Letter to the Editor

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Compound Heterozygous Mutations with a Novel Variant in Integrin Beta4 Cause Epidermolysis Bullosa with Pyloric Atresia and Urologic Abnormalities

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To the Editor,

Epidermolysis bullosa (EB) with pyloric atresia (PA) is an autosomal recessive form of EB subtype that affects the skin, as well as digestive and frequently urogenital tracts. EB-PA is classified as the simplex form caused by the plectin gene (PLEC) mutations and the junctional form caused by integrin α6β4 genes (ITGA6, ITGB4) mutations.[1-5] However, the intracellular domain of integrin β4 interacts with other hemidesmosomal components of basal keratinocytes, including plectin.[6] A recent review on the transmission electron microscopy (TEM) findings of EB-PA patients who showed absent expression of integrin β4 reported a consistent level of cleavage planes through concurrent low intra-basal epidermal and lamina lucida,[7] suggesting that the loss of integrin β4 can lead to this unique ultrastructural finding.

We previously reported a Korean male newborn who presented with PA with mucocutaneous blisters at birth.[8] Widespread blisters were found on the entire body and oral mucosa, and they eventually healed without significant scarring. Nail dystrophy was observed on the right thumb. Multiple urologic abnormalities including bilateral hydronephrosis, hydroureter, and a distended trabeculated bladder were noted at 12 months of age. Immunofluorescence mapping and TEM performed at infancy revealed the localization of type IV and VII collagen to the blister base and intra-basal epidermal cleavages with tonofilaments clumping, respectively, leading to a diagnosis of EB simplex, generalized severe, formerly called Dowling-Meara type with PA and urologic abnormalities.[8] The patient's father, paternal brother, and sister had reported bullae without any anomalies, which had spontaneously improved. In this report, we describe compound heterozygous mutations in integrin β4 in this patient, which were not previously identified. Next-generation sequencing performed after obtaining informed consent revealed compound heterozygous missense mutations, c.113G>T (p.C38F) in exon 3 and c1274A>C (p.Q425P) in exon 11 of ITGB4 gene, which were confirmed by additional Sanger sequencing (Fig. 1A). Mutations in PLEC or keratin genes have not been detected. Missense mutation of p.Q425P has been reported in EB-PA.[9-11] p.C38F in ITGB4 was reported as a codon variant, but has not been reported to be associated with EB.[12] Two in silico tools, including SIFT and PolyPhen-2, predicted that this amino acid substitution in ITGB4 is likely pathogenic. Cutaneous symptoms improved with age, showing only blistering limited to the extremities and inguinal area at age 22 (Fig. 1B).

Integrin β4 consists of an intracytoplasmic domain connected to keratin intermediate filaments via binding to plectin and type XVII collagen and an extracellular domain connected to laminin. ITGB4 mutations are the most frequent cause of EB-PA, and EB-PA caused by ITGB4 mutations has been classified as a form of junctional EB,[4] but a previous paper reported that the deletion of a cytoplasmic domain of integrin β4 causes EB simplex without PA.[13] This indicated that mutations in the intracytoplasmic domain of integrin β4 may result in intrabasal splits, suggesting EB simplex rather than junctional EB.[13] In this case, despite the compound heterozygous missense mutations in the

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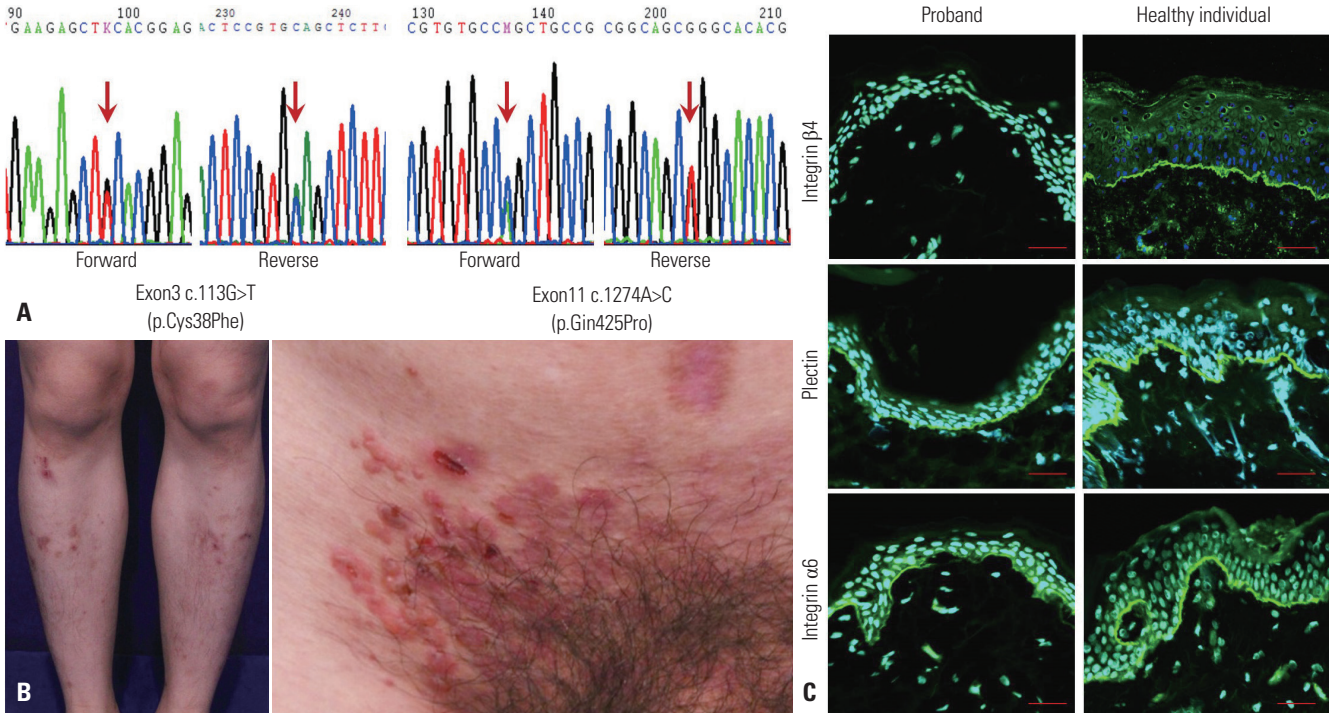

Fig. 1. Clinical features and genetic information of the patient. (A) Direct sequencing (Sanger method) of DNA identified compound heterozygous missense mutations in c.113G>T (p.C38F) in exon 3 and c1274A>C (p.Q425P) in exon 11 of ITGB4 in the patient's DNA. (B) Clinical features of the patient at age 22. (C) Representative immunofluorescence staining images of integrin β4, plectin, and integrin β6 in the skin of the patient and healthy individual (scale bars=50 μm).

extracellular domain of integrin β4, TEM showed cleavages above the hemidesmosome and keratin clumping in the basal keratinocytes, resembling the finding in EB simplex, generalized severe. Besides, the expression of plectin was reduced in the patient's skin, despite the absence of mutations in PLEC (Fig. 1C). These findings might be possibly due to the impaired stabilization of plectin by integrin β4, which in turn, may affect the interaction with keratin intermediate filaments. However, to exclude the possibility of artificial cleavages within the basal cells or dermo-epidermal junction and to confirm the type of EB-PA, thorough inspection of numerous sections of TEM samples will be further required. Based on the position of ITGB4 mutations, our case is thought to be junctional EB-PA.

The prognosis of junctional EB-PA is generally poor, but spontaneous amelioration of symptoms with aging has been reported in rare cases.[14,15] Our case is also considered to belong to this rare subgroup.

Among the ITGB4 missense mutations in our case, we found p.C38F in ITGB4. Another mutation at the same codon 38 (p.C38R) has been reported in EB-PA patients,[16] but p.C38F has not been reported to be associated with EB-PA. Another interesting finding in our case was that the patient presented with mild skin lesions possibly due to compound heterozygous missense mutations in ITGB4, but relatively severe and multiple congenital urologic abnormalities, suggesting that genotype-phenotype correlations are not always evident in EB-PA with ITGB4 mutations. Collectively, our case expands the genotypic and phenotypic spectrum and ultrastructural findings of EB-PA caused by ITGB4 mutations.

AUTHOR CONTRIBUTIONS

Conceptualization: Soo-Chan Kim and Sang Eun Lee. Data curation (gene sequencing): Song-Ee Kim. Formal analysis: Sang Eun Lee. Methodology: Soo-Chan Kim and Sang Eun Lee. Project administration: Sang Eun Lee. Resources: Dae San Yoo and Song-Ee Kim. Supervision: Sang Eun Lee. Visualization: Dae San Yoo and Seung-Ju Lee. Writing—original draft: Dae San Yoo. Writing—review & editing: Sang Eun Lee. Approval of final manuscript: all authors.

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REFERENCES

1. Nakamura H, Sawamura D, Goto M, Nakamura H, McMillan JR, Park S, et al. Epidermolysis bullosa simplex associated with pyloric atresia is a novel clinical subtype caused by mutations in the plectin gene (PLEC1). J Mol Diagn 2005;7:28-35.
2. Charlesworth A, Gagnoux-Palacios L, Bonduelle M, Ortonne JP, De Raeve L, Meneguzzi G. Identification of a lethal form of epi-

https://doi.org/10.3349/ymj.2020.61.9.831

dermolysis bullosa simplex associated with a homozygous genetic mutation in plectin. J Invest Dermatol 2003;121:1344-8.
3. Schaapveld RQ, Borradori L, Geerts D, van Leusden MR, Kuikman I, Nievers MG, et al. Hemidesmosome formation is initiated by the beta4 integrin subunit, requires complex formation of beta4 and HD1/plectin, and involves a direct interaction between beta4 and the bullous pemphigoid antigen 180. J Cell Biol 1998;142:271-84.
4. Chung HJ, Uitto J. Epidermolysis bullosa with pyloric atresia. Dermatol Clin 2010;28:43-54.
5. Dang N, Klingberg S, Rubin AI, Edwards M, Borelli S, Relic J, et al. Differential expression of pyloric atresia in junctional epidermolysis bullosa with ITGB4 mutations suggests that pyloric atresia is due to factors other than the mutations and not predictive of a poor outcome: three novel mutations and a review of the literature. Acta Derm Venereol 2008;88:438-48.
6. Koster J, van Wilpe S, Kuikman I, Litjens SH, Sonnenberg A. Role of binding of plectin to the integrin beta4 subunit in the assembly of hemidesmosomes. Mol Biol Cell 2004;15:1211-23.
7. Wang JY, Marinkovich MP, Rieger KE. Epidermolysis bullosa with pyloric atresia consistently demonstrates concurrent low intrabasal epidermal and lamina lucida cleavage planes: a survey of six cases. J Eur Acad Dermatol Venereol 2020;34:e200-3.
8. Kim DK, Kim SC, Chang SN, Kim SY. Epidermolysis bullosa simplex (Dowling-Meara type) associated with pyloric atresia and congenital urologic abnormalities. Yonsei Med J 2000;41:411-5.
9. Hattori M, Shimizu A, Nakano H, Ishikawa O. Mild phenotype of junctional epidermolysis bullosa with pyloric atresia due to a novel mutation of the ITGB4 gene. J Dermatol 2018;45:e203-4.
10. Masunaga T, Ishiko A, Takizawa Y, Kim SC, Lee JS, Nishikawa T, et al. Pyloric atresia-junctional epidermolysis bullosa syndrome showing novel 594insC/Q425P mutations in integrin beta4 gene (ITGB4). Exp Dermatol 2004;13:61-4.
11. Yoshihara N, Nakano H, Sawamura D, Kamata A, Matsuzaki H, Etoh T, et al. A case of junctional epidermolysis bullosa with pyloric atresia due to integrin β4 gene mutations. Dermatol Open J 2019;4:7-9.
12. National Center for Biotechnology Information. ClinVar; VCV000202108.5 [accessed on 2020 March 18]. Available at: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000202108.5.
13. Jonkman MF, Pas HH, Nijenhuis M, Kloosterhuis G, Steege G. Deletion of a cytoplasmic domain of integrin beta4 causes epidermolysis bullosa simplex. J Invest Dermatol 2002;119:1275-81.
14. Chavanas S, Gache Y, Vailly J, Kanitakis J, Pulkkinen L, Uitto J, et al. Splicing modulation of integrin beta4 pre-mRNA carrying a branch point mutation underlies epidermolysis bullosa with pyloric atresia undergoing spontaneous amelioration with ageing. Hum Mol Genet 1999;8:2097-105.
15. Hayashi AH, Galliani CA, Gillis DA. Congenital pyloric atresia and junctional epidermolysis bullosa: a report of long-term survival and a review of the literature. J Pediatr Surg 1991;26:1341-5.
16. Mellerio JE, Pulkkinen L, McMillan JR, Lake BD, Horn HM, Tidman MJ, et al. Pyloric atresia-junctional epidermolysis bullosa syndrome: mutations in the integrin beta4 gene (ITGB4) in two unrelated patients with mild disease. Br J Dermatol 1998;139:862-71.