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CASE REPORT

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A novel KRT1 c.1433A>G p.(Glu478Gly) mutation in a newborn with epidermolytic ichthyosis

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Abstract

Epidermolytic Ichthyosis is a rare genodermatosis related to point mutations affecting the genes encoding for keratin 1 or keratin 10. We report a case of Epidermolytic Ichthyosis in a newborn with a novel mutation (c.1433A>G) of KRT1 gene.

KEYWORDS

epidermolytic hyperkeratosis, epidermolytic ichthyosis, KRT1 gene, novel mutation

1 | INTRODUCTION

Epidermolytic ichthyosis (EI), also known as "epidermolytic hyperkeratosis," is a rare genodermatosis, classified among the "keratinopathic ichthyosis" with an incidence between 1/100 000 and 400 000 and similar frequency in males and females.[1,2]

Pathogenesis of EI is related to point mutations affecting the genes encoding for keratin 1 (*KRT1*) or keratin 10 (*KRT10*).[1-3]

Epidermolytic ichthyosis is inherited as autosomal dominant trait, and in about 50% of patients, it is due to de novo mutations.[1,2]

Diagnosis of EI is based on clinical manifestations, histological reports, and genetic analyses.

We describe a case of EI related to a novel mutation on KRT1 gene.

A male newborn patient, born by heterologous fertilization, attended our Pediatric Dermatology Unit for an intense erythroderma. Isolated bullous lesions on the trunk, upper and lower limbs appeared some hours after birth (Figure 1). Suspecting an inherited ichthyosis, a skin biopsy was performed.

Histological examination showed prominent hyperkeratosis, intracellular vacuolar degeneration of granular and spinous layers, lysis of keratinocytes, intraepidermal blisters, and eosinophilic granulocytes (Figure 2).

Genetic analysis was performed on genomic DNA extracted from peripheral blood leukocytes. The entire coding region and intron-exon boundaries of the *KRT1* and *KRT10* genes were analyzed using the Illumina Trusight One Expanded kit. Libraries were prepared according to the manufacturer's protocol and run in an Illumina NextSeq 550 sequencer. We identified a heterozygous variant

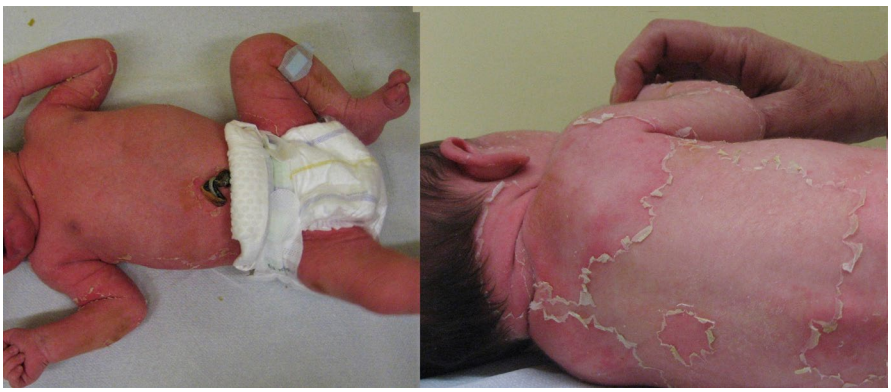

FIGURE 1 Intense erythroderma and isolated bullous lesions on the trunk, upper limbs and lower limbs in the newborn

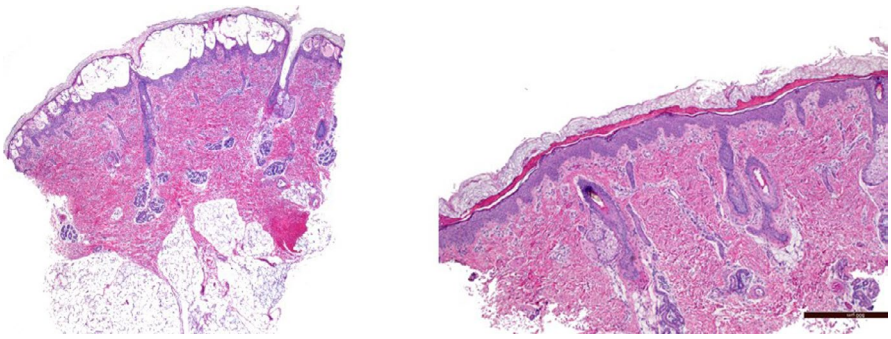

FIGURE 2 Hsistological examination showed prominent hyperkeratosis, intracellular vacuolar degeneration of the granular and spinous layers, lysis of keratinocytes, intraepidermal blisters, and eosinophilic granulocytes in blisters

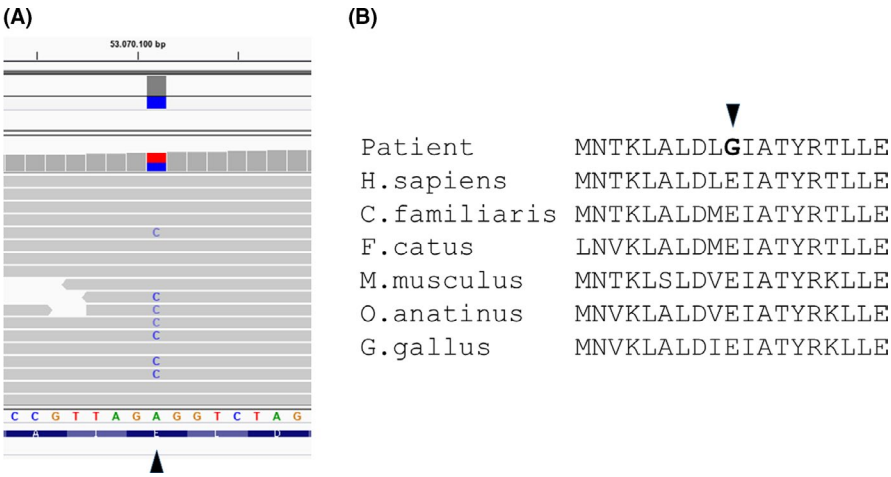

FIGURE 3 A, The c.1433A>G mutation as detected by the NGS analysis in patient's DNA. B, Alignment of KRT1 protein in different species. The arrowhead indicated the affected residue

NM_006121.3:c.1433A>G, p.(Glu478Gly) in the *KRT1* gene (Figure 3).

The variant was not present in his father. We could not analyze the donor of the ovocyte.

At birth, clinical features of EI include "burned" skin with erythroderma, diffuse flaccid bubbles, hyperkeratosis, and superficial erosions. From 2 to 4 years of age, the blisters decrease and localized or generalized hyperkeratosis gradually appears.[4]

In adulthood, the blisters disappear and hyperkeratosis remains.

The treatment of EI is usually symptomatic, according to the age of patient and the severity of disease. Systemic acitretin is the main drug used in severe cases of EI.

2 | DISCUSSION

Epidermolytic ichthyosis is a rare keratinopathic genodermatosis related to point mutations affecting the genes encoding for keratin 1 (*KRT1*) or keratin 10 (*KRT10*).[1-3]

We report a case of EI in a newborn with heterozygous single nucleotide substitution (A to G) at nucleotide 1433 of *KRT1*. The c.1433A>G variant was never described before in patients with EI and is absent in the general population (gnomAD). This nucleotide change resulted in a substitution p.(Glu478Gly) at the end of the 2B domain of KRT1 protein. The residue is conserved in all organisms carrying a orthologues of the KRT1 gene and is predicted to be damaging by several bioinformatic tools. Keratin has a central coiled-coil rod domain containing

four a-helical segments (1A, 1B, 2A, 2B), critical for keratin assembly and function. Interestingly, other pathogenic mutations affecting the same glutamic acid residue at codon 478 were reported in patients with EI. The changes p.Glu478Gln[5] and p.Glu478Lys[6] lead to a change in side-chain net charge and seem to correlate with severe phenotypes, whereas the p.Glu478Asp change, which retains the negatively charged residue, is associated with a milder phenotype.[6] The p.Glu478Asp substitution found in our patient also alters the charge of the residue in position 478 and is associated with a neonatal-onset phenotype. Our findings further support the notion that changes at position 478 specifically perturb KRT1 function with different degree of severity that correlates with the charge of the involved amino acid. In this scenario, we describe a new pathogenic mutation p.(Glu478Gly) in a patient affected by EI, expanding the knowledge about genotype-phenotype correlations of the disease.

3 | CONCLUSIONS

In patients with EI, genetic examination should be performed in order to conclude the diagnostic process, to predict the efficacy of treatments, and to clarify the potential transmissibility of EI.

The identification of any new mutations, as in our patient, is also useful to expand the database on KRT1/KRT10 mutations in EI.[2,7]

CONFLICT OF INTEREST

Authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Dr Francesca Caroppo, Dr Elena Cama, Dr Roberto Salmaso, Dr Cinzia Bertolin, Prof. Leonardo Salviati, and Prof. Anna Belloni Fortina: made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, participated in drafting the article, and gave final approval of the version to be submitted and any revised version.

ETHICAL APPROVAL

The parents of the child have given consent to publication of this case.

CONSENT STATEMENT

Published with written consent of the patient.

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