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□ Case Report □

A Case of *ITGA3* Mutation-Induced Junctional Epidermolysis Bullosa without Pulmonary or Renal Involvement

Seong Jin Ju, M.D., Sang Eun Lee, M.D., Ph.D.[1], Song-Ee Kim[1], Miri Kim, M.D., Ph.D.

Department of Dermatology, Yeouido St Mary's Hospital, College of Medicine, The Catholic University of Korea, Department of Dermatology, Gangnam Severance Hospital, Yonsei University College of Medicine[1], Seoul, Korea

Junctional epidermolysis bullosa (JEB) is a subtype of epidermolysis bullosa characterized by the formation of blisters within the basement membrane, particularly in the lamina lucida. Clinical manifestations of JEB include fragile skin with blisters and erosion. This case report presents a 35-year-old male with JEB caused by *ITGA3* mutations (p.Arg875Ter, p.Cys162Tyr) without pulmonary or renal complications. The patient exhibited various cutaneous signs such as persistent exfoliative patches, nail hypoplasia, and diffuse alopecia, with additional ophthalmic complications such as symblepharon and limbal stem cell deficiency. *ITGA3* mutations are typically linked to interstitial lung disease and nephrotic syndrome, a characteristic group of symptoms known as ILNEB ('Interstitial Lung disease, Nephrotic syndrome and Epidermolysis Bullosa'). However, the patient showed no evidence of renal or pulmonary involvement, with normal urinalysis and chest X-ray results, making the diagnosis more difficult until next generation sequencing confirmed the *ITGA3* mutation. **(Korean J Dermatol 2025;63(6):174～177)**

Key Words: Genetic skin diseases, Junctional epidermolysis bullosa

INTRODUCTION

Epidermolysis bullosa (EB) results from defects in the attachment of basal keratinocytes to the underlying dermis. Patients with EB may exhibit blistering as small vesicles or larger bullae on the skin. In severe cases, it can be fatal. The hallmark of EB is skin and mucosa fragility with trauma-induced painful blisters. However, the distribution, depth of blister formation, extra-cutaneous involvement, and severity can vary across EB subtypes. They are influenced by the specific underlying genetic defect[1].

Junctional epidermolysis bullosa (JEB), a subtype of EB[1], is a rare inherited disease. JEB is characterized by blister formation in the lamina lucida. It is further classified into several subtypes based on specific genetic mutations responsible for its occurrence[1]. One of the causative genetic mutations is in the *ITGA3* gene, which encodes integrin $\alpha 3$, a transmembrane adhesion receptor subunit that forms heterodimers with integrin $\beta 1$. Integrin $\alpha 3\beta 1$ plays a major role in the adhesion of basal keratinocytes and extracellular matrix by binding to laminin-332 and laminin-511[2]. Autosomal recessive loss-of-function mutations in *ITGA3* have been recognized as a causative factor for EB. They are specifically associated with interstitial lung disease and nephrotic syndrome. This characteristic group of symptoms is known as "ILNEB" (Interstitial Lung disease, Nephrotic syndrome and Epidermolysis Bullosa)[3]. To date, the majority of reported cases of *ITGA3* gene mutations have been associated with pulmonary or renal complications; however, cases without either pulmonary or renal involvement have been rarely reported[4].

Here, we report a rare case of JEB caused by an *ITGA3* gene mutation without renal or pulmonary involvement. This case underscores that the clinical manifestations of JEB associated with *ITGA3* mutations can occur without significant pulmonary or renal complications.

The patient provided written informed consent for the use of de-identified, anonymized, aggregated data, and case details for publication.

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Corresponding author: Miri Kim, Department of Dermatology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea. Tel: 82-2-3779-1230, Fax: 82-2-783-7604, E-mail: gimmil@naver.com

CASE REPORT

A 35-year-old male patient presented to our medical facility with persistent pruritic, exfoliative patches distributed across his entire body (Fig. 1). This condition that has been ongoing since his childhood. Additionally, the patient presented several congenital malformations of cutaneous appendages. First, he exhibited 20-nail hypoplasia, with aplasia particularly affecting both great toe nails (Fig. 2). Second, he experienced diffuse hair loss. Notably, there was a familial pattern, as his younger brother exhibited a milder form of nail dystrophy (Fig. 3) and hair loss. In contrast, his parents exhibited no clinical symptoms. The patient had also received ophthalmic care due to symblepharon, a condition in which the bulbar conjunctiva and the palpebral conjunctiva adhere. He was diagnosed with limbal stem cell deficiency, a condition in which proliferation of corneal epithelial cells is impaired. He had received treatment for dermatitis. However, there was no improvement. Given these symptoms and signs, we suspected a diagnosis of inherited EB. Accordingly, next generation sequencing was performed on the patient's ethylenediaminetetraacetic acid blood sample using NextSeq 550 (Illumina). It identified heterozygous mutations in *ITGA3* (c.485G>A, p.C162Y in exon 4) and *ITGA3* (c.2623C>T, p.R875Ter). In silico analysis (PolyPhen-2 and PROVEAN) provided supporting evidence, as both mutations are predicted to be deleterious. Both variants were absent from the Human Gene Mutation Database and the gnomAD v4.1.0 population database, supporting their rarity in the general population. This satisfies the criterion for PM2 (moderate evidence) for pathogenicity. The c.485G>A missense variant has been reported in a case with a similar phenotype, providing supporting evidence for its pathogenic role[4]. In summary, the collective evidence supports classification of the c.485G>A variant as 'likely pathogenic' according to ACMG guidelines. The p.R875Ter variant is a nonsense mutation, which represents a known disease mechanism for *ITGA3*-related disorders; thus, the PVS1 (very strong pathogenic evidence) criterion can be applied. Furthermore, this variant has been submitted to ClinVar as 'likely pathogenic,' which provides additional support for our

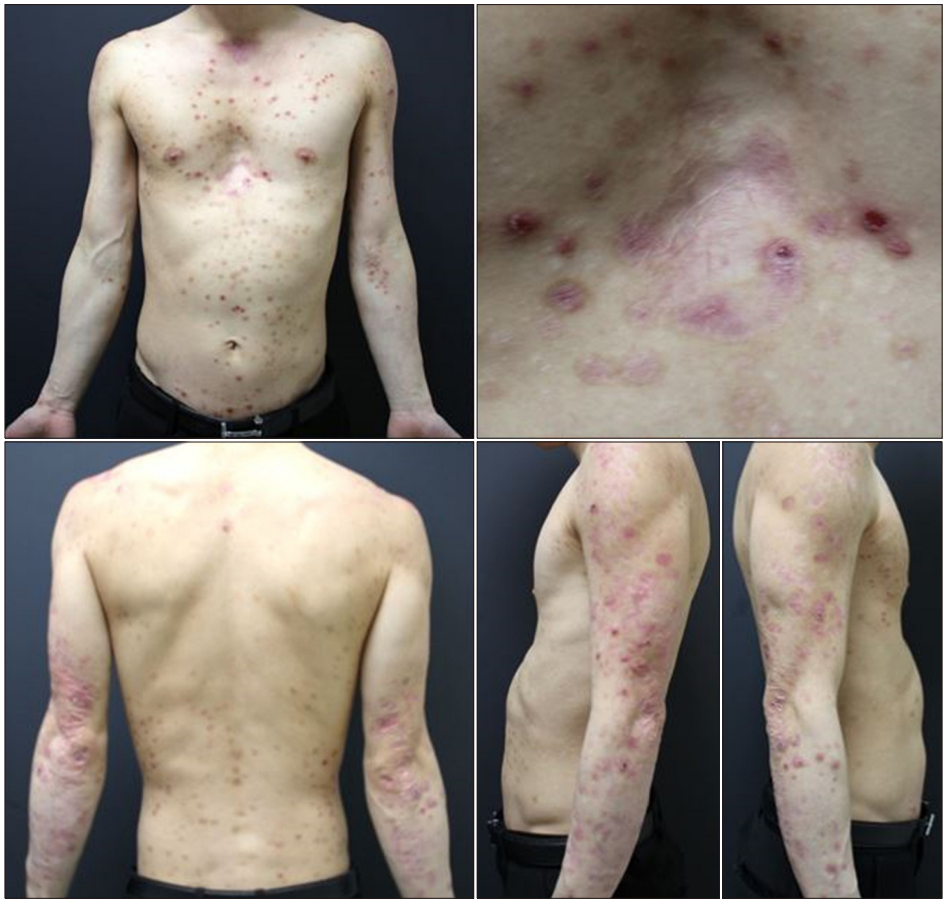

Fig. 1. Exfoliative skin lesions covering the patient's entire body.

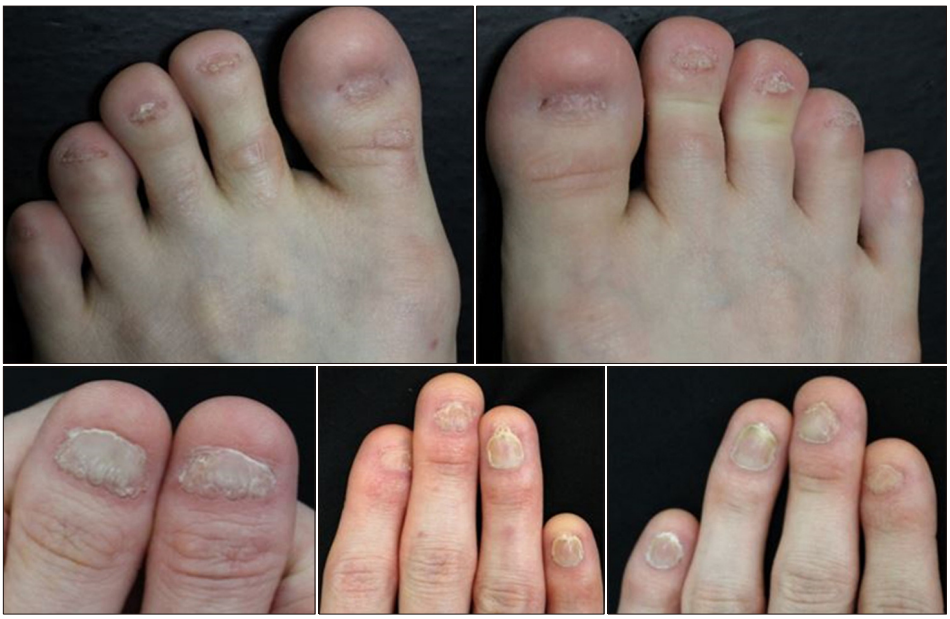

Fig. 2. The patient has 20-nail hypoplasia with notable aplasia of both great toe nails.

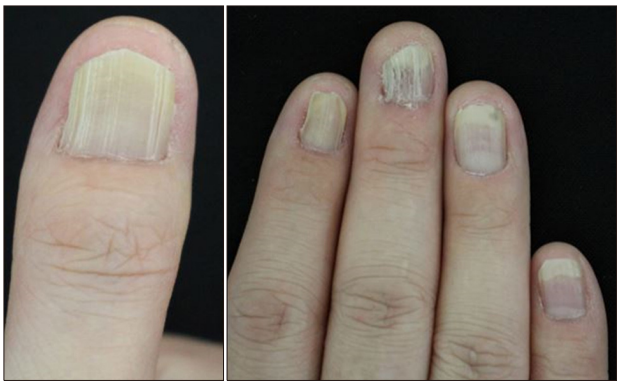

Fig. 3. The patient's brother has milder nail dystrophy affecting five nails.

classification of it as 'pathogenic' based on integrated functional and genetic evidence.

The patient has not had any respiratory symptoms. He demonstrated no signs of interstitial lung disease in chest X-rays. Urinalysis revealed no indications of nephrotic syndrome. For further evaluation, the patient was referred to the departments of nephrology and pulmonology. In the pulmonology department, a chest computed tomography scan was performed, revealing no significant findings other than mild bronchitis. The patient declined further comprehensive evaluation by the nephrology department.

DISCUSSION

This case report illustrates a rare instance of JEB, a subtype of EB. JEB is characterized by blister formation in the lamina lucida. It is further categorized into several subtypes based on specific genetic mutations. One such gene is *ITGA3*, which encodes integrin $\alpha 3$, a crucial transmembrane adhesion receptor subunit pairs with integrin $\beta 1$ to form integrin $\alpha 3\beta 1$. Autosomal recessive loss-of-function mutations in *ITGA3* can disrupt cell adhesion, leading to the clinical phenotype. The cutaneous manifestation of this subtype is relatively mild. Blistering of the skin begins early in life. It is generally mild or sometimes absent. It may be associated with diffuse alopecia and nail dystrophy[5].

The patient presented multiple cutaneous manifestations, including persistent pruritic and exfoliative patches, 20-nail hypoplasia, diffuse hair loss, and ophthalmic complications such as symblepharon and limbal stem cell deficiency. One of the limitations of this paper is the inability to determine whether the two identified *ITGA3* mutations are located in 'cis' (on the same allele) or in 'trans' (on different alleles). Although analysis through parental genetic testing would have allowed clarification of the allelic configuration, this could not be performed due to the unavailability of coordination. However, given that JEB follows an autosomal recessive inheritance pattern, it is reasonable to presume that the two variants are in 'trans,' resulting in a compound heterozygous mutations that likely underlies the patient's clinical phenotype.

ITGA3 mutations are typically associated not only with EB but also specifically linked to interstitial lung disease and nephrotic syndrome, a characteristic group of symptoms known as 'ILNEB.' In this case, due to the absence of signs of pulmonary and renal involvement, it was challenging to immediately suspect *ITGA3*-mutation-associated JEB. Several mutations in *ITGA3* have been documented in cases exhibiting comparatively milder symptoms[6,7]. One previous report described a patient with compound heterozygous mutations in *ITGA3*—c.485G>A (p.C162Y) and c.1382G>A (p.R461Q)—who exhibited neither lung nor kidney involvement[4]. In our case, we presume that the nonsense mutation (p.R875Ter) on one allele results in a significant loss of function. A ClinVar record (RCV002481814.1) associates p.R875Ter with EB accompanied by both nephrotic and pulmonary involvement. Accordingly, we speculate that the missense mutation (p.C162Y) may retain partial function, which could explain the absence of lung and kidney involvement in our patient. However, further studies are needed to clarify the pathogenicity of each individual variant.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Seong Jin Ju, https://orcid.org/0009-0007-9467-7619
Sang Eun Lee, https://orcid.org/0000-0003-4720-9955
Song-Ee Kim, https://orcid.org/0000-0001-7369-7310
Miri Kim, https://orcid.org/0000-0001-5167-3449

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