Acta Derm Venereol 2013; 93: 719–720

SHORT COMMUNICATION

A Novel *ATP2C1* Early Truncation Mutation Suggests Haploinsufficiency as a Pathogenic Mechanism in a Patient with Hailey-Hailey Disease

Akitaka Shibata[1], Kazumitsu Sugiura[1], Utako Kimura[2], Kenji Takamori[2] and Masashi Akiyama[1]*

*Departments of Dermatology, [1]Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, and [2]Juntendo University Urayasu Hospital, Urayasu, Japan. *E-mail: makiyama@med.nagoya-u.ac.jp*

Accepted Nov 5, 2012; Epub ahead of print Mar 8, 2013

Hailey-Hailey disease (HHD, MIM 16960) is an autosomal dominant disease characterized by suprabasal cell separation (acantholysis) of the epidermis. The clinical features vary and include crusted erosions with vesicular pustules, and erythematous scaly plaques at sites of friction and flexures. The skin lesions are often exacerbated by heat, sweating, mechanical trauma, infection and exposure in ultraviolet B (UVB) (1). Patients have a defect in *ATP2C1* encoding the ATPase, Ca^{2+}-transporting, type 2C, member 1; (ATP2C1) on the Golgi apparatus (2).

We performed mutation analysis of *ATP2C1* in a Japanese patient with HHD and identified the heterozygous novel mutation c.212delT (p.Leu71ArgfsX26). This is a very early truncating mutation, which clearly suggests that haploinsufficiency is an underlying pathomechanism of HHD.

CASE REPORT

A 62-year-old Japanese man showed typical clinical features of HHD, with erythema and painful erosions in his axillae and groin (Fig. 1). He had had these skin symptoms from his late fifties, and they often worsened in summer and improved in winter. Neither the palms nor the nails were involved. He had no apparent family history of any skin disorder. Biopsy specimens from the breast revealed acantholysis and dyskeratosis in the suprabasal layers of the epidermis. From these findings, he was diagnosed with HHD.

The ethics committee of Nagoya University approved the studies described below, which were conducted according to the principles of the Declaration of Helsinki. The participant gave written informed consent.

The coding region of *ATP2C1* was amplified from genomic DNA by PCR, as described previously (3). Direct sequencing of the patient's PCR products revealed the patient to be heterozygous for the previously unreported deletion mutation c.212delT in *ATP2C1*, resulting in the frameshift p.Leu71ArgfsX26 (Fig. 2).

DISCUSSION

The phenotypic variations in HHD might be attributable to the interplay of extrinsic and intrinsic factors. The extrinsic factors might include exposure to environmental temperature, amounts of ultraviolet exposure, minor mechanical stimuli from everyday and occupational activities, and environmental pathogens, etc. (4, 5). Modifying the genes might affect ATP2C1 expression level and disease severity in an individual patient.

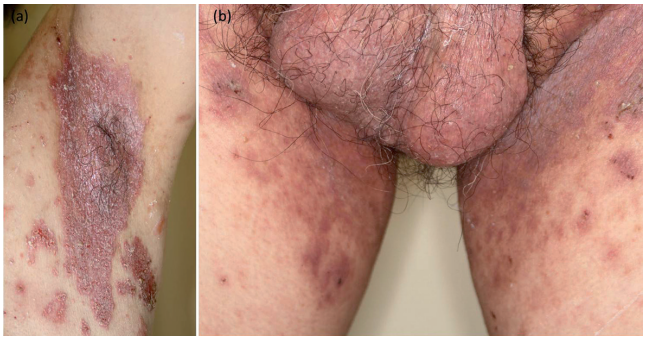

Fig. 1. Clinical features of the patient. (a) Demarcated erythema with erosions in the left axilla. (b) Brownish keratotic papules and plaques in the groin.

The identification of a mutation in the *ATP2C1* gene as a cause of HHD has important implications in the management of this condition. Based on genetic information, HHD patients might be offered genetic counselling and prenatal diagnosis. To date, more than 100 pathological mutations scattered throughout the *ATP2C1* gene have been described; however, no hot spot

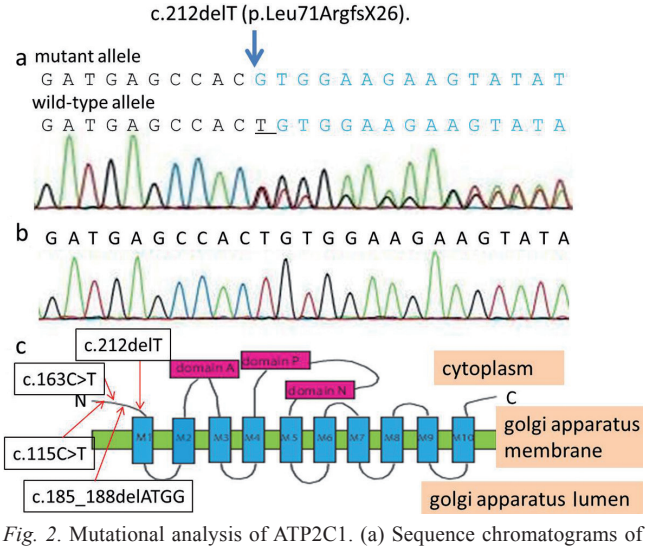

Fig. 2. Mutational analysis of ATP2C1. (a) Sequence chromatograms of *ATP2C1* in the patient show a heterozygous c.212delT allele. (b) Sequence chromatograms of *ATP2C1* in a healthy control. (c) Domain structure of ATP2C1 and the mutation site.

for causative mutations has been identified. Approximately 20% of these are nonsense mutations, 30% are frame-shift mutations leading to premature termination codons (PTCs) and 28% are missense mutations (6). The fact that 50% of the causative mutations reported to date lead to PTCs suggests that haploinsufficiency is a prevalent mechanism for the dominant inheritance of HHD (7–9) rather than the dominant negative mechanisms that some researchers believe (10).

In the case described here, c.212delT (p.Leu71ArgfsX26) was identified. It is noteworthy that this truncation mutation is in the vicinity of the N-terminus of ATP2C1. In most cases, the protein produced from the mutant allele is absent or markedly reduced as a consequence of nonsense-mediated mRNA decay. Even if the protein were produced from the mutant allele, the protein product would lack most of the ATP2C1 active domains that are typically found on ATPase-Ca^{2+} pump, and it is thought that the protein would have severely or completely abolished Ca^{2+} pump function. Thus, it would not be able to cause the dominant negative effect on ATP2C1 function. Haploinsufficiency is considered to be the pathogenetic mechanism of this case. A review of the literature showed an earlier truncating mutation of *ATP2C1*, c.185_188delATGG, in a patient with HHD (11). The severity of both our case and the patient with the mutation c.185_188delATGG was moderate, and there was no apparent clinical difference between them.

Furthermore, there are 2 reported nonsense mutations c.115C>T and c.163C>T located upstream of our case (3, 12). We think the present patient further supports that haploinsufficiency, rather than dominant negative effect, of *ATP2C1* mutations is the causative mechanism of HHD.

ACKNOWLEDGEMENT

This study was supported in part by a Grant-in-Aid for Scientific Research (A) 23249058 (MA) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by "Research on Measures for Intractable Diseases" Project: matching fund subsidy (H23-028) from Ministry of Health, Labour and Welfare of Japan.

The authors declare no conflicts of interest.

REFERENCES

1. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. Br J Dermatol 1992; 126: 275–282.
2. Hu Z, Bonifas MB, Beech J, Bench G, Shigihara T, Ogawa H, et al. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. Nature Genet 2000; 24: 61–65.
3. Sudbrak R, Brown J, Dobson-Stone C, Carter S, Ramser J, White J, et al. Hailey-Hailey disease is caused by mutations in ATP2C1 encoding a novel Ca2+ pump. Hum Mol Genet 2000; 9: 1131–1140.
4. Dobson-Stone C, Fairclough R, Dunne E, Brown J, Dissanayake M, Munro CS, et al. Hailey-Hailey diseases: molecular and clinical characterization of novel mutations in the ATP2C1 genes. J Invest Dermatol 2002; 118: 338–343.
5. Ikeda S, Shigihara T, Mayuzumi N, Yu X, Ogawa H. Mutations of ATP2C1 in Japanese patients with Hailey-Hailey disease: intrafamilial and interfamilial phenotype variations and lack of correlation with mutation patterns. J Invest Dermatol 2001; 117: 1654–1656.
6. Re'ka S, Richard K. Autosomal-dominant calcium ATPase disorders. J Invest Dermatol 2006; 126: 2370–2376.
7. Fairclough RJ, Dode L, Vanoevelen J, Anderson JP, Missiaen L, Raeymaekers L, et al. Effect of Hailey-Hailey disease mutations on the function of a new variant of human secretory pathway Ca2+/Mn2+-ATPase (hSPCA1). J Biol Chem 2003; 278: 24721–24729.
8. Fairclough RJ, Lonie L, Baelen KV, Haftek M, Munro CS, Burge SM, et al. Hailey-Hailey disease: identification of novel mutations in ATP2C1 and effect of missense mutation A528P on protein expression levels. J Invest Dermatol 2004; 123: 67–71.
9. Ton VK, Rao R. Expression of Hailey-Hailey disease mutations in yeast. J Invest Dermatol 2004; 123: 1192–1194.
10. Cheng Y, Cheng YM, Zhao G, Jia MC. A novel missense mutation of the ATP2C1 gene in a Chinese patient with Hailey-Hailey disease. Biochem Biophys Res Commun 2011; 406: 420–422.
11. Cheng TS, Ho KM, Lam CW. Heterogeneous mutations of the ATP2C1 gene causing Hailey-Hailey disease in Hong Kong Chinese. J Eur Acad Dermatol Venereol 2010; 24: 1202–1206.
12. Zhang GL, Sun YT, Shi HJ, Gu Y, Shao MH, Du XF. Mutation analysis of ATP2C1 gene in a Chinese family with Hailey-Hailey disease. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2010; 27: 414–416.