ISSN 2473-4799

DERMATOLOGY
Open Journal

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Case Report

A Case of Junctional Epidermolysis Bullosa with Pyloric Atresia Due to Integrin β4 Gene Mutations

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Article information
Received: March 11th, 2019; **Revised:** April 4th, 2019; **Accepted:** April 8th, 2019; **Published:** April 10th, 2019

Cite this article
Yoshihara N, Nakano H, Sawamura D, et al. A case of junctional epidermolysis bullosa with pyloric atresia due to integrin β4 gene mutations. *Dermatol Open J*. 2019; 4(1): 7-9. doi: 10.17140/DRMTOJ-4-134

ABSTRACT

Junctional epidermolysis bullosa with pyloric atresia is a rare bullous disease with autosomal recessive inheritance caused by abnormalities in the integrin α6 (*ITGA6*) or integrin β4 (*ITGB4*) gene. Its clinical symptoms range from mild to fatal. Herein, we report a case of mild junctional epidermolysis bullosa with pyloric atresia caused by compound heterozygous mutations in the *ITGB4* gene.

Keywords
Epidermolysis bullosa, Pyloric atresia, *ITGB4* mutation.

INTRODUCTION

Epidermolysis bullosa is a rare hereditary disorder characterized by mucocutaneous fragility and is caused by mutations in the genes that encode structural proteins in the epidermal basement membrane.[1] Even a slight external force can cause separation of the epidermis from the dermis, leading to the formation of blisters and erosions on the skin and mucosa. Epidermolysis bullosa is largely classified into simplex, junctional and dystrophic types according to the site of cleft formation. There is also a subtype associated with pyloric atresia called epidermolysis bullosa with pyloric atresia (EB-PA), which is divided into epidermolysis bullosa simplex with pyloric atresia (EBS-PA) and junctional epidermolysis bullosa with pyloric atresia (JEB-PA). JEB-PA is caused by abnormalities in the *ITGA6* or *ITGB4* gene. The *ITGA6* and *ITGB4* genes encode integrin α6 and integrin β4, respectively.[2] Since these genes are also expressed in organs other than the skin, including the gastrointestinal tract, pyloric atresia and the other symptoms of JEB-PA are considered to occur as complications. Most cases of JEB-PA show autosomal recessive inheritance and have mutations in both alleles of the gene. Abnormalities in the *ITGB4* gene have been reported to account for approximately 85% of all cases of JEB-PA.[3,4] Herein, we report a case of mild JEB-PA with abnormalities in the *ITGB4* gene.

CASE REPORT

The patient was a 49-year-old Japanese female born to healthy parents. She was found to have pyloric atresia at birth and underwent surgery for congenital pyloric atresia 1-week after birth. She developed blisters on her body at the age of 6-years. As shown in Figure 1, at present, she has blisters and erosions on the trunk and limbs, and pigmentation and mild skin atrophy are seen in the cured areas. All her nails are fragile and deformed with thickening. There are no tooth or hair abnormalities or pseudosyndactyly. Any other organs were not affected. Her family history includes her elder brother's death from malnutrition due to pyloric atresia in the neonatal period. A skin biopsy revealed subepidermal blisters and mild lymphocytic infiltration in the upper dermis (Figure 2). She was sent to Juntendo University Hospital for a consultation at the age of 48-years. Sanger sequencing of all coding exons and adjacent intronic boundaries of *ITGB4* compound heterozygous mutations of c.600dupC(p.F201Lfs*15) and c.1274A>C(p. Q425P) in the *ITGB4* gene. Based on the above findings, we made a final

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diagnosis of junctional epidermolysis bullosa with pyloric atresia due to the mutations in the *ITGB4* gene. We conducted detailed genetic counseling including that the mutation was inherited in an autosomal recessive fashion. The erosions on the trunk and limbs were treated symptomatically with topical 1% silver sulfadiazine cream, and the patient and the patient apply this cream once a day for the affected area. One year has passed since she started treatment at our hospital, and her general condition is good. Her rash tends to worsen slightly in summer.

Figure 1. *Clinical Findings: (a) Blisters and Erosions with Pigmentation on the Thigh. (b) Pigmentation and Erosions are Seen on the Lower Leg. The Toenails are Deformed and Thickened (c) Tense Blisters and Erosions at the Site of the Rash (d) the Pedigree: The Arrow Indicates the Patient of the Present Case.*

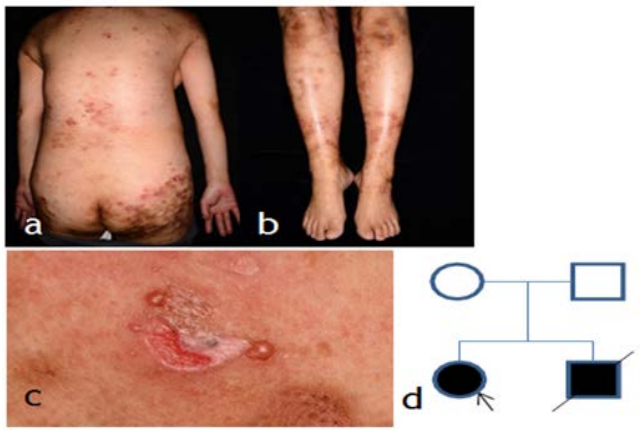
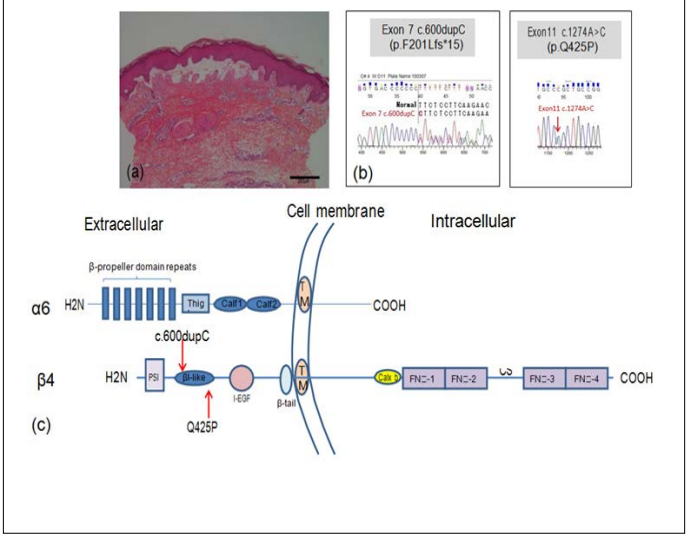


Figure 2. *(a) Pathological Findings: Subepidermal Blisters with Mild Lymphocytic Infiltration (b) Direct Sequencing of the Patient's ITGB4 Gene. Compound Heterozygous Mutations were Identified. (c) Schematic Structure of α6β4 Integrin. This Figure is Quoted from the Reference from Goletz and Schmidt. [10] The Arrows Show the Position of the ITGB4 Mutations. The Both Positions of the Predicted Amino Acid Substitution are Close to the N-terminus of ITGB4. H2N, N-terminus; COOH, C-terminus; TM, Transmembrane Domain; PSI, Cysteine-rich Plexin-Sema-Phorin-Integrin Domain; β I-like, β1-like Domain; I-EGF, Cysteine-Rich Integrin Epidermal Growth Factor Domain; β-tail, β-tail Domain; FNIII, Fibronectin Type III; CS, Connecting Segment*



DISCUSSION

JEB-PA involves both lethal and non-lethal mutations.[5] Lethal JEB-PA is generally caused by premature stop codons (PTCs) in both alleles, while nonlethal JEB-PA is mainly caused by a missense or splicing mutation in at least one allele. The c.600dupC(p.F201Lfs*15) mutation observed in the present case generates a PTC and has also been previously reported in one case by Masunaga et al.[6] Moreover, the missense mutation c.1274A>C(p. Q425P) has also been reported in some cases.[7] The combination of the gene abnormalities found in the present case was previously reported by Masunaga et al, and the JEB-PA patient, in that case, was a Korean patient who died of malnutrition at the age of 2-years.[6] Masunaga et al reported that an amino acid substitution from glutamine to proline at position 425 reduced the α-helix formation ability of integrin β4 in the adjacent region and that the gene abnormality Q425P was the pathogenic factor in that case. Furthermore, they described that since there have been fatal JEB-PA cases caused by a combination of a PTC and a missense mutation, "this combination may be regarded as a mediator of lethal and non-lethal cases." The patient reported by Masunaga et al died in childhood, while the present patient remains alive at the age of 49-years. Although her elder brother's gene polymorphisms are unknown, he likely carried the same gene abnormalities as the present patient and died in the neonatal period. Therefore, the gene abnormality Q425P may be a missense mutation that could be a lethal factor in some cases. In addition, Hattori et al reported a 5-year-old mild-JEB-PA patient with the E517Sfs*252/Q425P mutation.[7] The patient reported by Hattori et al was a Japanese girl with a mild form of the disease in whom erosions on the body spontaneously disappeared with age, and only mild nail deformities remained. We think that the present case is similar to the case reported by Hattori et al. In non-lethal case, skin lesions tend to improve with years.[8] Schumann H et al studied genotype-phenotype correlations and indicates that solely mild skin involvement was associated with deletion of the C-terminus of β4 integrin.[9] In the present case, both positions of the predicted amino acid substitution are close to the N-terminus of *ITGB4* (Figure 2c). These positions also may influence the clinical severity.

Further accumulation of genetic data from JEB-PA patients is required for a deeper exploration of the relationships between the genotype and phenotype and could lead to a deeper understanding of the role of integrin α6 and β4 in dermal-epidermis adhesions.

CONCLUSION

To the best of our knowledge, this is the second reported case of junctional epidermolysis bullosa with pyloric atresia caused by the compound heterozygous mutations of c.600dupC (p.F201Lfs*15) and c.1274A>C (p.Q425P). The genotype was consistent between the present case and the previously reported first case, but the clinical course differed greatly between the two cases. We think that the present case is very important in understanding the relationship between the genotype and phenotype in JEB-PA.

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CONSENT

The authors have received oral informed consent from the patient whose photographs are included in the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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