Six novel mutations of ATP2C1 identified in eight Chinese patients with Hailey-Hailey disease

Sir,

Hailey–Hailey disease (HHD; MIM 169600), also known as familial benign chronic pemphigus, is a rare autosomal dominant dermatosis. The disease is characterized by

recurrent blisters, crusted erosions, and warty papules occurring mainly in the sites of friction and flexures, particularly the groin [Figure 1], neck, and axillary, perianal, and submammary regions. Histology reveals acantholysis of the epidermis, giving the appearance of a "dilapidated brick wall" [Figure 1]. The ATP2C1 gene on 3q22.1 was identified as the defective gene of HHD. The gene encodes an Adenosine Triphosphate (ATP) powered calcium channel pump,[1,2] also known as human secretory pathway Ca^{2+}/Mn^{2+} ATPase protein 1 (hSPCA1), localized in the Golgi apparatus.[3] In this paper, we performed mutation analysis of the ATP2C1 gene in four familial HHD patients and four sporadic HHD patients. The patients were diagnosed on clinical and histopathological findings [Figure 1].

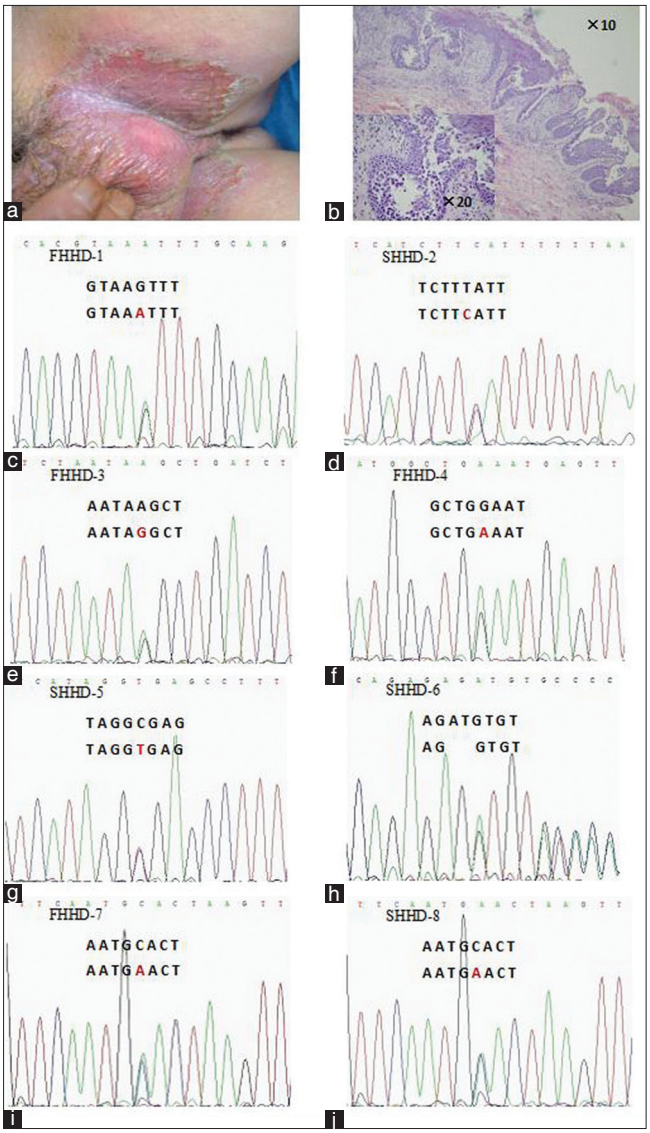

Figure 1: (a) Clinical features of familial case 4 Hailey–Hailey disease (FHHD-4), erythematous and erosive plaques in the genitals, (b) histological features of FHHD-4, the loss of cohesion between the keratinocytes (acantholysis) with a "dilapidated brick wall" appearance (H and E, ×10); (c-j) The sequences shown the mutations of ATP2C1 in FHHD-1, sporadic case 2 Hailey–Hailey disease (SHHD-2), FHHD-3, FHHD-4, SHHD-5, SHHD-6, FHHD-7, and SHHD-8

After written informed consent and obtaining approval of the ethics committee of the institute, genomic DNA was extracted from the peripheral blood of eight patients (four men, four women; mean ± SD age: 41 ± 9 years, range: 25) and 100 unrelated controls. Exons including exon–intron boundaries of the ATP2C1 gene were amplified by polymerase chain reaction using previous published primers.[4] After amplification, products were purified and directly sequenced on ABI 3130xl genetic analyzer (Applied Biosystems ABI, Carlsbad, CA, USA).

Seven mutations were identified in our eight HHD patients; six of these were novel [Table 1 and Figure 1].

In familial case 1 (FHHD-1), sporadic case 2 (SHHD-2), and FHHD-3, three splicing-site mutations (c.2629 + 5A > G in intron 23, c.2561-17C > T in intron 22, and C.621-1A > G in intron 2) were conformed [Figure 1, Table 1], which may affect mRNA splicing though alteration of the invariant splice donor site consensus sequence. The heterozygous mutation A > G at nucleotide 683 in exon 3 was identified in FHHD-4 [Figure 1, Table 1], resulted in a nonsense mutation P.W60X. One missense mutation c.666T > C (P.R66G) in exon 3 was detected in SHHD-5 [Figure 1, Table 1]. And another mutation c.2971A > C (P.A823E) in exon 25 was found in both FHHD-7 and SHHD-8 [Figure 1, Table 1]. The two missense mutations may affect the transport function for Ca^{2+}, and should be useful for further studies on the effect of the mutations on ATP2C1 gene expression. In SHHD-6, a previously reported frameshift mutant c.1523delAT in exon 17 was conformed [Figure 1, Table 1],[4] which generated pre-terminating codons at 9 and 23 codons downstream of

Table 1: ATP2C1 mutations in eight patients with Hailey–Hailey disease

Patient ID	Location	DNA change	Nucleotide change	Remarks
FHHD-1	Exon 22	C.2629 (+5A>G)	Aberrant splicing	Novel
SHHD-2	Exon 22	C.2561 (–17C>T)	Aberrant splicing	Novel
FHHD-3	Exon 3	C.621 (–1A>G)	Aberrant splicing	Novel
FHHD-4	Exon 3	C.683A>G	P.W60X	Novel
SHHD-5	Exon 3	C.666T>C	P.R66G	Novel
SHHD-6	Exon 17	c.1523delAT	GAGATGTGT → GAGGTGT	Recurrent
FHHD-7	Exon 25	C.2971A>C	P.A823E	Novel
SHHD-8	Exon 25	C.2971A>C	P.A823E	Novel

the deletion site. None of these mutations were found in 100 control individuals.

The ATP-powered calcium channel pump of the human keratinocyte localizes on the Golgi apparatus and competitively transports Ca^{2+} and Mn^{2+} into it. So, it has an irreplaceable role in controlling the Golgi Ca^{2+} stores. To date, more than 110 mutations of ATP2C1 gene have been reported.[5] In this paper, we reported three splicing-site mutations (c.2629 + 5A > G, c.2561-17C > T, and C.621-1A >) in FHHD-1, SHHD-2, and FHHD-3, respectively and one missense mutations c.666T > C in SHHD-5. An APT2C1 gene with these mutations may encode abnormal gene products. Two mutations, c.683 A > G in FHHD-4 and c.1523delAT in SHHD-6, resulting in premature termination and frameshift may cause a significant and an absence in the level of hSPCA1.

In summary, we report six novel mutations of the ATP2C1 gene and one reported mutation of the ATP2C1 gene in eight Chinese patients, which will further expand the database of ATP2C1 mutations in HHD. We failed to find any relationship between genotype and phenotype, just like the previous reports.

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