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Clinical and genetic findings in 13 Chinese children with keratinopathic ichthyosis

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ABSTRACT

Importance: Keratinopathic ichthyosis (KPI) represents a group of predominantly autosomal dominant genodermatoses resulting from mutations in the *KRT1*, *KRT2*, or *KRT10* genes. In KPI, the relationship between genotype and phenotype is complex.

Objective: To analyze the clinical manifestations and gene mutations in Chinese patients with KPI.

Methods: Clinical data were collected from 13 children diagnosed with KPI, and peripheral blood DNA samples were extracted from both the patients and their parents Next-generation sequencing was performed using a congenital ichthyosis multi-gene panel, and the selected variants in the patients and their parents were further validated using the Sanger sequencing method.

Results: Genetic analysis identified missense mutations in either *KRT1* or *KRT10* in ten patients exhibiting varying degrees of severity and distinct features of epidermolytic ichthyosis. A missense hotspot mutation in *KRT2* was identified in one patient with superficial epidermolytic ichthyosis. Additionally, two truncation mutations in *KRT10* were detected, leading to the development of generalized ichthyosiform erythroderma. Ear malformation and ectropion at birth, scalp involvement, and palmoplantar hyperkeratosis were observed as early signs of ichthyosis with confetti.

Interpretation: We analyzed the genotype-phenotype correlations in KPI, revealing that the types and locations of different mutations are associated with distinct phenotypic characteristics. Oral acitretin could be considered a treatment option for severe patients at an appropriate dosage and timing.

KEYWORDS

Epidermolytic ichthyosis, Ichthyosis with confetti, Keratinopathic ichthyosis, *KRT1*, *KRT10*, *KRT2*

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INTRODUCTION

Keratinopathic ichthyosis (KPI) is a group of rare inherited non-syndromic ichthyoses caused by mutations in keratin genes, resulting in abnormalities in the keratin intermediate filaments and components of the keratinocyte cell cytoskeleton. KPI includes a spectrum of clinical phenotypes with varying degrees of severity. Mutations in the *KRT1* or *KRT10* genes underlie epidermolytic ichthyosis (EI), ichthyosis with confetti (IWC), ichthyosis Curth-Macklin, cyclic ichthyosis with epidermolytic hyperkeratosis, autosomal recessive and nevoid forms. Additionally, mutations in *KRT2* are associated with superficial EI (SEI).[1,2]

EI is characterized by diffuse erythroderma and blistering at birth, followed by progressive hyperkeratosis in life later. It is typically caused by heterozygous mutations in either the *KRT1* or *KRT10* genes. These mutations disrupt the alignment of keratin protein and the assembly of intermediate filaments in suprabasal keratinocytes, resulting in keratin clumping, cytolysis, cellular collapse, blistering, and impaired barrier function. Approximately 50% of EI cases occur as a result of *de novo* missense mutations.[3,4] SEI caused by mutations in the *KRT2* gene exhibits milder clinical features than the typical form of EI. SEI is characterized by the absence of erythroderma and instead presents with more superficial epidermal fragility. This results in a characteristic shedding phenomenon known as the Mauserung phenomenon.[5] IWC can be caused by heterozygous mutations in either the *KRT10* gene (IWC-I) or the *KRT1* gene (IWC-II). These mutations result in arginine or alanine-rich C-terminal frameshift, leading to the mislocalization of the protein to the nucleus. This impairs the normal function of the keratin network. IWC shares similarities with congenital ichthyosiform erythroderma (CIE) in their presentation at birth. However, IWC is distinguished by the presence of small patches of normal skin that develop within the erythroderma later in life and these patches increase in size over time. Normal skin spots due to independent revertant clones are caused by the loss of a *KRT10* heterozygous mutation, which can be explained by mitotic recombination and revertant mosaicism from the clonal expansion of a corrected stem cell.[6–8]

In KPI, the relationship between genotype and phenotype is complex. Different genes can lead to similar clinical manifestations, and different mutations within the same gene can result in different phenotypes. To gain a better understanding of these genotype-phenotype correlations, we conducted an analysis on 13 Chinese patients.

METHODS

Ethical approval

This study has been approved by the Ethical Committee of Beijing Children's Hospital, Capital Medical University (No. 2018-130), and was conducted according to the Declaration of Helsinki principles. Informed consent was obtained from the parents of all patients.

Patients

Ten patients with EI (P1–P10), one patient with SEI (P11), and two patients with IWC-like (P12 and P13) were clinically diagnosed based on the clinical characteristics by two experienced genetic dermatologists at the Department of Dermatology, Beijing Children's Hospital, respectively. The clinical data of 13 patients aged from 6 months to 6 years was collected. All the patients belonged to non-consanguineous families, and no similar disorders were observed in their family members.

DNA sequencing

Peripheral blood DNA was extracted from the patients and their parents. Genomic DNA was extracted from white blood cells using standard procedures. Next-generation sequencing of a panel of genes involved in inherited ichthyosis including *KRT1, KRT2*, and *KRT10* was performed. The selected variants in the patients and their parents were further validated using the Sanger sequencing method. A protein model of parallel heterodimers of keratin 10 and keratin 1 was performed by PyMOL.

Histopathological examination

Biopsy samples from P1 and P12 were processed for light microscopy, embedded in paraffin, and stained with hematoxylin-eosin according to standard methods.

RESULTS

The clinical findings and identified mutations are summarized in Table 1. Thirteen heterozygous mutations were identified: nine missense mutations (p.Met150Thr, p.Met150Val, p.Asn154His, p.Arg156His [twice], p.Arg156Cys [twice], p.Leu436Pro and p.Leu453Pro), and two truncation mutations (p.Ile446Asnfs135 and p.Gly524Argfs57) in *KRT10*; while one missense mutation (p.Leu187Phe) in *KRT1* and one missense mutation (p.Glu487Lys) in *KRT2*. All the mutations were highly conserved evolutionarily and predicted to be "harmful" according to SIFT, PolyPhen2, and Mutation Taster and were neither present in public databases (1000 Genomes

TABLE 1 Summary of clinical features and mutations in patients with keratinopathic ichthyosis (KPI)

Patient	Sex/Age	Gene/ Exon/ Domain	Mutation	Pheno-type	Blister at an early stage	Erythema	Hyperkeratosis				PPK
							Trunk	Elbow, knee	Neck	Flexural areas	
P1[†]	F/6 months	KRT10/ EX1/1A	c.449T>C, p.Met 150Thr	EI	++++ (reduced in 16 months)	+ (localized)	+	+++	++	++	−
P2[‡]	M/3 years	KRT10/ EX1/1A	c.448A>G, p.Met 150Val	EI	+ (little blister only on ankles every three months in the infant period, no blister at 3 years old)	++++ (generalized ichthyosiform erythroderma at birth) +++ (generalized at 3 years old)	+++	+++	+++	+	−
P3[†]	F/20 months	KRT10/ EX1/1A	c.460A>C, p.Asn 154His	EI	+++ (reduced in 16 months)	+ (localized)	++	++	+	+	−
P4[†]	M/8 months	KRT10/ EX1/1A	c.467G>A, p.Arg 156His	EI	++	−	+	+	++	++	−
P5[†]	M/20 months	KRT10/ EX1/1A	c.467G>A, p.Arg 156His	EI	++++ (reduced in 3 years old)	+ (localized)	+	++++	++	++	−
P6[†]	M/2 years	KRT10/ EX1/1A	c.466C>T, p.Arg 156Cys	EI	+++ (no blister at 9 years old)	+ (localized)	+	+++	+	+	−
P7[†]	F/5 years	KRT10/ EX1/1A	c.466C>T, p.Arg 156Cys	EI	+++	++++ (generalized)	++++	++++	+++	++++	−
P8[†]	M/18 months	KRT10/ EX6/2B	c.1307T>C, p.Leu 436Pro	EI	−	−	+	+++	++	++	−
P9[†]	F/28 months	KRT10/ EX6/2B	c.1358T>C, p.Leu 453Pro	EI	++++ (reduced in 2 years old)	++ (generalized)	++	++	++	+++	−
P10[†]	F/5 years	KRT1/ EX1/1A	c.559C>T, p.Leu 187Phe	EI	++ (reduced in 2 years old)	+++ (localized)	++	++	+	++	++++
P11[†]	F/6 years	KRT2/ EX7/2B	c.1459G>A, p.Glu 487Lys	SEI	+ (reduced in 3 months old)	−	+	++	−	+	−
P12[†]	M/6 months	KRT10/ EX6/2B	c.1336dupA, p.Ile446 Asnfs135	IWC	−	++++ (generalized ichthyosiform erythroderma on the whole body, the large size of scales; ectropion at birth, and ear malformation)	++	++	++	++	+++
P13[‡]	M/3 months	KRT10/ EX7/2B	c.1568dupG, p.Gly524 Argfs57	IWC	−	++++ (generalized ichthyosiform erythroderma on the whole body, the large size of scales; ectropion at birth, ear malformation, unguis inflex, short statures, and chronic diarrhea)	++	++	++	++	++

[†]The mutations were previously published; [‡]the novel mutation detected in the study. EI, epidermolytic ichthyosis; F, female; IWC, ichthyosis with confetti; M, male; PPK, palmoplantar hyperkeratosis; SEI, superficial epidermolytic ichthyosis.

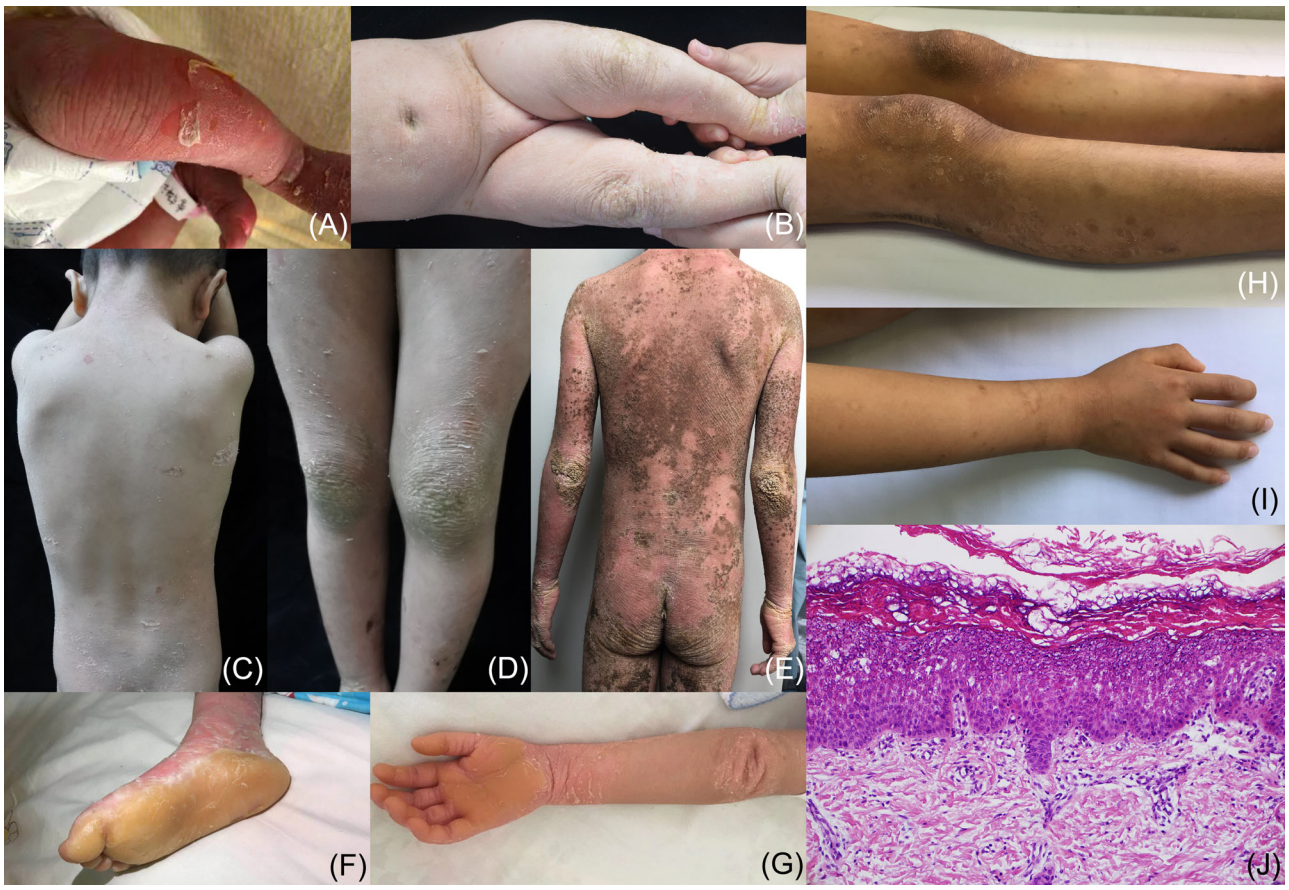

FIGURE 1 Images of the patients with typical epidermolytic ichthyosis manifestations. (A, B) P1 presented broken blisters and erosions on the leg at birth and diffuse hyperkeratosis with localized mild erythema (+) at 6 months old. (C, D) P6 presented diffuse hyperkeratosis, pronounced at the extensor side of the joints (+++) and localized erythema (+) in 2 years old. (E) P7 showed severe diffuse hyperkeratosis on the whole body, pronounced at the extensor side of the joints, and prominent generalized erythema (++++). (F, G) P10 had diffuse hyperkeratosis (++) and severe diffuse PPK. (H, I) P11 has superficial denuded areas of hyperkeratosis on the extensor side of arms and legs typically showing the Mauserung phenomenon. (J) Histological examination of the skin biopsy of P1 showed hyperkeratosis, acanthosis, vacuolar degeneration of suprabasal keratinocytes, and coarse keratohyalin granules in the thickened granular layer (hematoxylin and eosin, original magnification ×200). PPK, palmoplantar hyperkeratosis.

Database or the Exome Aggregation Consortium), nor referenced as single nucleotide polymorphisms (SNPs). Two mutations (p.Met150Val, p.Gly524Argfs57) have not been previously reported. None of the identified mutations were detected in the corresponding parents of the affected probands.

Seven patients (P1, P3–P7, P9) carrying missense mutations in *KRT10* presented with typical EI manifestations (Table 1). These patients had a history of blistering, erythema, and scaling at birth. The blisters were reduced between 16 months and 3 years old. Subsequently, they developed diffuse hyperkeratosis of varying severities in the later stage (Figure 1A–E). P1 (Figure 1A, B), P5, and P9 exhibited the most severe blisters in the early stage. P4 had relatively mild hyperkeratosis, whereas P7 had the most severe diffuse hyperkeratosis on the whole body, which was pronounced on the extensor side of the joints (Figure 1E). Histological examination of the skin biopsy of P1 showed hyperkeratosis, acanthosis, vacuolar degeneration of the suprabasal keratinocytes, and coarse keratohyalin granules in the thickened granular layer (Figure 1J).

P10 with a mutation in *KRT1* presented not only typical EI but also severe diffuse palmoplantar hyperkeratosis (PPK) with sharp demarcation (Figure 1F, G). Oral acitretin ($0.5\,mg{\cdot}kg^{-1}{\cdot}d^{-1}$) reduced hyperkeratosis and PPK, but lead to a slight increase in blisters on the dorsum of his feet.

KRT10-P2 (p.Met150Val) presented with generalized ichthyosiform erythroderma since birth (Figure 2A). During the infant period, the patient experienced occasional blisters only on the ankles every 3 months. By the age of 3 years, diffuse and prominent hyperkeratosis developed on the trunk, limbs, and acral sites without the presence of blisters (Figure 2B). After administration of oral acitretin

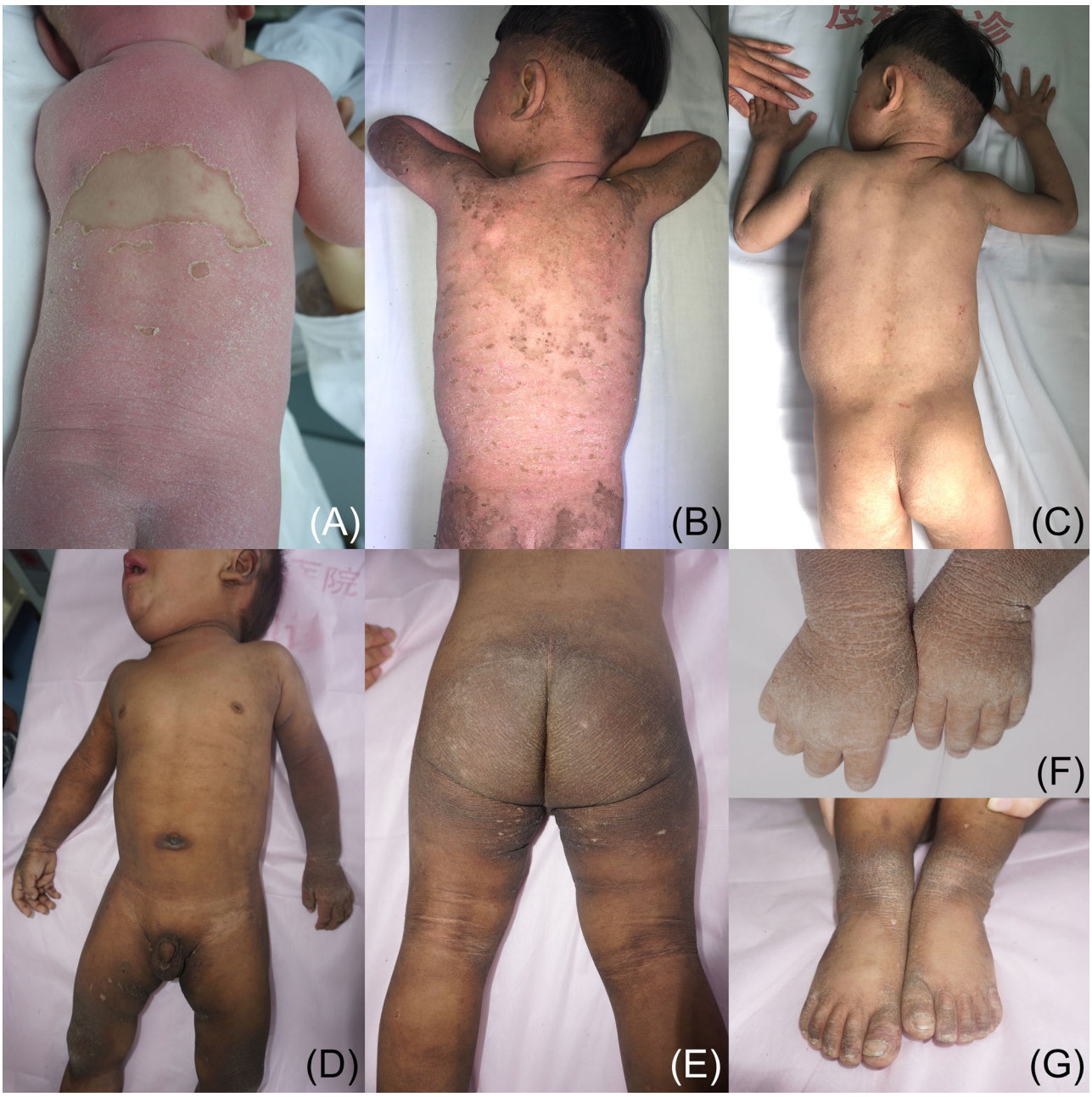

FIGURE 2 The clinical presentation of the patients 2 and 8 with mutations in *KRT10*. (A, B) P2 exhibited generalized ichthyosiform erythroderma (++++) at 4 months old and diffuse prominent hyperkeratosis (+++) on the trunk at 3 years old. (C) The erythema and hyperkeratosis in P2 were reduced after oral acitretin treatment for one month. (D–G) P8 had diffuse and brownish paved hyperkeratosis (++–+++), extensive hyperpigmentation on his body, prominently on the acral sites and extensor side of limbs.

for one month, the erythema and hyperkeratosis were reduced by 60% (Figure 2C). KRT10–P8 (p.Leu436Pro) presented with diffuse and brownish paved hyperkeratosis, prominently on the elbows, knees, acral sites, and extensor side of limbs, and extensive hyperpigmentation on his body. However, he had no history of erythema or blisters (Figure 2D–G).

Patient P11 presented with SEI, resulting from a recurrent mutation (p.Glu487Lys) in *KRT2*. This patient exhibited shallow blisters on the limbs at birth, which were reduced at 3 months of age. She had no erythema, but superficial denuded areas of hyperkeratosis concentrated on the joint areas of arms and legs, and the characteristic shedding (Mauserung phenomenon) (Figure 1H, I).

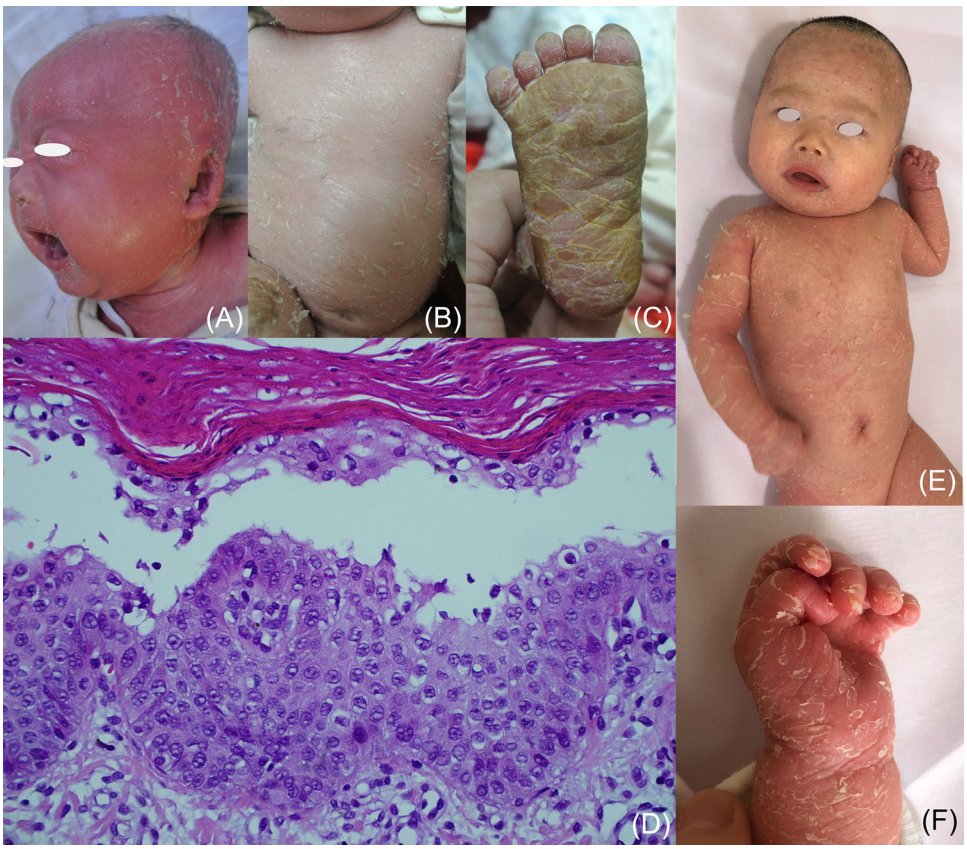

FIGURE 3 Images of the patients 12 and 13 with truncation mutations in *KRT10*. (A–C) P12 showed generalized ichthyosiform erythroderma with large size of scales, ear malformation, and PPK. (D) Histological examination of P12 revealed hyperkeratosis, parakeratosis, epidermal thickness, pronounced perinuclear vacuolization, and absent keratohyalin granules (hematoxylin and eosin, original magnification ×200). (E, F) P13 exhibited generalized ichthyosiform erythroderma with scales and unguis inflex. PPK, palmoplantar hyperkeratosis.

In particular, KRT10-P12 and KRT10-P13 both had generalized ichthyosiform erythroderma since birth. They did not have a history of blistering but had larger size of scales, ectropion at birth, ear malformation, scalp involvement, and PPK (Figure 3A–E). P13 additionally exhibited unguis inflexus (Figure 3F) and chronic diarrhea. Genetic analysis revealed that P12 carried a truncation mutation p.Ile446Asnfs135 in exon 6 of *KRT10*, while P13 had a truncation mutation p.Gly524Argfs57 in exon 7. Histological examination of P12's skin revealed hyperkeratosis, parakeratosis, epidermal thickening, pronounced perinuclear vacuolization, and absence of keratohyalin granules (Figure 3D). The clinical and histological characteristics of these patients indicated early manifestations of IWC-I. Based on the clinical and genetic testing, a clear diagnosis of IWC-I was made.

DISCUSSION

Keratin is a member of the intermediate filament protein superfamily and is the most important protein involved in the development of epidermal structure. It can self-assemble into 10 nm nuclear or cytoskeletal matrix fibers in vitro. The general structure of the keratin protein consists of a conserved rod domain along with four distinct alpha-helical structures (1A, 1B, 2A, and 2B domains), which are separated by linker sequences (L1, L12, and L2). Type II keratin 1 and type I keratin 10 form parallel heterodimers that constitute the intermediate filament cytoskeleton of keratinocytes in the spinous and granular layers.[9,10]

In ten patients with EI, nine missense mutations were found in the 1A domain (exon 1) and 2B domain (exon 6) of *KRT10*, while one missense mutation was found in the 1A domain (exon 1) of *KRT1*. This was consistent with previous studies.[10,11] Eight patients, KRT10-(P1, P3–P7, and P9) and KRT1-P10 all presented with typical EI phenotype, characterized by the presence of blisters, erythema, and hyperkeratosis, which were similar with previous reports.[2–5] However, there were variations in the severity of epidermolysis, skin fragility, erythema, and hyperkeratosis. Patients P1, P5, and P9 had prominent blisters since birth, which need to be distinguished from other disorders, including epidermolysis bullosa, herpes simplex

virus infection, Staphylococcal scalded skin syndrome, and autoimmune bullous diseases. Four patients, KRT10-(P4–P7) all had missense mutations at the same locus, p.Arg156, with two types of hydrophilic amino acid changes (His and Cys), indicating that the p.Arg156 locus might also be a hotspot mutation in Chinese populations, as reported previously in other populations.[2–5] Modeling of Arg156Cys in parallel heterodimers of keratin 10 suggests there is a decrease in the contact distance between the mutant Arg156 and adjacent amino acids. Additionally, modeling of Arg156His suggests there is a steric hindrance between Arg156 and adjacent amino acids (Figure S1). These two molecular changes are likely to alter intra-dimeric interaction and destabilize the keratin 1A dimer interface, which affects mature filament formation and function. Interestingly, no significant differences are observed between the phenotypes caused by these two changes. These four patients presented with the typical phenotype of EI without PPK. P4 (8 months old) had the mildest hyperkeratosis, while P7 (5 years old) had the most severe hyperkeratosis, suggesting the progress of hyperkeratosis with age. A previous study has shown that the majorities of patients with mutations at the p.Arg156 locus were adults or adolescents, characterized by generalized erythema and severe hyperkeratosis.[12]

Interestingly, KRT10-P2 had generalized ichthyosiform erythroderma at birth. This needs to be identified with CIE in autosomal recessive congenital ichthyosis.[13] A novel mutation, p.Met150Val identified in the 1A domain of *KRT10* clarified the diagnosis. The clinical manifestation of KRT10-P2 was obviously different from KRT10-P1 (p.Met150Thr) and two other previously reported patients (p.Met150Thr and p.Met150Arg in KRT10) who all presented with typical EI with prominent blister histories.[3] The modeling of Met150Val and Met150Thr suggests an increase in the contact distance between the mutant Met150 and adjacent amino acids (Figure S1). While Met and Val are hydrophobic amino acids, Thr is a hydrophilic neutral amino acid, and Arg is a hydrophilic amino acid with a positive charge. The loss of hydrophobicity resulting from Thr and Arg substitutions contributes to a more severe phenotype than the Val substitution. We considered that the different polarities and charge properties of amino acids could also result in different tertiary structural conformations of proteins,[14] with different degrees of damage to the stability of the K1/K10 heterodimer, leading to different clinical manifestations. The recommendation for the dosage of acitretin in ichthyosis was 0.5–1 $mg \cdot kg^{-1} \cdot d^{-1}$.[15] KRT10-P2 had a good response to oral acitretin ($0.5\ mg \cdot kg^{-1} \cdot d^{-1}$). This indicates that oral acitretin may be a suitable treatment option.

Moreover, we found KRT10-P8 exhibited diffuse and brownish-paved hyperkeratosis and extensive hyperpigmentation. The mutation Leu436Pro is located in the middle of a helix, and modeling analysis suggests that it results in steric hindrance and a decrease in the contact distance between the mutant Leu436 and adjacent amino acids (Figure S2). This may disrupt intra-dimeric interactions and destroy the helical structure. This mutation has been reported in only one patient who had a similar phenotype but with relatively limited skin lesions.[16] We assumed that p.Leu436Pro mutation may be related to a distinct phenotype of EI characterized by brown hyperkeratosis, without the presence of erythema or blisters.

P10 with a recurrent mutation p.Leu187Phe located at the helix initiation peptides of *KRT1* developed an EI phenotype and severe diffuse PPK, similar to the patients with p.Leu187Phe mutations and p.Asn188 residue mutations (p.Asn188Ser, p.Asn188Thr, and p.Asn188Lys).[17] Modeling of Leu187Phe suggests the presence of steric hindrance that may lead to protein structural damage (Figure S1). PPK was not found in the other nine KRT10-EI patients, confirming that *KRT1* mutations differed from *KRT10* in the presence of significant PPK.[18] Systemic acitretin ($0.5\ mg \cdot kg^{-1} \cdot d^{-1}$) for patient P10 significantly reduced hyperkeratosis and PPK, and improved the quality of life, although there was a potential increased risk of blister formation. Therefore, the dosage and timing for acitretin use need to be considered, preferably using a lower dosage ($0.5\ mg \cdot kg^{-1} \cdot d^{-1}$) and at the age when hyperkeratosis symptoms are more pronounced and blistering is relieved.

In contrast to patients with EI, patient P11 had a very shallow blister history and localized superficial denuded areas of hyperkeratosis without erythroderma. We made a clinical diagnosis of SEI, which was later confirmed by the identification of the hotspot mutation p.Glu487Lys in *KRT2*. Most patients with p.Glu487Lys have not exhibited erythroderma.[19]

Although KRT10-P2, P12, and P13 all had generalized ichthyosiform erythroderma in the infant period, P12 and P13 had a larger area of erythroderma involving the whole body, larger scales, and no history of blistering. Although P12 and P13 did not have small confetti-like spots of almost normal skin, they had other features of IWC-I, such as generalized ichthyosiform erythroderma, ectropion at birth, ear malformation, scalp involvement, and PPK.[7] Special pathological characteristics of P12 could be distinguished from EI and CIE, in particular the existence of parakeratosis, absence of keratohyalin granules and perinuclear vacuolization.[6] P12 and P13 both had truncation mutations. In IWC-I, various genetic changes have been found, such as deletions, insertions, duplications, or splice site mutations in exon 7 and flanking introns in the tail domain of *KRT10*. All the mutations could lead to replacement of glycine/serine-rich keratin 10 tail with arginine or

alanine-rich frameshift sequences (Table S1).[7,20] Although the p.Ile446Asnfs135 mutation in exon 6 is located in the 2B domain of *KRT10*, near but not exactly in the tail domain, it also led to an arginine-rich C-terminal peptide with a premature stop, similar to the p.Gly524Argfs57 mutation in the tail domain (Table S2).

We analyzed the genotype and phenotype characteristics of 42 patients with IWC-I in previous literature and this study (Table S1) and found that IWC-I had a broad phenotypic spectrum without apparent genotype-phenotype correlations. In the 42 patients, 27 mutations in *KRT10* were identified, including deletion/insertion mutations (10), duplication mutations (9), intron mutations (8), and missense mutations leading to abnormal splicing (1). Most patients had these common characteristics including ichthyosiform erythroderma at birth, scales and hyperkeratosis, the confetti-like healthy spots mostly appeared at 2–16 years old, PPK, short statures, ectropion of eyes, hypertrichosis and ear malformation. Some patients also presented with hyperplasia of the nipples, joint contractions, large lunule/long nail plates, unguis inflex, reduced finger length, scalp involvement, hyperpigmentation, pruritus, and reduced eyebrows/eyelashes. The rare manifestations of IWC-I included strabismus, hair loss, sepsis, facial dysmorphism, symblepharon, and diarrhea. Meanwhile, we found that neurological and psychomotor abnormalities (6) in IWC-I were not rare. Furthermore, multiple cutaneous squamous cell carcinomas and malignant melanoma had been found in IWC-I patients.[21,22] Particularly, the mutation c.1336dupA found in P12, had been reported in one typical IWC-I patient previously. He had some clinical manifestations that were not found in patient P12, such as unguis inflexus, large lunulae, long nail plates, decreased finger length, joint contractions, and numerous pale spots that appeared after 3 years of age.[23] The mutation c.1568dupG in P13 had not been reported before, he had extra features than P12, such as unguis inflex, short statures, and chronic diarrhea. The revertant confetti-like spots of almost healthy skin that are widely distributed in IWC-I typically appear in early childhood or puberty, and increase in number and size over time.[6,20,23] As P12 and P13 were only 6 and 3 months old infants, we strongly recommend a careful examination of the whole body during the further long-term follow-up to find the appearance of such spots, and development of phenotypes, and monitor the risk of malignant tumors.

In conclusion, our study adds new data to the genotype-phenotype correlations of KPI. In patients with EI, mutations at the same site in *KRT10* can lead to different severities, and p.Arg156 may be a hotspot mutation locus. A novel missense mutation p.Met150Val in *KRT10* resulted in ichthyosiform erythroderma with very mild blisters in the early stages, and a missense mutation p.Leu436Pro in *KRT10* led to diffuse brown hyperkeratosis and hyperpigmentation without erythema or blister. Acitretin should be considered as a treatment option for severe cases. A duplication mutation in exon 6 and a novel duplication mutation in exon 7 of *KRT10* leading to the arginine-rich truncated C-terminal peptides, contributed to the early performance of IWC-I. The detection of specific IWC-I genotypes can facilitate early diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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