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CASE REPORT

# A Novel COL7A1 Mutation in a Patient With Dystrophic Epidermolysis Bullosa. Successful Treatment With Upadacitinib

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**Abstract:** Dystrophic epidermolysis bullosa (DEB) is a heterogeneous and rare genetic skin disease caused by mutations in the *COL7A1* gene, which encodes Type VII collagen. The absence or dysfunction of Type VII collagen can cause the dense lower layer of the basal membrane zone of the skin to separate from the dermis, leading to blister formation and various complications. In different DEB subtypes, the severity of the phenotype is associated, to some extent, with the outcome of Type VII collagen caused by mutations in the *COL7A1* gene, which may be reduced in expression, remarkably reduced, or completely absent. Here, we report a case of DEB caused by a mutation in the *COL7A1* gene at a novel site, where the patient achieved favorable outcomes after treatment with upadacitinib. This study further expands the known *COL7A1* gene mutation sites in the DEB subtype, providing new data for understanding the genotype-phenotype correlation and treatment of this disease.

**Keywords:** dystrophic epidermolysis bullosa, *COL7A1*, type VII collagen, gene mutation, gene detection

## Introduction

Dystrophic epidermolysis bullosa (DEB) is a rare subtype of epidermolysis bullosa (EB), a hereditary skin fragility disorder characterized by mechanical vulnerability to minor physical damage. It is marked by widespread painful blisters and erosions at birth, accompanied by scarring, a miliary rash, and nail dystrophy, often affecting the extremities most severely.[1] The molecular basis of DEB is a pathogenic mutation in the *COL7A1* gene, which encodes the collagen VII component of the basal membrane zone of the skin, damaging the dermo-epidermal junction and leading to blisters after minimal mechanical trauma.[2] Type VII collagen is the main component of anchoring fibrils and is involved in the connection between the epidermal basement membrane and dermal extracellular matrix. The *COL7A1* gene, which encodes Type VII collagen, is the only known gene associated with DEB. Mutations in this gene can lead to changes in skin basement membrane morphology or reduction and loss of anchoring fibrils, resulting in different DEB phenotypes.[3] To date, more than 1200 mutations in the *COL7A1* gene have been reported, contributing to varying degrees of Type VII collagen deficiency.[4] However, most of the previously reported guanine substitutions were located in exons 73–87. We report a novel case of DEB caused by a guanine substitution at position 4714, located in exon 49. The patient achieved satisfactory outcomes after upadacitinib treatment.

## Case Report

A 32-year-old female presented to the doctor with itching rashes on her limbs that had persisted for more than 10 years. She reported that the rashes occurred without any obvious triggers. Due to severe itching, she had received topical

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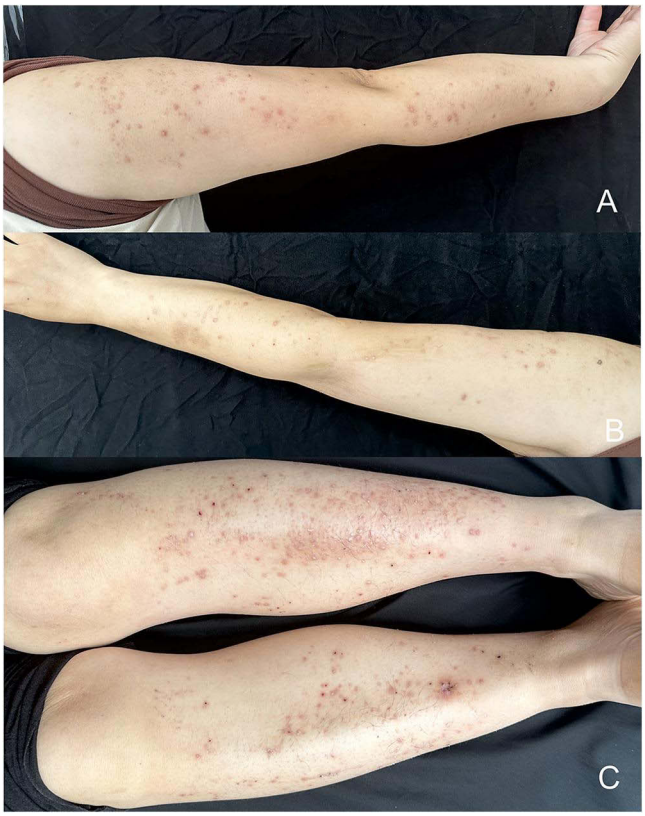


**Figure 1** Clinical manifestation: Reddish papules and blisters scattered on both upper limbs (**A** and **B**) and legs (**C**), some densely clustered and covered with a few scales.

glucocorticoids, oral antihistamines, and other medications over the past 10 years. The treatments provided limited relief. The rashes worsened in summer and improved in winter, accompanied by changes in the intensity of itching. The patient had no relevant medical history, and other family members were healthy. In June 2024, the patient came to our hospital for treatment. Physical examination revealed scattered reddish papules and blisters on her upper and lower limbs (Figure 1). Pathological examination of lower extremity skin lesions revealed subepidermal blister formation (Figure 2). Skin immunohistochemistry showed that Type IV collagen staining indicated cracks beneath the dense plate (Figure 3A), and C4d staining was negative (Figure 3B). Direct immunofluorescence was negative for IgA, IgG, IgM, C3, and fibrinogen (KingMed Diagnostics platform, Guangzhou, China).[5–7] Tests for pemphigus antibodies (Anti-desmoglein (Dsg) 1 antibody and Anti-desmoglein (Dsg) 3 antibody) and pemphigoid (Anti-BP180 antibody and Anti-BP230 antibody)[8] were negative (Table 1).

After obtaining informed consent and approval from the Ethics Committee of Gannan Medical University, genomic DNA was extracted from the patient's peripheral blood. Whole exome sequencing (WES) revealed a mutation in the patient's *COL7A1* gene, c.4714G>A (p.Gly1572Arg). This finding was verified by Sanger sequencing of *COL7A1* (Figure 4). Based on predictions by Polyphen-2, the G1572R change was probably damaging. No protein structure prediction model for the human *COL7A1* gene was found in the UniProt database. However, the murine α1 (VII) collagen polypeptide shares 84.7% identity and 90.4% similarity with the corresponding human sequence at the amino acid level, and defects and breaks in the collagen domain consisting of Gly-X-Y repeats are highly conserved. So, we showed the location of the variation of this protein in the mouse protein structure from the AlphaFold protein structure database (https://alphafold.ebi.ac.uk/entry/D3ZE04) (Figure 5).

Based on clinical manifestations, laboratory and pathological examinations, and genetic testing, the patient was diagnosed with DEB. Currently, the patient is being treated orally with upadacitinib (15 mg; once daily for two months and every other day afterward). After 4 months of follow-up (Figure 6), the rash subsided remarkably, and pruritus was markedly reduced.

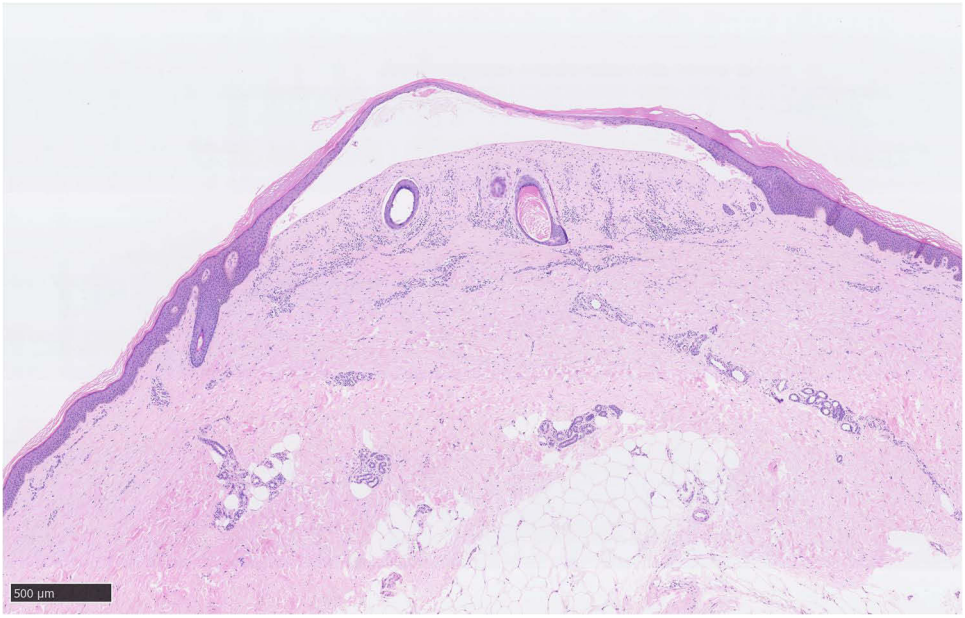


**Figure 2** Histopathological images of lower extremity skin lesions (Hematoxylin and Eosin): local epidermal atrophy with mild hyperkeratosis and subepidermal blister formation, hypodermal fibrous tissue hyperplasia with collagenization.

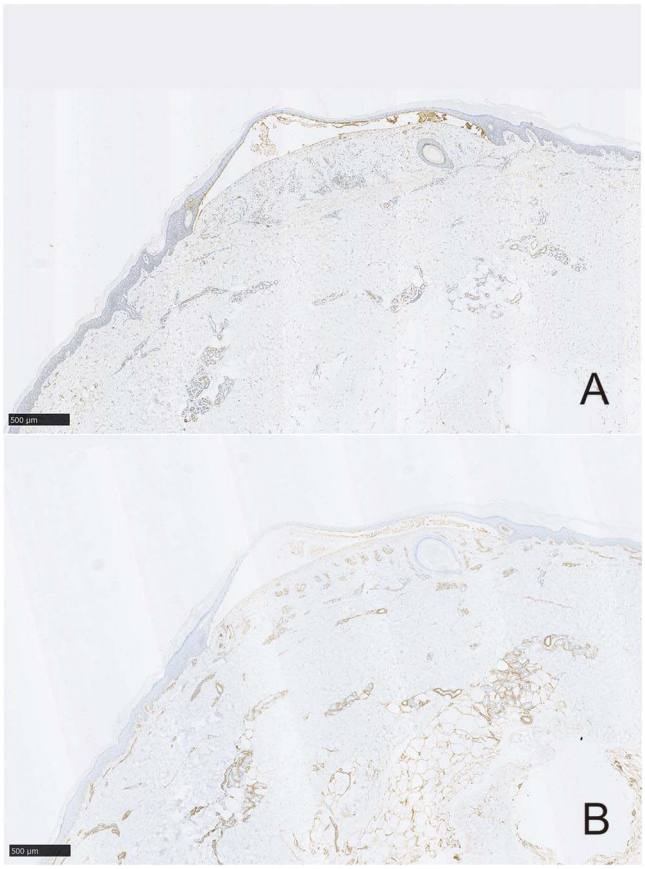


**Figure 3** Immunohistochemistry: (**A**) Type IV collagen staining is located at the top of the blister, indicating that the fissure is located below the lamina densa. (**B**) Negative C4d staining.

**Table 1** The Antibody Test Results

| The Antibodies of Pemphigus and Pemphigoid | Detection Methods | Results | Reference Interval |
|---|---|---|---|
| Anti-desmoglein (Dsg) 1 antibody | ELISA:The recombinant desmoglein (Dsg) 1 reacts with the specimen as an antigen. After washing, goat anti-human IgG polyclonal antibody labelled with peroxidase was added. Then, a complex consisting of antigens, antibodies, and enzyme-labeled antibodies was obtained. Washing again, after that, add a matrix solution of 3,3′,5,5′-tetramethylbenzidine and hydrogen peroxide. After the reaction was terminated, the anti-desmoglein 1 antibody was detected according to the absorbance at 450nm. | <5.00 U/mL | Negative <14.00 U/mL Uncertainty 14.00–20.00 U/mL Positive ≥20.00 U/mL |
| Anti-desmoglein (Dsg) 3 antibody | ELISA:The recombinant desmoglein (Dsg) 3 reacts with the specimen as an antigen. After washing, goat anti-human IgG polyclonal antibody labelled with peroxidase was added. Then, a complex consisting of antigens, antibodies, and enzyme-labeled antibodies was obtained. Washing again, after that, add a matrix solution of 3,3′,5,5′-tetramethylbenzidine and hydrogen peroxide. After the reaction was terminated, the anti-desmoglein 3 antibody was detected according to the absorbance at 450nm. | <5.00 U/mL | Negative <7.00 U/mL Uncertainty 7.00–20.00 U/mL Positive ≥20.00 U/mL |
| Anti-BP180 antibody | Magnetic particle-based chemiluminescence immunoassay:The magnetic particles which had conjugated to BP180 antigen were dissolved in 0.01 M PBS buffer to bring its concentration to 0.4 mg/L. Then it reacted with the sample for 10 minutes. After washing, anti-human IgG labeled with alkaline phosphatase was added and reacted for 10 minutes. So, a solid phase complex consisting of antigens, antibodies, and enzyme-labeled secondary antibodies was obtained. Washing again, then the chemiluminescent substrate 3-(2′-Spiroadamantane)-4-methoxy-4-(3″-phosphoryloxy) phenyl-1,2-dioxetane (AMPPD) was added. The chemiluminescent substrate emitted photons when it catalyzed by alkaline phosphatase, and the number of photons was proportional to the concentration of anti-BP180 antibody in the sample. | <2.00 RU/mL | Negative <20.00 RU/mL Positive ≥20.00 RU/mL |
| Anti-BP230 antibody | Magnetic particle-based chemiluminescence immunoassay:The magnetic particles which had conjugated to BP230 antigen were dissolved in 0.01 M PBS buffer to bring its concentration to 0.4 mg/L. Then it reacted with the sample for 10 minutes. After washing, anti-human IgG labeled with alkaline phosphatase was added and reacted for 10 minutes. So, a solid phase complex consisting of antigens, antibodies, and enzyme-labeled secondary antibodies was obtained. Washing again, then the chemiluminescent substrate 3-(2′-Spiroadamantane)-4-methoxy-4-(3″-phosphoryloxy) phenyl-1,2-dioxetane (AMPPD) was added. The chemiluminescent substrate emitted photons when it catalyzed by alkaline phosphatase, and the number of photons was proportional to the concentration of anti-BP230 antibody in the sample. | 2.44 RU/mL | Negative <20.00 RU/mL Positive ≥20.00 RU/mL |

## Discussion

Epidermolysis bullosa (EB) is a rare hereditary subepidermal bullous dermatosis, which can be divided into four types according to the difference of skin microstructure: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB).[9] DEB can be classified as autosomal dominant (DDEB) or autosomal recessive (RDEB), with RDEB typically being more severe than DDEB. Loss or significant reduction in Type VII collagen expression in severe RDEB (RDEB-S) may manifest as widespread and persistent blistering at birth. It may be accompanied by a miliary rash, inflammation, atrophic scarring, nail dystrophy or loss, dental caries, anemia, and aggressive cutaneous squamous cell carcinoma (SCC).[10] SCC is the major cause of mortality in early adulthood in RDEB-S and it is very critical to treat it.[11] However, Type VII collagen expression in DDEB is slightly reduced, which may lead to mild blistering at or after birth. The blisters are usually confined to the limbs and may sometimes subside with age. This condition may be accompanied

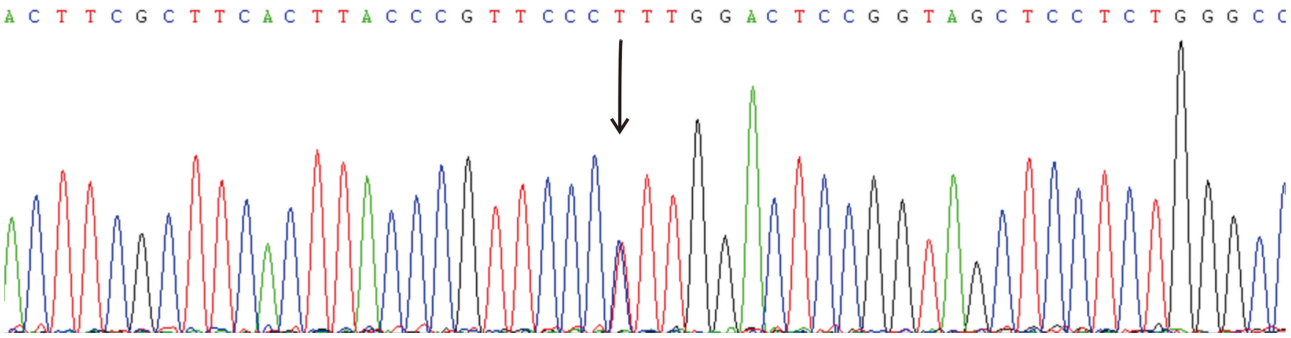


**Figure 4** The sequencing map: the black arrow indicates the mutation site.

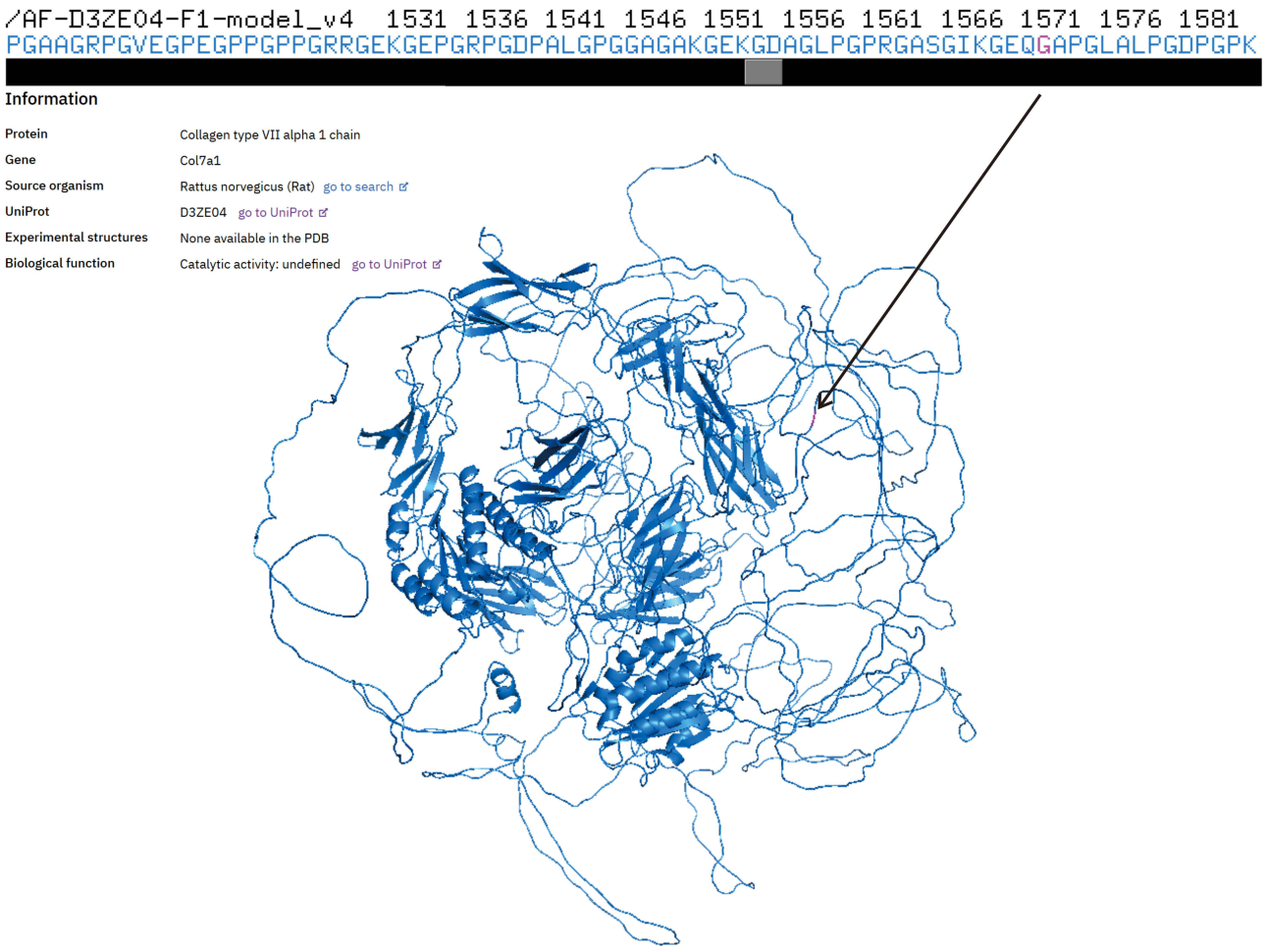


**Figure 5** Protein structure prediction model: the black arrow indicates the mutation site (AlphaFold protein structure database).

by miliary rash, atrophic scarring, and nail dystrophy. The teeth and oral mucosa are rarely involved, and the prognosis is generally good.[12] In this case, the patient presented with a mild form of the condition, developing blisters and papules on the limbs after adulthood, without any other clinical manifestations such as missing nails. These clinical manifestations were consistent with those of DDEB. EBS is also mostly autosomal dominant inheritance, and blisters appear at birth or shortly after birth, with mild symptoms. Most cases are caused by mutations in the coding gene of keratin 5 (K5) or keratin 14 (K14), and are intraepidermal blisters, which is inconsistent with this case.[1] According to the latest classification report on genetic EB,[9] DEB can be divided into four main subtypes, including localized DDEB,

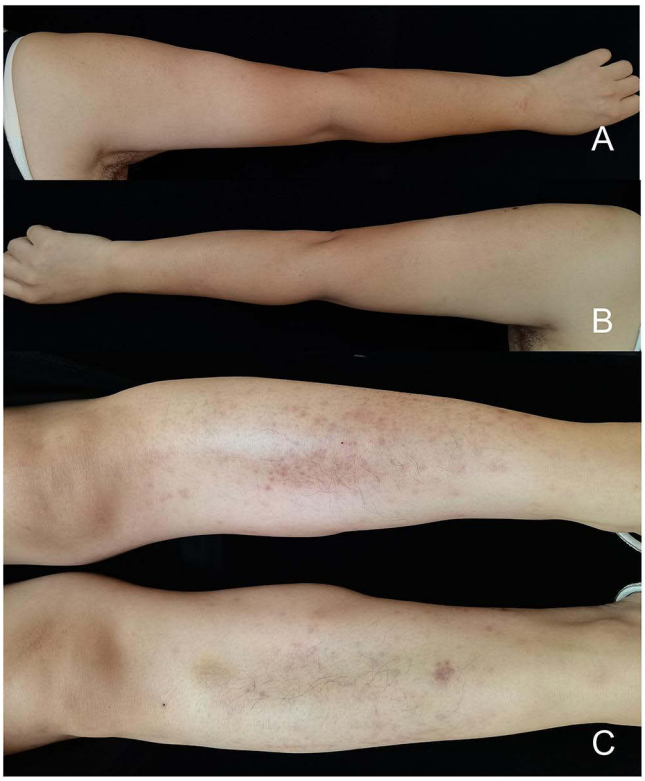


**Figure 6** Clinical manifestation: After 4 months of treatment, papules and blisters on both upper limbs (**A** and **B**) and legs (**C**) were significantly reduced, and some remained pigmentation.

intermediate DDEB, intermediate RDEB and severe RDEB, all caused by mutations in the *COL7A1* gene, which encodes Type VII collagen. Type VII collagen is an important structure for maintaining skin stability, and attention should be paid to the identification of epidermolysis bullosa acquisita (EBA) in this case. EBA is an autoimmune bullous disease, and anti-collagen type VII is its pathogenic autoantibody. Similar to DEB, it presented as a subepidermal blister, and immunohistochemistry revealed that type IV collagen was located at the apex of the blister. However, direct immunofluorescence showed that IgG deposition in the basement membrane band could be identified.[13] The *COL7A1* gene is composed of 118 separate exons, approximately 32 kb in size, encoding approximately 8.9 kb of mRNA transcripts that are translated into a procollagen α 1 (VII) chain consisting of 2499 amino acids. Three procollagens α 1 (VII) chains combine to form the homologous trimer, creating the stable dermo-epidermal structure of Type VII collagen.[14] Each procollagen α 1 (VII) strand contains an amino-terminal non-collagenous domain (NC1), a central collagen domain, and a carboxy-terminal NC2 domain. The central collagen domain consists of repeated Gly-X-Y sequences that fold to form a characteristic triple-helical structure.[15] According to a UniProt database query, there is currently no predictive model for the protein structure of the human *COL7A1* gene. The mouse α 1 (VII) collagen polypeptide exhibits 84.7% identity and 90.4% homology with the corresponding human sequence at the amino acid level. The defects and disruptions in the collagen domain composed of Gly-X-Y repeats are highly conserved.[16] Therefore, we modeled the AlphaFold structure using a mouse protein. Most mutations in DDEB involve the substitution of glycine in the Gly-X-Y repeat sequence, thus disrupting the stability of the collagen triple-helix structure. Notably, the substitution of glycine can also lead to RDEB, depending on the location of the mutation within the protein and the properties of the substituted amino acid.[17] In this case, the patient carried the c.4714G>A (encoding a change at nucleotide 4714 from guanine (G) to adenine (A)). This represents a heterozygous nucleotide mutation resulting in an amino acid change from glycine to arginine at position 1572 (p.Gly1572Arg), considering it a missense mutation. Most RDEBs result from mutations in both alleles of the *COL7A1* gene, caused by premature stop codon mutations due to nonsense mutations, frameshift insertions, or deletions. These mutations lead to nonsense-mediated mRNA decay and the deletion of Type VII collagen and anchor fibrils.[14] In

patients with DDEB caused by heterozygous variation, such as in this case, glycine substitution in the collagen α 1(VII) chain domain is usually associated with heterozygous variation involving only one allele, resulting in missense mutations. Glycine is the smallest and most common amino acid in collagen, and when it is replaced by a large number of positively charged amino acids (such as arginine), the structure and function of the protein change, resulting in protein defects.[18]

Most of the previously reported guanine substitutions in DDEB were located in exons 73–87, resulting in glycine substitution mainly concentrated in amino acids 1770–2704. No literature or large-scale population frequency database reported guanine substitution in exon 49, resulting in glycine substitution at position 1572. The Polyphen-2 software predicted that the mutation was probably damaging. Glycine can be replaced by different amino acids in various disease subtypes, resulting in dominant or recessive inheritance owing to the obvious heterogeneity of the disease. Two non-glycine missense mutations were also found as causes of DDEB: an arginine substitution for lysine (K2682R) and a methionine substitution for valine (V760M).[19] In addition, there are relatively rare exon frameshifts caused by single allelic splicing sites or indel mutations, such as the heterozygous indel *COL7A1* mutation 8068del17insGA and the heterozygous c.6215delA mutation. These mutations can lead to the formation of DDEB with varying severities of collagen triple helix structure abnormalities.[20,21]

Currently, there is no specific therapy for EB, and symptomatic treatment and prevention remain the primary management methods. In recent years, cell therapy, lentiviral gene therapy, gene editing, monoclonal antibody therapy, and other innovative methods have gained popularity. Different subtypes of DEB may cause varying degrees of chronic inflammation and infection, and the upregulation of inflammatory factors and Janus kinase (JAK) signaling may be related to pruritus in DEB.[22] Consistent with previous reports,[23] the JAK inhibitor (upadacitinib) used in this patient selectively inhibited JAK1 targets in the JAK-STAT pathway, effectively reduced inflammatory factors, and alleviated pruritus symptoms. The patient has been followed up for only 4 months, limiting our study. The longer-term efficacy of upadacitinib in this patient is unknown. In addition, a larger sample size is required to study whether upadacitinib is effective only for patients with DEB caused by this mutation or includes patients carrying mutations at other sites.

## Conclusion

DEB mutation analysis has important implications for the subclassification of DEB, DNA-based prenatal diagnosis, and the assessment of disease recurrence risk in certain families. The newly identified *COL7A1* c.4714G>A (p.Gly1572Arg) mutation provides new clinical data and molecular genetic insights for the diagnosis and treatment of related inherited dermatoses. Improving diagnostic accuracy and therapeutic efficacy requires further studies exploring the long-term effects of interventions such as JAK inhibitors on DEB patients and the clinical significance of the novel *COL7A1* mutation.

## Ethics Statement

The study involving humans was approved by The First Affiliated Hospital of Gannan Medical University. The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the participant, for the publication of any potentially identifiable images or data included in this article.

## Consent for Publication

We have obtained written informed consent from the patient for the publication and accompanying images. All authors have read and approved the final manuscript for submission.

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## Disclosure

Shuqin Lai and Chunli Lin are co-first authors for this study. The authors report no conflicts of interest in this work.

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