Dermatology Practical & Conceptual

Three Novel Mutations in *ALOX12B* Gene in Patients with Autosomal Recessive Congenital Ichthyosis from Turkey

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Introduction

ALOX12B mutations are usually associated with milder phenotypes of autosomal recessive congenital ichthyosis (ARCI), including minimal erythema, fine scaling, or self-improving collodion ichthyosis (SICI) [1-3]. We report three novel *ALOX12B* mutations in unrelated patients with ARCI. The genetic analysis was performed using the NextSeq500 (Illumina Inc., San Diego, CA, USA) instrument. All variants identified in index cases were confirmed by Sanger sequencing.

Case Presentation

Patient 1, a 1-day-old girl from a nonconsanguineous family, had collodion membrane (CM), ectropion, and eclabium at birth. No systemic or organ abnormality was revealed, except low-set ears and conductive hearing loss (CHL) on the left side. Her family history was unremarkable. An *ALOX12B* mutation (c.1533-2A>G) was revealed (Table 1). After three months, the CM completely regressed, exposing xerotic skin. After three years, the child has xerotic skin, slight erythema, and scaling on her scalp without developmental delay. She is using only emollients.

Patient 2, a 40-year-old female from a consanguineous family, had had diffuse dusky erythema and ichthyotic scaling throughout the entire body since birth, without any seasonal change, ectropion, eclabium, palmoplantar keratoderma, or alopecia (Figures 1A and 1B). The history of CM is unknown. Bilateral minimal CHL was present. She was otherwise healthy. No family history of ichthyosis was present. Genetic tests revealed an *ALOX12B* mutation (c.1808C>T) (Table 1). She has been continuing acitretin treatment, with a good response.

Patient 3, a 1-day-old boy from first-degree consanguineous parents, had intrauterine growth retardation, CM, ectropion, eclabium, bilateral anteriorly overfolded ears, bilateral CHL, and left renal ectasia at birth (Figures 1C and 1D).

Table 1. Mutations Identified in *ALOX12B*.

Patient no	Mutation	Zygosity	Consequence on Protein	Site	Domain	ACMG [6]
1	c.1533-2A>G -	Homozygous	Splicing	Intron 11	LPG	Likely pathogenic
2	c.1808C>T p.Pro603Leu	Homozygous	Missense	Exon 14	LPG	Likely pathogenic
3	c.695C>T p.Ser232Leu	Homozygous	Missense	Exon 6	LPG	Variant of uncertain significance

Abbreviations: LPG: lipoxygenase domain; ACMG: American College of Medical Genetics and Genomics.

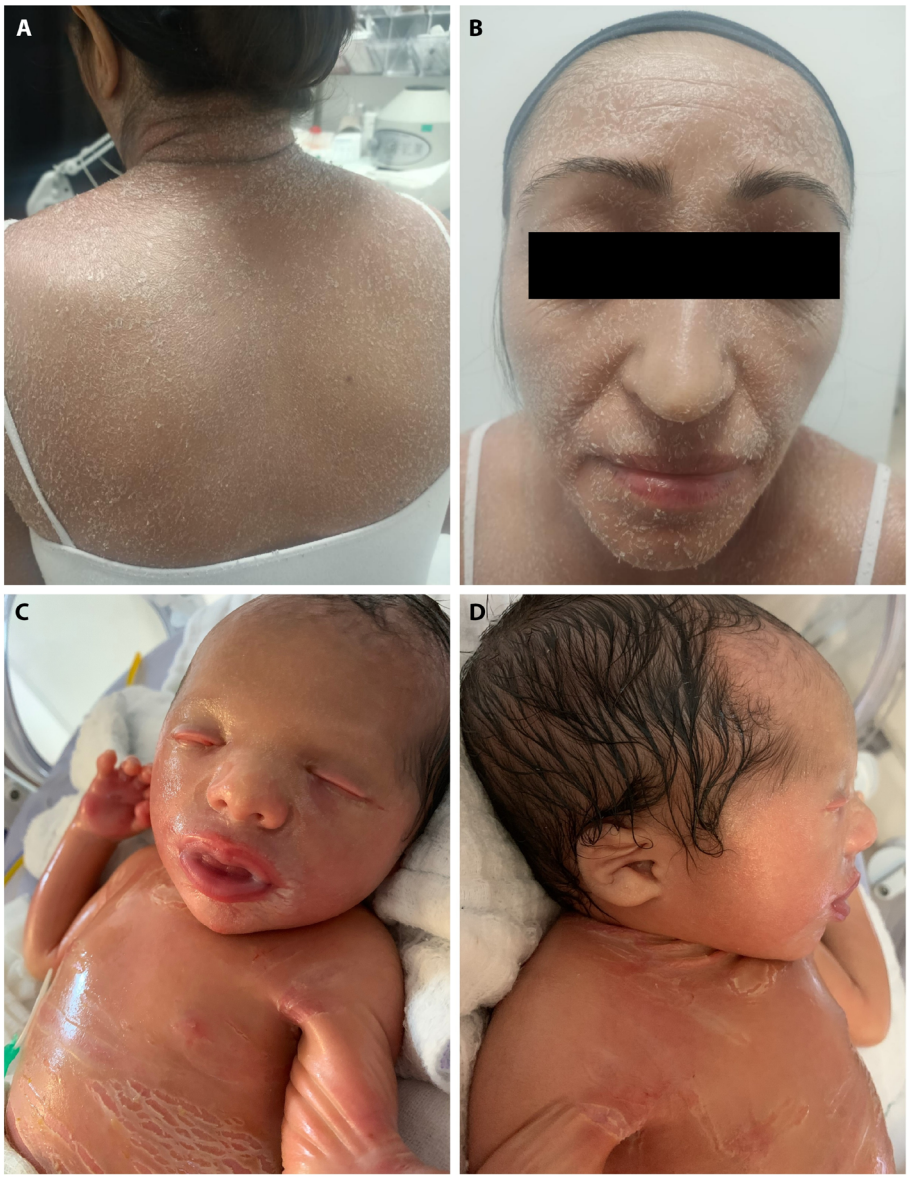

Figure 1. (A, B) Clinical features of Patient 2. Diffuse, dusky erythema and ichthyotic scaling on the back and face. (C) Clinical features of Patient 3. Collodion membrane, ectropion, and eclabium at birth. (D) Anteriorly overfolded right ear at birth.

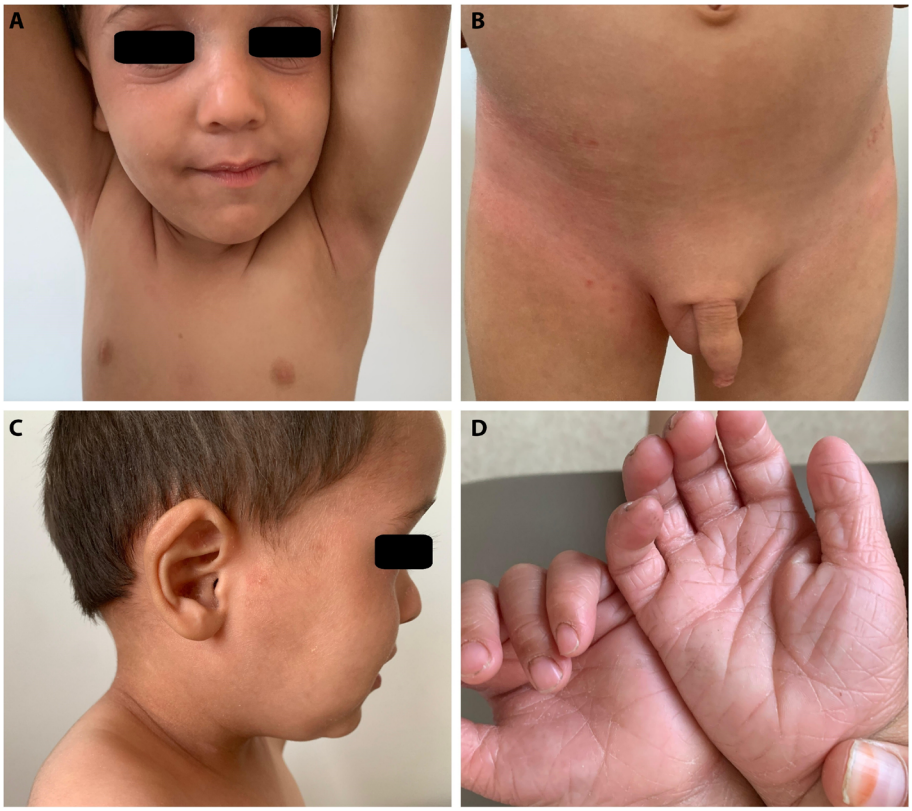

Figure 2. Clinical features of Patient 3. Resolution of skin lesions at three years of age. (A) Dennie-Morgan lines, fine scaling, and minimal erythema on the axillas. (B) Slight erythema with fine scaling around inguinal regions. (C) Fine scaling inside the ear and around the neck. Partially improved right ear that was anteriorly overfolded at birth. (D) Palmar hyperlinearity.

He was otherwise healthy. His family history was unremarkable. An *ALOX12B* mutation (c.695C>T) was present (Table 1). After four weeks, the CM completely regressed, exposing xerotic skin. After almost three years, the child has xerotic skin, fine scaling with focal accentuation around the flexural regions, feet and ankles, neck, and armpits, slight palmar erythema, palmar hyperlinearity, Dennie-Morgan lines, attention deficit hyperreactivity disorder, and speech delay (Figure 2). He is otherwise healthy and continues to use emollients.

ALOX12B mutations often lead to milder phenotypes of ARCI, yet variabilities in severity can occur [1,4]. Patients 1 and 3 have milder phenotypes compatible with SICI. However, patient 2 still has more severe ichthyosiform lesions on the entire body, compatible with congenital ichthyosiform erythroderma, and needs systemic treatment.

In patients with SICI, the skin is near normal following the shedding of the CM. Mild signs of ichthyosis, such as xerosis and fine scaling with focal accentuations, can be present in older ages [1,2,4]. As possible explanations for improvement of keratinization after birth, high intrauterine hydrostatic pressure, variants of mutations, epigenetic, and environmental factors were suggested [1,4,5].

An anteriorly overfolded ear was reported as associated with *ALOX12B* mutation and might be used as a clinical diagnostic marker [4]. We observed bilateral anteriorly overfolded ears in only Patient 3.

Conclusion

Due to the rarity of the disease and genetic heterogeneity, a detailed description of each case is crucial to establish an exact genotype-phenotype correlation.

Consent Statement: Informed consents were obtained from patients/parents of Patient 2 and 3. Because Patient 1 did not give informed consent to publish her photographs, we do not share them in the manuscript.

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