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Letter to the editor

A mild case of Hailey-Hailey disease caused by a novel *ATP2C1* mutation

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Hailey-Hailey disease (HHD, MIM_#169600) is an autosomal dominant inherited disorder of cornification caused by the defective functioning of intracellular calcium pumps in keratinocytes. HHD is associated with mutations in *ATP2C1*, which encodes the secretory pathway Ca^{2+}-ATPase 1 protein (SPCA1) that is responsible for Ca^{2+} and Mn^{2+} uptake by the Golgi apparatus.[1] In HHD, painful blisters and vesicles that develop into erosions and scaly erythematous plaques occur at sites of friction such as the axillae, groins, neck and perineum.[2,3] Even mild disease can severely affect quality of life.[2]

The present patient is a 56-year-old Japanese woman who had erythematous plaques on the flexor aspect of the knees for 2 years. Additionally, she noticed erythema on the forearms 8 months ago (Fig. 1a, b). These had failed to heal with topical heparinoid ointment and topical anti-fungal therapy. The skin lesions were limited to parts of the extremities and were not seen on the groins or the axillae. No member of her family had similar skin lesions. A skin biopsy from the plaque of the right elbow revealed moderate acantholysis of the epidermis accompanied by hyperkeratosis (Fig. 1c).

Ethical approval was obtained, and all research was performed in accordance with the *Declaration of Helsinki* principles. Following informed consent, whole-exome sequencing was performed using genomic DNA extracted from peripheral blood from the patient.[4] The nonsense mutation c.2385G>A (p.Trp795*) was identified in exon 24 of *ATP2C1* (NM_014382.3) and was validated by Sanger sequencing (Fig. 1d). The identical truncation p.Trp795* caused by a different base change (c.2384G>A) was reported previously as a pathogenic mutation in an individual with HHD.[5] It is located in the fourth of five golgi apparatus lumens of the SPCA1 (Fig. 1e). We were unable to assess phenotype/genotype corelations for this truncation, because the clinical features

of HHD were lacking in the previous report.[5]

Our case had relatively mild cutaneous features, showing only erythematous papules on the flexor side of joints and knees during summer. HHD can present with a wide range of severity. This could be associated with either genetic or environmental factors, or both. Nellen et al. reported that, among 13 HDD cases, four patients (31%), two patients (15%) and seven patients (54%) showed mild, moderate and severe phenotypes, respectively.[2] From 2000 to 2016, 167 *ATP2C1* mutations have been reported in 209 families and sporadic patients with HHD.[2] *ATP2C1* mutation of any type or location seems to disrupt Golgi Ca^{2+} homeostasis, which is enough for HHD to develop.[2] The extensive phenotypic variation suggests the influence of other yet unknown modifying genes. Additionally, the skin lesions are often exacerbated by heat, sweating, mechanical trauma, infection and exposure to ultraviolet B. Our case suggests that it is necessary to consider the possibility of HHD even if the patient does not show the typical clinical features of HHD. The present patient showed extraordinarily mild skin manifestations, with papules restricted to the flexor aspect of the knees at her first visit. Accordingly, skin biopsy and molecular mutational analysis are important for the accurate diagnosis of HHD.

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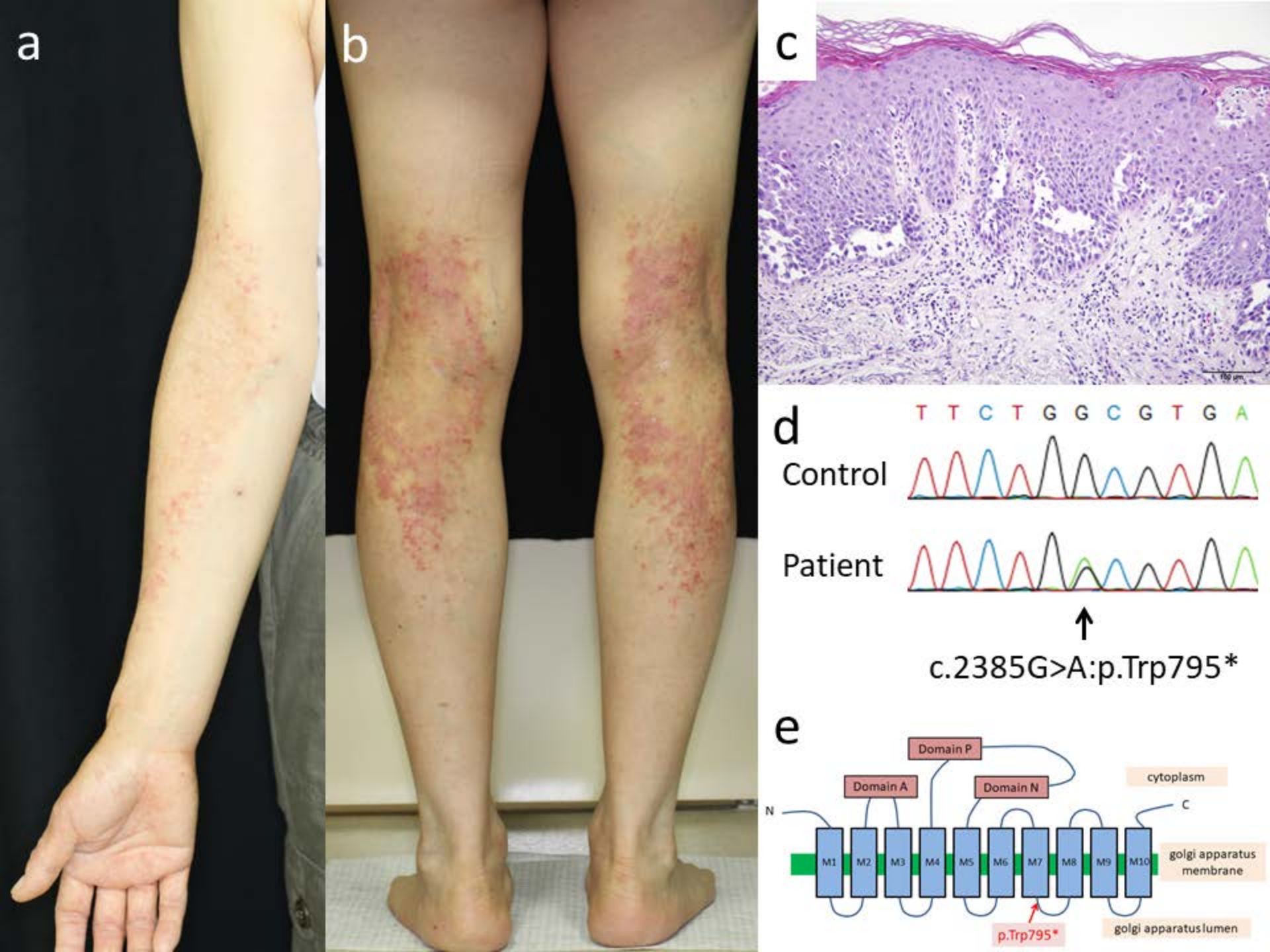
Figure legends

Figure 1. The clinicopathological features of the patient and the domain structure of SPCA1

(a, b) Erosive erythematous plaques and pigmentation on the flexor aspect of the right elbow (a) and the knees (b). (c) A biopsy specimen from an erythematous plaque shows acantholysis in the epidermis with mild hyperkeratosis. Scale bar: 100μm. (d) Sanger sequencing confirms a heterozygous c.2385G>A transition (p.Trp795*) of *ATP2C1* in the patient. (e) Schematic model of the domain structure of SPCA1. Blue areas: transmembrane domains (from M1 to M10). The present mutation site is marked by a red arrow.


a
b
c
d
T T C T G G C G T G A
Control
Patient
c.2385G>A:p.Trp795*
e
Domain P
Domain A
Domain N
cytoplasm
N
C
M1
M2
M3
M4
M5
M6
M7
M8
M9
M10
golgi apparatus membrane
p.Trp795*
golgi apparatus lumen