Annular epidermolytic ichthyosis: An exceptional mild subtype of epidermolytic ichthyosis without genotype and phenotype correlation

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INTRODUCTION

Annular epidermolytic ichthyosis (AEI) is a rare subtype of epidermolytic ichthyosis (EI) characterized by recurrent flares of erythematous and scaly lesions alternating with periods of almost normal skin with or without associated palmoplantar keratoderma (PPK).[1] We report on 2 different patients with AEI showing pathogenic variants in the *KRT1* and *KRT10* genes respectively, and review the main clinical, histologic and molecular findings of this exceptional subset of EI.

Abbreviations used:

AEI: annular epidermolytic ichthyosis
EI: epidermolytic ichthyosis
KRT: keratin
PPK: palmoplantar keratoderma

CASE REPORTS

Case 1

A 6-month-old boy was brought for consultation because of blisters and erosions since birth. The child had been born at term by vaginal birth to a healthy mother. Maternal family background was unremarkable, and paternal family history could not be tracked. On physical examination, there were annular erythematous and scaly lesions on the diaper area and proximal lower extremities. There was mild hyperkeratosis on the armpits, elbows, and intergluteal fold, as well as superficial blisters on the palms and soles. Pathologic analysis showed hyperkeratosis with epidermal detachment within the granular layer and acantholysis in the upper spinous layers. Targeted DNA sequencing of the *KRT1* gene from peripheral blood identified a heterozygous missense variant c.1436T>C; p.(Ile479Thr) in *KRT1*. After 2 years of follow-up, the patient developed diffuse PPK and continues to show recurrent crops of transient annular scaly lesions on the lower portion of the trunk (Figs 1 and 2).

Case 2

A 3-month-old boy, born at term to healthy, nonconsanguineous parents, was brought for consultation for recurrent crops of cutaneous lesions. Large areas of blisters and erosions over the genital area and limbs were observed shortly after birth. On physical examination, there were transient annular polycyclic erythematous plaques over the trunk, knees, ankles, and lateral aspects of the feet and upper limbs (Figs 3 and 4). Palms and soles were uninvolved. Periods of almost complete clearing were observed. Biopsy of an erythematous and scaly lesion on the trunk showed thick hyperkeratosis with foci of parakeratosis, hypergranulosis with prominent and coarse keratohyalin granules,

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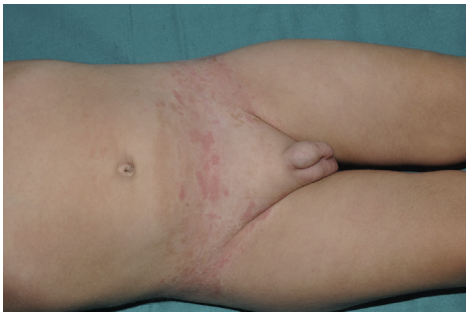

Fig 1. Case 1: clinical findings when the patient was 2 years old, showing annular erythematous and scaly lesions on the diaper area and inguinal folds.

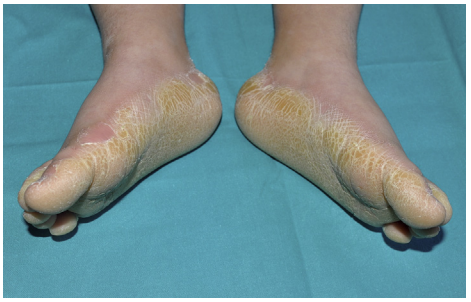

Fig 2. Case 1: clinical findings when the patient was 2 years old, showing diffuse hyperkeratosis of the soles.

and vacuolar degeneration of the superficial spinous and granular layers. Targeted DNA sequencing from peripheral blood identified the pathogenic variant c.467G>A;p.Arg156His in the *KRT10* gene in heterozygosis. After 1 year of follow-up, the boy continues to have waxing and waning annular and polycyclic erythematous scaly lesions and shows mild hyperkeratosis on knees, elbows, and major folds.

DISCUSSION

AEI was included as a minor variant of epidermolytic ichthyosis (EI) in the last consensus classification of congenital ichthyosis.[1] The name was coined in 1992 by Sahn et al,[2] who reported the first family with AEI. Although the researchers did not provide genetic testing, their patient showed palmoplantar involvement consistent with a *KRT1* gene variant. Since then, only 16 additional cases due to either *KRT1*[3-5] or *KRT10*[6-9] gene pathogenic variants, belonging to 7 different families, have been published in the literature (Table I).

AEI clinical findings are distinctive and relatively easy to recognize. The condition is characterized by intermittent flares of annular and polycyclic erythematous and scaly plaques over the trunk and extremities from early infancy[3,4,6] or, more rarely,

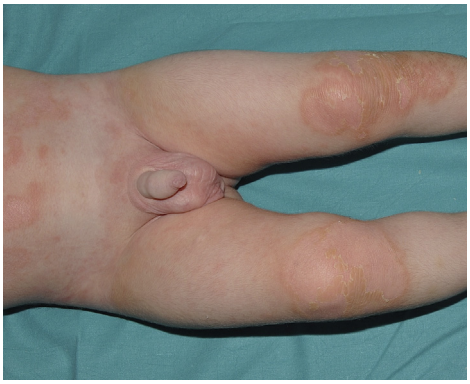

Fig 3. Case 2: erythematous and scaly plaques over the trunk, along with discrete annular hyperkeratotic and scaly lesions on the knees.

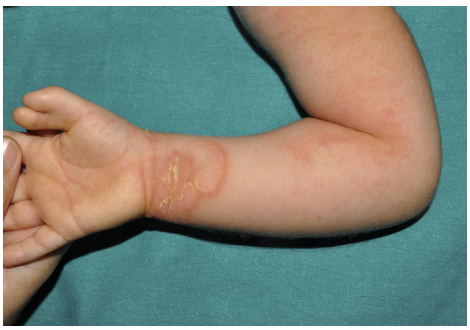

Fig 4. Case 2: annular hyperkeratotic and scaly lesions on the wrists. Preaxial polydactyly in the right first finger was observed.

from childhood or adult life.[7,8] Blistering and superficial erosions are commonly present at birth, with[3,6] or without accompanying erythema.[2,4,5,7,8] Inconstant diffuse hyperkeratosis in the flexural areas and extensor surfaces is seen.[3,4,6,7] *KRT1* gene variants are associated with PPK,[3-5] whereas *KRT10* variants result in sparing of the palms and soles.[6-9] Unlike major forms of EI, periods of almost complete clearing are possible, except for PPK in patients with *KRT1* gene variants.[3-5,7] Histologically, orthokeratotic hyperkeratosis, prominent acantholysis, and a thickened granular layer with coarse keratohyalin granules are common findings, whereas vacuolar degeneration appears in both in AEI and major forms of EI, in EAI it appears in upper layers of the epidermis.[3-9]

Like all keratins, KRT1 and K1RT0 are composed of a globular head and a tail domain with an alpha helical central rod domain composed of 4 distinct segments (1A, 1B, 2A, and 2B) separated by non-helical linkers (Fig 5). Pathogenic variants in *KRT10* are located in the 2B segment of *KRT10*[6,7] and in the 1A rod domain of the gene.[8] Keratin gene variants

Table I. Phenotypic and genotypic findings of all reported cases of AEI

			Clinical Features			Mutation		
Reference	Case Number	Age/Sex	Blistering at Birth	Migratory Annular Erythematous Scaly Plaques	PPK	KRT Gene	Genetic Locus; Protein	Treatment
Sybert et al (1999)[3]	1	3 years/M	+	+	+	*KRT1* 2B segment (case 1)	c.1436T>C; p.(Ile479Thr) (case 1)	NS
	2	18 years/M	-	+	+			
	3 (mother of case 2)	NS/F	-	-	+			
	4 (aunt of case 2)	NS/F	-	+	+	*KRT1* 2B segment (cases 2, 3, and 4	c.1435A>T; p.(Ile479Phe) (cases 2, 3, and 4)	
Michael et al (1999)[5]	5, 6, 7, 8 (same family)	NS	+	+	+	*KRT1* 2B segment	c.1435A>T; p.(Ile479Phe)	Emollients
Zaki et al (2018)[4]	9	5 years/F	+	+	+	*KRT1* 2B segment	c.1436T-C; p.(Ile479Thr)	Emollients + topical keratolytics + topical steroids
Case 1	17	6 months/M	+	+	+	KRT1 2B segment	c.1436T>C; p.(Ile479Thr)	Emollients + topical keratolytics
Joh et al (1997)[6]	10 (father of case 11)	33 years/M	+	+	-	*KRT10* 2B segment	c.1264_1265delinsGA; p.(Arg422Glu)	Emollients + acitretin
	11 (daughter of case 10)	2 months/F	+	+	-			
Suga et al (1998)[7]	12	11 years/M	-	+	-	*KRT10* 2B segment	c.1337T>C; p.(Ile446Thr)	NS
	13 (mother of case 12)	NS/F	-	-	-			
	14 (sister of case 12)	NS/F	-	-	-			
Yoneda et al (1999)[9]	15	18 years/M	+	+	-	*KRT10* 1A segment	c.472G>C; p.(Ala158Pro)	Emollients, etretinate
	16 (mother of 15)	48 years/F	+	+	-			
Case 2	18	3.5 months/M	+	+	-	*KRT10* 1A segment	c.467G>A; (p.Arg156His)	Emollients

AEI, Annular epidermolytic ichthyosis; *F*, female; *KRT*, keratin; *M*, male; *NS*, not stated; *PPK*, palmoplantar keratoderma.

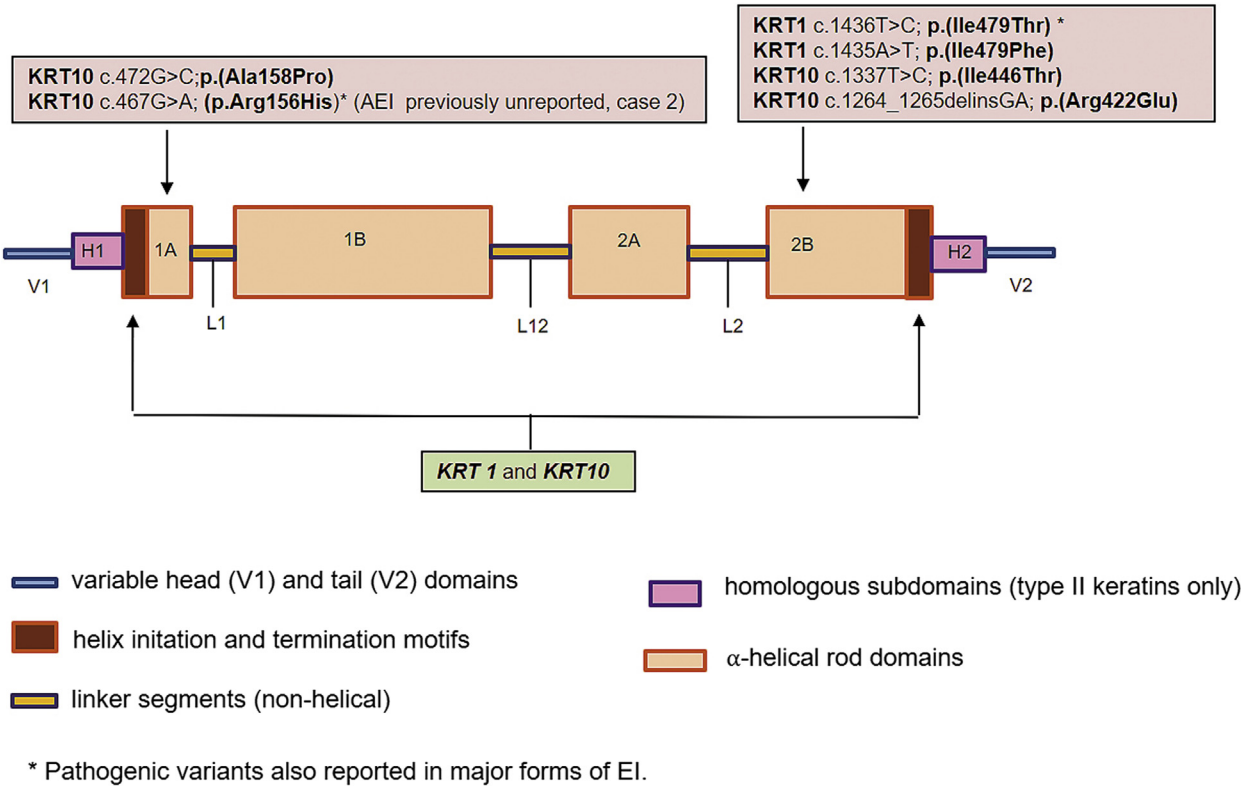

Fig 5. Structure of the *KRT1* and *KRT10* genes showing the pathogenic variants reported in AEI. Major forms of EI with the same mutation are highlighted. *AEI*, Annular epidermolytic ichthyosis; *EI*, epidermolytic ichthyosis.

affecting the residues at the ends of the central rod domains of the keratin proteins (helix initiation and termination motifs), such as the variant c.467G>A (p.Arg156His) in the 1A rod domain found in our patient (case 2), interfere with proper keratin intermediate filament assembly and function, resulting in skin fragility and/or hyperkeratosis. Although this pathogenic variant has previously been reported in patients with major forms of EI,[10] to our knowledge, our patient is the first to show an AEI phenotype.

Only 2 different keratin (KRT) 1 (*KRT1*) gene pathogenic variants resulting in the AEI phenotype have been reported to date[3-5]: c.1435A>T; p.(Ile479Phe) and c.1436T>C; p.(Ile479Thr). Both pathogenic variants are located in the 2B segment of *KRT1* and predict a change of amino acids located in the same codon (codon 479) in the highly conserved 2B helix-termination motif.[3-5] Interestingly, the c.1436T>C; (p.Ile479Thr) pathogenic variant has also been reported in multiple families with major forms of EI,[3,10] suggesting a lack of direct correlation between genotype and phenotype.

Because 14 of the 16 previously reported cases occurred in children, no conclusions can be drawn about the course of the disease. Although nearly all patients show large blisters and erosions at birth, making them indistinguishable from those with major forms of EI, it seems that the degree of cutaneous involvement is considerably milder in AEI except for the palms and soles, which show progressive thickening in patients with *KRT1* pathogenic variants. The variable phenotypic expression of similar *KRT1* and *KRT10* variants led us to hypothesize that patients with major forms of EI might have additional *cis*- or *trans*-regulatory changes affecting the expression of the wild-type allele. However, tissue expression studies are needed to further investigate this hypothesis.

There is no definitive therapy for AEI. Symptomatic therapy includes daily use of emollients, topical keratolytics, and systemic retinoids, but treatment response varies considerably among patients and families.[4,6,8] Thus, although retinoid therapy is particularly effective in patients with *KRT10* pathogenic variants, those with *KRT1* variants may experience an exacerbation.[11]

In summary, we add to the phenotypic and genotypic findings of all reported cases of AEI, an extremely uncommon subtype of EI, and we add 2 new cases of AEI due to mutations in *KRT1* and

KRT10, respectively. The lack of genotype and phenotype correlation supports the idea that AEI is a milder phenotype of EI rather than a true subtype, an important fact that must be addressed when providing genetic counseling.

REFERENCES

1. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Sorèze 2009. *J Am Acad Dermatol*. 2010;63:607-641.
2. Sahn EE, Weimer CE Jr, Garen PD. Annular epidermolytic ichthyosis: a unique phenotype. *J Am Acad Dermatol*. 1992;27:348-355.
3. Sybert VP, Francis JS, Corden LD, et al. Cyclic ichthyosis with epidermolytic hyperkeratosis: a phenotype conferred by mutations in the 2B domain of keratin K1. *Am J Hum Genet*. 1999;64:732-738.
4. Zaki TD, Yoo KY, Kassardjian M, et al. A p.478I>T KRT1 mutation in a case of annular epidermolytic ichthyosis. *Pediatr Dermatol*. 2018;35:e414-e415.
5. Michael EJ, Schneiderman P, Grossman ME, et al. Epidermolytic hyperkeratosis with polycyclic psoriasiform plaques resulting from a mutation in the keratin 1 gene. *Exp Dermatol*. 1999;8:501-503.
6. Joh GY, Traupe H, Metze D, et al. A novel dinucleotide mutation in keratin 10 in the annular epidermolytic ichthyosis variant of bullous congenital ichthyosiform erythroderma. *J Invest Dermatol*. 1997;108:357-361.
7. Suga Y, Duncan KO, Heald PW, et al. A novel helix termination mutation in keratin 10 in annular epidermolytic ichthyosis, a variant of bullous congenital ichthyosiform erythroderma. *J Invest Dermatol*. 1998;111:1220-1223.
8. Yoneda K, Morita E, Akiyama M, et al. Annular epidermolytic ichthyosis. *Br J Dermatol*. 1999;141:748-750.
9. Yang JM, Yoneda K, Morita, et al. An alanine to proline mutation in the 1A rod domain of the keratin 10 chain in epidermolytic hyperkeratosis. *J Invest Dermatol*. 1997;109:692-694.
10. Arin MJ, Oji V, Emmert S, et al. Expanding the keratin mutation database: novel and recurrent mutations and genotype-phenotype correlations in 28 patients with epidermolytic ichthyosis. *Br J Dermatol*. 2011;164:442-447.
11. Virtanen M, Gedde-Dahl T, Mörk JN, Leigh I, Bowden PE, Vahlquist A. Phenotypic/genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy on keratin expression. *Acta Derm Venereol*. 2001;81:163-170.