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A Case of Hailey-Hailey Disease with a Novel Nonsense Mutation in the *ATP2C1* Gene

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Dear Editor:

Hailey-Hailey disease (HHD) is an autosomal dominant hereditary skin disease typically presenting with vesicles, erosions and crusts on the intertriginous areas such as the neck, axillae, groins, and perineum after the middle age. The responsible gene for HHD is *ATP2C1*, which encodes human secretory pathway Ca^{2+}/Mn^{2+}-ATPase protein 1 (SPCA1), a Ca^{2+} pump expressed in the Golgi apparatus[1]. Although over 150 pathological mutations have been identified throughout *ATP2C1*, no clear genotype-phenotype correlation has been revealed[2].

A 50-year-old Japanese male had a 2-year history of recurrent erythemas with vesicles and erosions on the posterior neck, axillae and popliteal fossae. Despite application of topical steroids, he had difficulty in walking due to painful inguinal erosions and was admitted. Skin lesions of the patient included erosions with pustular discharge on the inguinal area and erythemas with vesicles and crusts on the back, abdomen, axillae and thighs (Fig. 1A, B). The serum level of C-reactive protein was elevated (2.9 mg/dl), and *Streptococcus agalactiae* was cultured from inguinal discharge. Histopathological examination of vesicular erythema on the back revealed a separation of keratinocytes (acantholysis) at the suprabasal layers of the epidermis, which gave the appearance of "dilapidated brick wall" (Fig. 1C). Direct immunofluorescence was negative and generalized HHD with secondary bacterial infection was suspected. The lesions were improved by staying calm with oral clarithromycin and olopatadine hydrochloride, as well as topical zinc oxide for inguinal lesions and difluprednate for other lesions. After discharge, skin lesions occasionally flared and temporal administration of oral steroid was required.

By genetic analysis of the patient's peripheral blood, a

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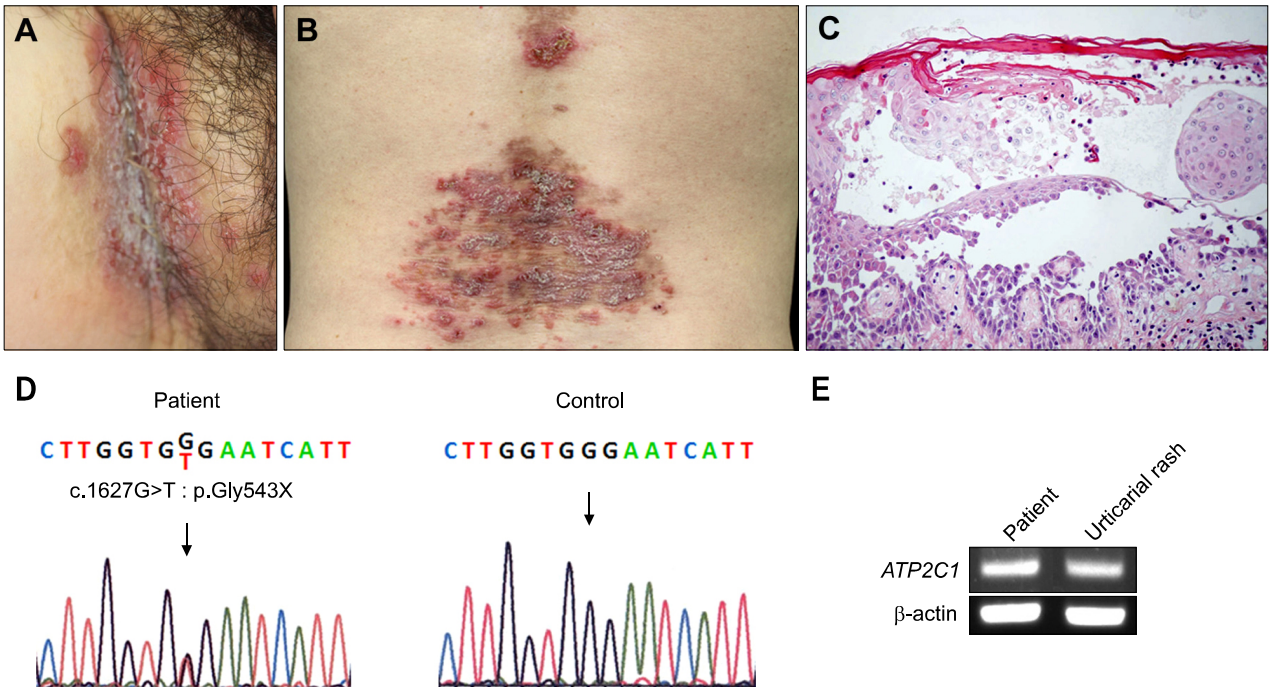

Fig. 1. (A) Erosive lesion on the inguinal area of the patient. (B) Erythematous lesion with vesicles and crusts on the back of the patient. (C) Separation of keratinocytes at the suprabasal layers of the epidermis observed in the lesional back skin (H&E, ×100). (D) Heterozygous c.1627G>T transition causing a premature termination (p.Gly543X) of the *ATP2C1* gene identified by the genetic analysis of the patient's peripheral blood. (E) Sufficient *ATP2C1* mRNA expression in the lesional skin of the patient, comparable in positive control skin with intact epidermis from a patient with urticarial rash. Gene-specific primer pairs used for RT-PCR were as follows: 5′-CCTTATTATGCTGCTTCTGG-3′ and 5′-CTTTGCTTTGCCACATCTGA-3′ for *ATP2C1*, and 5′-CTCCATCATGAAGTGTGACG-3′ and 5′-TGCTTGCTGATCCACATCTG-3′ for *β*-actin, which was examined as an internal control.

novel heterozygous c.1627G>T transition on exon 18 of *ATP2C1*, causing a premature termination (PT) at amino acid 543 (p.Gly543X), was identified and the diagnosis of HHD was confirmed (Fig. 1D). We recently reported that the severe phenotype of a case with a PT-causing mutation is possibly caused by nonsense-mediated mRNA decay[3]. To confirm this possibility in the present case, *ATP2C1* mRNA expression was examined with reverse transcription-polymerase chain reaction (RT-PCR) using mRNA extracted from the biopsy specimen and *ATP2C1*-specific primer pairs which amplify an upstream portion of the mutation described elsewhere[4]. Biopsy specimen of the lesional skin from a patient with urticarial rash was simultaneously examined for the control. As a result, sufficient *ATP2C1* mRNA expression was unexpectedly observed in our case as compared to the case of urticarial rash with intact epidermis (Fig. 1E). Aminoglycosides, which reportedly induce readthrough of pathogenic nonsense mutations, had never been applied topically or systemically in our case[5]. Even if the mutant *ATP2C1* mRNA was sufficiently expressed, severe functional defect of the mutant SPCA1 is expected because Gly543 is located within the cytoplasmic ATP-binding domain and PT at this residue causes deletion of the following 350 amino acids containing the C-terminal 6 transmembrane domains[3]. These observations suggest that functional impairment, rather than reduced mRNA expression, contributes to the phenotype in our case. Further study should be required to clarify how expression of the mutant *ATP2C1* mRNA is regulated and relates to the disease severity.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Eruptive Melanocytic Nevi without Any Trigger in a 5-Year-Old Healthy Girl

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Dear Editor:

Eruptive melanocytic nevi (EMN) are rare skin manifestations characterized by the simultaneous and abrupt development of numerous melanocytic nevi on the skin[1]. Although the exact mechanism of EMN development is not well understood, it has been associated with various triggers including light exposure, cutaneous injury such as the Koebner phenomenon, bullous dermatoses, systemic immunosuppression, biologic chemotherapeutics, increased hormone levels, and others including atopic dermatitis in children, postoperative fever, and seizures[2]. However, EMN without any trigger, especially in a healthy girl, are rather rare.

A 5-year-old Korean girl presented with multiple hyperpigmented maculopapules over the whole body. The lesions first appeared on her chest when she was 1 year old, and then hundreds of similar lesions covering her entire skin surface developed continuously during the next 2 years. The girl was of Fitzpatrick skin type IV and had no specific medical and family histories including multiple nevi. On physical examination, there were no systemic abnormalities except for the skin lesions that appeared as multiple small (0.5～3 mm diameter) brown to black pigmented maculopapules with a globular pattern on dermoscopy (Fig. 1). The histopathologic finding was compatible with compound nevus. Findings of routine laboratory examinations including complete blood counts, peripheral blood smear, liver/renal function test, venereal disease research laboratory test, antinuclear antibody, and urine analysis were either negative or within the normal limits. The test for BRAF V600E mutation was negative.

There have been very limited data about the changes in

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