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 \( \text{ATP2C1} \) encoding the ATPase, Ca\(^{2+}\)-transporting, type 2C, member 1; (ATP2C1) on the Golgi apparatus (2).

We performed mutation analysis of \( \text{ATP2C1} \) 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 \( \text{ATP2C1} \) 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 \( \text{ATP2C1} \), 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 environmen-
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-Ca2+ pump, and it is thought that the protein would have severely or completely abolished Ca2+ 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.

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The authors declare no conflicts of interest.

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