exon7	Heterozygous	c.1459G>A	p.E487K	Missense	Pathogenic
31	M	30 y	CIE	SEI	KRT2	AD	exon7	Heterozygous	c.1459G>A	p.E487K	Missense	Pathogenic
32	M	29 y	CIE	Chanarin–Dorfman syndrome	ABHD5	AR	exon6	Homozygous	c.933dupA[b]	p.R312Tfs*45	Insertion	Likely pathogenic
33	M	12 y	Netherton syndrome	Netherton syndrome	SPINK5	AR	exon26	Compound heterozygous	c.2472_2473delAG	p.K824fs*2	Deletion	Pathogenic
							intron27		c2666+5G>A	/	Splicing	Uncertain
34	M	1 m	CIE	Netherton syndrome	SPINK5	AR	exon15	Compound heterozygous	c.1303-2A>G[a]	/	Splicing	Likely pathogenic
							exon24		c.2260A>T	p.K754*	Nonsense	Pathogenic
35	M	33 y	Netherton syndrome	Netherton syndrome	SPINK5	AR	exon13	Compound heterozygous	c.1111C>T	p.R371*	Nonsense	Pathogenic
							exon21		c.2015+1G>T[a]	/	Splicing	Pathogenic

Novel mutations are marked with "[a]". Novel mutations reported by our group previously are marked with "[b]".
y: years; m: months; CIE: congenital ichthyosiform erythroderma; LI: lamellar ichthyosis; EKV: erythrokeratodermia variabilis; EI: epidermolytic ichthyosis; SEI: superficial epidermolytic ichthyosis; ARCI: autosomal recessive congenital ichthyosis; EI: epidermolytic ichthyosis; AD: autosomal dominant; AR: autosomal recessive.

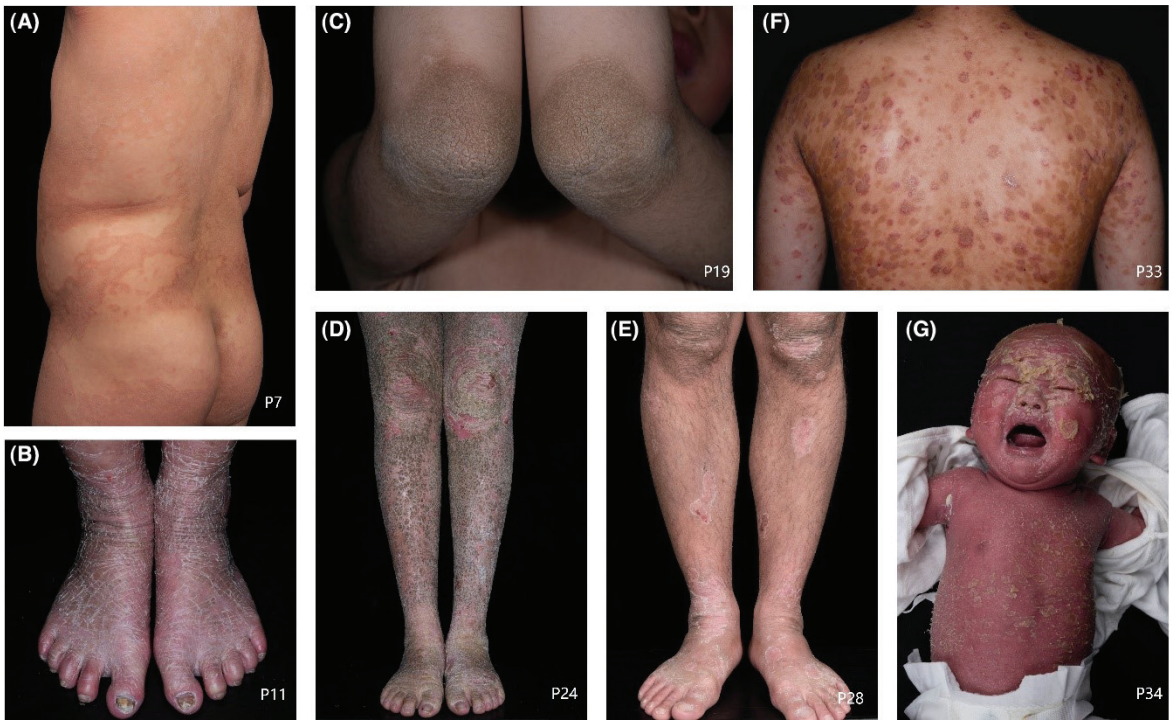

Fig. 1. Clinical photographs of patients with inherited ichthyosis. (A–B) Patients with autosomal recessive congenital ichthyosis. (A) P7, map-like erythroderma and desquamation. (B) P11, lamellar ichthyosis with onychomycosis (37). (C–E) Patients with keratinopathic ichthyosis. (C) P19, hyperkeratosis of the elbow. (D) P24, marble-like hyperkeratosis. (E) P28, collar-like desquamation. (F–G) Patients with Netherton syndrome. (F) P33, ichthyosis linearis circumflexa: erythematous patches with double-edged scales. (G) P34, erythroderma with massive desquamation.

deletion mutation c.911_922delTGGAAATGAATG in *KRT10*. P28, showing collar-like desquamation in the trunk and upper extremities, was found to have a mutation in *KRT2* (Fig. 1E).

Syndromic ichthyosis

In the group of patients with syndromic ichthyosis, 2 genes were implicated: *ABHD5* (1/4) and *SPINK5* (3/4), revealing 2 novel variants within this subgroup. Patient P32, presenting with mild diffuse erythroderma and desquamation, alongside fatty liver and mild hearing loss, was diagnosed with Chanarin–Dorfman syndrome (12). P33–P35 were diagnosed with Netherton syndrome. P33 displayed classical ichthyosis linearis circumflexa (Fig. 1F). P34, born with extensive desquamation, resembling a collodion baby (Fig. 1G), had a novel missense mutation c.1303-2A>G. A splicing mutation (c.2015+1G>T) was detected in P35.

DISCUSSION

Inherited ichthyosis comprises a group of genetically heterogeneous skin disorders with more than 50 known disease-causing genes. Genetic testing plays a pivotal role in the precise classification of its subtypes. In our cohort of 35 patients, we identified 18 cases of ARCI, 13 of KPI, and 4 of syndromic ichthyosis. The majority of patients underwent next-generation sequencing, followed by Sanger sequencing for validation to minimize the likelihood of missed variants. In five cases with a high degree of clinical certainty, Sanger sequencing only was performed. However, as Sanger sequencing detects only targeted genes, it does not rule out the presence of variants in other pathogenic genes.

Genotypic and phenotypic concordance was observed in most patients. According to ACMG guidelines, the majority of identified variants were classified as "pathogenic", while a minority were designated as "uncertain" (see Table I). This classification was primarily due to limited supporting evidence, particularly variants meeting only the PM2_Supporting criterion, preventing definitive classification as "pathogenic" or "likely pathogenic". Nevertheless, our analysis suggests that these variants are likely causative in affected individuals, given the overall genotype–phenotype correlation. ARCI exhibits both genetic and clinical heterogeneity, with biallelic variants identified in at least 13 genes, including *TGM1* (13), *ABCA12* (14), *ALOX12B* (15), *ALOXE3* (15), *CERS3* (16), *CYP4F22* (17), *LIPN* (18), *NIPAL4* (19), *PNPLA1* (20), *SDR9C7* (21), *SLC27A4* (22), *SULT2B1* (23), and *CASP14* (24). The prevalence of pathogenic variants differs geographically. *TGM1* and *NIPAL4* are more frequently detected in Western populations (6), whereas *CYP4F22* and *ABCA12* are predominant in the Middle East (25).

In our cohort, we identified 8 disease-associated genes with a total of 31 variants, including 13 variants and 9

previously first reported by our group. *PNPLA1*(5/17) and *ABCA12* (5/17) were the most frequently implicated genes in Chinese patients, though this finding may be influenced by the relatively small sample size and potential ethnic differences. Notably, 2 ARCI patients (P8 and P14) carried a heterozygous variant in the *FLG*, and the combination of *FLG* variants was also observed in XLI (26) and ARCI with *TGM1* variants (27). Comprehensive analysis revealed that the additional *FLG* variant did not exacerbate the core ichthyosis phenotype but may have contributed to other dermatological features, such as palmar and plantar hyperlinearity.

Traditionally, ARCI is classified into 3 major subtypes based on clinical presentation: CIE, LI, and HI. However, in our cohort, the phenotypic spectrum of ARCI was better delineated into 3 clinical subtypes: CIE (12/18), LI (3/18), and EKV (3/18). Notably, no patient exhibited HI, likely due to its high neonatal mortality rate and the tendency for such cases to be diagnosed in obstetric and paediatric settings rather than dermatology clinics.

Among the patients, 3 exhibited EKV-like lesions, despite carrying distinct mutations. P6 and P7 harboured *PNPLA1* deletion variants and were diagnosed with EKV based on their clinical presentation. P17, another EKV patient, carried compound heterozygous *ABCA12* variants, including 1 of uncertain significance (*ABCA12*: c.3653A>G, p.Y1218C). Notably, none of these patients carried known pathogenic variants in *GJB3*, *GJB4*, or *GJA1*, which are commonly associated with EKV. Detailed physical examinations revealed localized ichthyosis-like features on the extensor surfaces of the limbs and trunk in P6, P7, and P17, supporting their classification as ARCI, complicated by EKV-like features. Previous studies have predominantly linked *ABCA12* variants to HI, LI, and CIE, while *PNPLA1* variants are commonly associated with CIE (28, 29). Interestingly, recent reports have described similar EKV-like lesions in ARCI patients with *ABCA12* (30) and *PNPLA1* variants (31). These findings suggest that EKV-like lesions may represent an additional phenotypic manifestation of ARCI, particularly in cases involving disruptions in genes governing lipid metabolism and transport. The observed genetic and clinical heterogeneity underscores the necessity of genetic testing for accurate classification and diagnosis.

Regarding KPI (32–34), 3 patients in our cohort carried novel frameshift variants in *KRT1* or *KRT10* (35). Notably, none exhibited the characteristic phenotypes of ichthyosis with confetti or ichthyosis hystrix Curth-Macklin, leading to their classification as EI. Long-term clinical follow-up remains crucial for recognizing potential disease progression. While missense variants are typically associated with EI and SEI, P26 presented with only mild desquamation, without overt skin blistering. His *KRT10* variant (c.911_922del, p.V304_N307del) is an in-frame deletion located in the linker region of the KRT10 protein, a region not typically associated with keratinopathies, which may explain his mild phenotype and initial misdiagnosis as SEI.

Among the 3 cases of Netherton syndrome (36), 2 harboured novel variants in the intron of *SPINK5* resulting in aberrant splicing. Notably, patient P34 exhibited a collodion-like massive desquamation, an atypical presentation for Netherton syndrome.

Our study expands the understanding of the genetic landscape of inherited ichthyosis in the Jiangsu–Anhui region of China and highlights the frequent absence of clear genotype-phenotype correlations. Further studies involving larger cohorts and multicentre collaborations are necessary to refine our understanding of this complex disease spectrum. The widespread application of DNA sequencing has significantly improved the differential diagnosis of ichthyosis. Advances in Sanger sequencing and NGS have deepened our comprehension of the pathophysiology of inherited diseases. In our clinic, genetic testing is guided by clinical presentation, allowing for targeted selection of whole-genome sequencing, whole-exome sequencing, or NGS panel testing, with Sanger sequencing used for validation when necessary. This approach enhances diagnostic efficiency while reducing costs. Molecular diagnosis not only facilitates genetic counselling but also serves as a crucial tool for elucidating disease mechanisms and guiding therapeutic development.

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The authors have no conflicts of interest to declare.

REFERENCES

1. Gutiérrez-Cerrajero C, Sprecher E, Paller AS, Akiyama M, Mazereeuw-Hautier J, Hernández-Martín A, et al. Ichthyosis. Nat Rev Dis Primers 2023; 9: 2. https://doi.org/10.1038/s41572-022-00412-3
2. Sybert VP, Dale BA, Holbrook KA. Ichthyosis vulgaris: identification of a defect in synthesis of filaggrin correlated with an absence of keratohyaline granules. J Invest Dermatol 1985; 84: 191–194. https://doi.org/10.1111/1523-1747.ep12264813
3. Mohandas T, Shapiro LJ, Sparkes RS, Sparkes MC. Regional assignment of the steroid sulfatase-X-linked ichthyosis locus: implications for a noninactivated region on the short arm of human X chromosome. Proc Natl Acad Sci U S A 1979; 76: 5779–5783. https://doi.org/10.1073/pnas.76.11.5779
4. Park JS, Saeidian AH, Youssefian L, Kondratuk KE, Pride HB, Vahidnezhad H, et al. Inherited ichthyosis as a paradigm of rare skin disorders: genomic medicine, pathogenesis, and management. J Am Acad Dermatol 2023; 89: 1215–1226. https://doi.org/10.1016/j.jaad.2022.08.012
5. Sun Q, Burgren NM, Cheraghlou S, Paller AS, Larralde M,

Bercovitch L, et al. The genomic and phenotypic landscape of ichthyosis: an analysis of 1000 kindreds. JAMA Dermatol 2022; 158: 16–25. https://doi.org/10.1001/jamadermatol.2021.4242
6. Simpson JK, Martinez-Queipo M, Onoufriadis A, Tso S, Glass E, Liu L, et al. Genotype–phenotype correlation in a large English cohort of patients with autosomal recessive ichthyosis. Br J Dermatol 2020; 182: 729–737. https://doi.org/10.1111/bjd.18211
7. Cheng R, Liang J, Li Y, Zhang J, Ni C, Yu H, et al. Next-generation sequencing through multi-gene panel testing for diagnosis of hereditary ichthyosis in Chinese. Clin Genet 2020; 97: 770–778. https://doi.org/10.1111/cge.13704
8. Liu J, Chen Z, Hu L, Song Z, Mo R, Tsang LS, et al. Investigation of Nagashima-type palmoplantar keratoderma in China: a cross-sectional study of 234 patients. J Dermatol 2023; 50: 375–382. https://doi.org/10.1111/1346-8138.16621
9. Liu Y, Tan Y, Liu J, Song Z, Hu L, Mo R, et al. Novel and founder variants of SERPINA12 in Chinese patients with autosomal recessive palmoplantar keratoderma. Br J Dermatol 2022; 187: 267–270. https://doi.org/10.1111/bjd.21064
10. Akiyama M. ABCA12 mutations and autosomal recessive congenital ichthyosis: a review of genotype/phenotype correlations and of pathogenetic concepts. Hum Mutat 2010; 31: 1090–1096. https://doi.org/10.1002/humu.21326
11. Liu Y, Mo R, Chen Z, Yang Y. Novel variants in ABCA12 cause erythrokeratodermia variabilis. Br J Dermatol 2024; 190: 454. https://doi.org/10.1093/bjd/ljad494
12. liu Y, Chen ZM, Yang Y. Chanarin–Dorfman syndrome: the first case reported in China. Chin J Dermatol 2021; 54: 673–676.
13. Huber M, Rettler I, Bernasconi K, Frenk E, Lavrijsen SP, Ponec M, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. Science 1995; 267: 525–528. https://doi.org/10.1126/science.7824952
14. Lefévre C, Audebert S, Jobard F, Bouadjar B, Lakhdar H, Boughdene-Stambouli O, et al. Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. Hum Mol Genet 2003; 12: 2369–2378. https://doi.org/10.1093/hmg/ddg235
15. Jobard F, Lefèvre C, Karaduman A, Blanchet-Bardon C, Emre S, Weissenbach J, et al. Lipoxygenase-3 (ALOXE3) and 12(R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13.1. Hum Mol Genet 2002; 11: 107–113. https://doi.org/10.1093/hmg/11.1.107
16. Radner FP, Marrakchi S, Kirchmeier P, Kim GJ, Ribierre F, Kamoun B, et al. Mutations in CERS3 cause autosomal recessive congenital ichthyosis in humans. PLoS Genet 2013; 9: e1003536. https://doi.org/10.1371/journal.pgen.1003536
17. Lefèvre C, Bouadjar B, Ferrand V, Tadini G, Mégarbané A, Lathrop M, et al. Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. Hum Mol Genet 2006; 15: 767–776. https://doi.org/10.1093/hmg/ddi491
18. Israeli S, Khamaysi Z, Fuchs-Telem D, Nousbeck J, Bergman R, Sarig O, et al. A mutation in LIPN, encoding epidermal lipase N, causes a late-onset form of autosomal-recessive congenital ichthyosis. Am J Hum Genet 2011; 88: 482–487. https://doi.org/10.1016/j.ajhg.2011.02.011
19. Lefèvre C, Bouadjar B, Karaduman A, Jobard F, Saker S, Ozguc M, et al. Mutations in ichthyin a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. Hum Mol Genet 2004; 13: 2473–2482. https://doi.org/10.1093/hmg/ddh263
20. Grall A, Guaguère E, Planchais S, Grond S, Bourrat E, Hausser I, et al. PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nat Genet 2012; 44: 140–147. https://doi.org/10.1038/ng.1056
21. Shigehara Y, Okuda S, Nemer G, Chedraoui A, Hayashi R, Bitar F, et al. Mutations in SDR9C7 gene encoding an enzyme for vitamin A metabolism underlie autosomal recessive congenital ichthyosis. Hum Mol Genet 2016; 25: 4484–4493. https://doi.org/10.1093/hmg/ddw277
22. Klar J, Schweiger M, Zimmerman R, Zechner R, Li H, Törmä H, et al. Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. Am J Hum Genet 2009; 85: 248–253. https://doi.org/10.1016/j.ajhg.2009.06.021
23. Heinz L, Kim GJ, Marrakchi S, Christiansen J, Turki H, Rauschendorf MA, et al. Mutations in SULT2B1 cause autosomal-recessive congenital ichthyosis in humans. Am J Hum Genet 2017; 100: 926–939. https://doi.org/10.1016/j.ajhg.2017.05.007
24. Kirchmeier P, Zimmer A, Bouadjar B, Rösler B, Fischer J. Whole-exome-sequencing reveals small deletions in CASP14 in patients with autosomal recessive inherited ichthyosis. Acta Derm Venereol 2017; 97: 102–104. https://doi.org/10.2340/00015555-2510
25. Mohamad J, Samuelov L, Malchin N, Rabinowitz T, Assaf S, Malki L, et al. Molecular epidemiology of non-syndromic autosomal recessive congenital ichthyosis in a Middle-Eastern population. Exp Dermatol 2021; 30: 1290–1297. https://doi.org/10.1111/exd.14345
26. Nagtzaam IF, van Leersum FS, Kouwenberg LCM, Blok MJ, Vreeburg M, Steijlen PM, et al. STS pathogenic variants in a Dutch patient cohort clinically suspected for X-linked ichthyosis show genetic heterogeneity. Br J Dermatol 2022; 187: 820–822. https://doi.org/10.1111/bjd.21775
27. Shearer Z, White G, Steed JZ, Brown C, Venable T, Baber M. A novel combination of mutations leading to congenital ichthyosis and ichthyosis vulgaris. Clin Case Rep 2023; 11: e7910. https://doi.org/10.1002/ccr3.7910
28. Hotz A, Kopp J, Bourrat E, Oji V, Süßmuth K, Komlosi K, et al. Mutational spectrum of the ABCA12 gene and genotype-phenotype correlation in a cohort of 64 patients with autosomal recessive congenital ichthyosis. Genes (Basel) 2023; 14. https://doi.org/10.3390/genes14030717
29. Rossel SVJ, Clabbers JMK, Steijlen PM, van den Akker PC, Spuls PI, Middelkamp Hup MA, et al. Expanding the molecular and clinical spectrum of autosomal recessive congenital ichthyosis caused by pathogenic variants in NIPAL4 and PNPLA1 and evaluation of novel therapeutic interventions. J Eur Acad Dermatol Venereol 2023; 37: e1405–e1409. https://doi.org/10.1111/jdv.19340
30. Terrinoni A, Sala G, Bruno E, Pitolli C, Minieri M, Pieri M, et al. Partial loss of function ABCA12 mutations generate reduced deposition of glucosyl-ceramide, leading to patchy ichthyosis and erythrodermia resembling erythrokeratodermia variabilis et progressiva (EKVP). Int J Mol Sci 2023; 24. https://doi.org/10.3390/ijms241813962
31. Liu J, Chen ZM, Yang Y. Mutation analysis of the PNPLA1 gene in three families with congenital ichthyosiform erythroderma. Chin J Dermatol 2022; 55: 685–689.
32. Rothnagel JA, Dominey AM, Dempsey LD, Longley MA, Greenhalgh DA, Gagne TA, et al. Mutations in the rod domains of keratins 1 and 10 in epidermolytic hyperkeratosis. Science 1992; 257: 1128–1130. https://doi.org/10.1126/science.257.5073.1128
33. Rothnagel JA, Traupe H, Wojcik S, Huber M, Hohl D, Pittelkow MR, et al. Mutations in the rod domain of keratin 2e in patients with ichthyosis bullosa of Siemens. Nat Genet 1994; 7: 485–490. https://doi.org/10.1038/ng0894-485
34. Choate KA, Lu Y, Zhou J, Choi M, Elias PM, Farhi A, et al. Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in KRT10. Science (New York, NY) 2010; 330: 94–97. https://doi.org/10.1126/science.1192280
35. Pan Y, Feng C, Wang H, Lee M, Tang Z, Lin Z. Ichthyosis with confetti caused by new and recurrent mutations in KRT10 associated with varying degrees of keratin 10 mislocalization. J Dermatol Sci 2020; 98: 35–40. https://doi.org/10.1016/j.jdermsci.2020.02.005
36. Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet 2000; 25: 141–142. https://doi.org/10.1038/75977
37. Huang X, Chen Z-M, Yang Y. Homozygous nonsense mutation in SDR9C7 in a Chinese patient with autosomal recessive congenital ichthyosis. Int J Dermatol Venereol 2023; 6: 52–54. https://doi.org/10.1097/JD9.0000000000000236