Identification of 2 Novel Mutations in ATP2C1 Gene in Hailey-Hailey Disease and a Literature Review of Variations in a Chinese Han Population

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Background:
Hailey-Hailey disease (HHD) is a rare autosomal dominant skin condition. The ATP2C1 gene was identified as the defective gene in HHD. To date, 166 pathogenic mutations in ATP2C1 have been observed worldwide. The aim of this study was to identify variations in HHD and summarize the features of the mutations identified in China.

Material/Methods:
We examined 2 familial and 2 sporadic cases of HHD. Genomic DNA polymerase chain reaction and direct sequencing of the ATP2C1 were performed from HHD patients, unaffected family members, and 200 healthy individuals. We also searched the published literature for data about the ATP2C1 gene using PubMed and the Chinese Biological Medicine Database.

Results:
We detected 3 heterozygous mutations, including 2 novel frameshift mutations (c.819insA (273LfsX) and c.1264insTAGATGG (421LfsX)) and 1 recurrent nonsense mutation (c.115C>T (R39X)). To the best of our knowledge, 90 different mutations (including our current results) have been reported in China, all of which occurred in the Chinese Han population.

Conclusions:
Our data may add to the existing list of ATP2C1 mutations and provide new insight into genetic variants of HHD in China.

MeSH Keywords:
DNA Mutational Analysis • Genes, vif • Organic Anion Transport Polypeptide C • Pemphigus, Benign Familial

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Background

Hailey-Hailey disease (HHD; MIM 169600), also known as benign familial chronic pemphigus, is a rare, autosomal dominant, genetic skin disease, characterized by relapsing blisters and erosions affecting the neck, skin folds, armpits, and genitals. It has an approximate prevalence of 1: 50 000 worldwide [1,2]. Onset of symptoms usually occurs around puberty or middle age, and may be exacerbated by trauma, perspiration, infection, ultraviolet radiation, pregnancy, and weight gain [3]. Mutations in the ATP2C1 gene, encoding the secretory pathway Ca\(^{2+}\)/Mn\(^{2+}\)-ATPase protein 1 (hSPCA1), have been identified as the cause of HHD [4]. Since ATP2C1 was first reported as the causative gene for HHD in 2000, 166 pathogenic mutations have been observed worldwide [5]. In this report, the ATP2C1 gene was screened in 2 ethnically unrelated HHD families and in 2 unrelated sporadic HHD patients in China. Three different disease-causing variations in ATP2C1 were identified. These mutations were analyzed for genetic and clinical characteristics among the Chinese Han population.

Material and Methods

Mutation screening

Two Chinese Han families (Figure 1A), which included 11 affected and 17 unaffected individuals, as well as 2 sporadic cases, were recruited from Chongqing. Written informed consent was obtained from all study participants. The proband of family 1 was a 52-year-old female with an 8-year history of repeated rash showing no seasonal differences. She presented with itchy erythematous, erosive plaques with fissures, and shallow ulcerations in the groin, vulva, and bilateral submammary folds. Her father had similar lesions in the groin and scrotum. The proband of family 2 exhibited recurrent pruritic erythematous, erosive plaques, macerations, and painful erosions secondary to fetid odor in his axillae, groin, and scrotum. He had experienced these symptoms since the age of 26 and they were likely aggravated in the summer (Figure 1B). Similarly, his daughter had mild dermatosis localized in axillae. The 2 sporadic cases showed typical skin lesions of HHD. HHD was confirmed in all patients by biopsy results.

Prior to the start of this study, ethics approval was obtained from the Ethics Committee of the First People’s Hospital of Chongqing.

Subjects in this study consisted of HHD patients, unaffected individuals in each pedigree, and 200 unrelated healthy controls. Genomic DNA was extracted from peripheral blood of subjects using standard techniques. All 28 coding exons and flanking intron-exon boundaries of the ATP2C1 gene (GenBank accession no. NM_001001487) were amplified using touchdown polymerase chain reaction (PCR). Purified PCR products were directly sequenced to an Applied Biosystems 3730 DNA Analyzer (Thermo Fisher).

Results

Three mutations – c.819insA(273LfsX), c.1264insTAGATGG(421LfsX), and 1 previously reported variant (c.115C>T) – were detected in family 1, family 2, and sporadic case 1 (Figure 2). The first 2 mutations were not previously reported. Such variations were absent in healthy individuals and in 200 unrelated controls, but were present in other affected members of the families. To the best of our knowledge, a total of 90 different mutations in the ATP2C1 gene (including our current results) have been reported in China. All of these mutations occurred in the Chinese Han population. A summary of these mutations, including the frequency, locations, effects, and clinical features, are summarized in Table 1.

Discussion

HHD is an autosomal dominant skin disorder characterized by abnormal keratinocyte adhesion in the suprabasal layer of the epidermis. The ATP2C1 gene, encoding the hSPCA1 protein, was identified as the defective gene in HHD. In human keratinocytes, hSPCA1 plays a significant role in maintaining calcium homeostasis between the cytoplasm and the Golgi apparatus [6]. Mutations in the ATP2C1 gene have been shown to generate a truncated protein, which may be targeted for degradation. As such, ATP2C1 mutations may impair normal cell functions, including cell adhesion, inducing the ability of keratinocytes to tightly bind each other [7].

Direct sequencing results indicated 2 novel mutations (c.819insA(273LfsX) and c.1264insTAGATGG(421LfsX)) and 1 previously reported variant (c.115C>T). The mutations and variant were verified by 2-directional sequencing. In family 1, a single adenine residue inserted in exon 10 at nucleotide 819 was detected, which changed the amino acid at position 273. This resulted in the abnormal sequence “Arg-Tyr-Pro-Gly-Asn-Val-Tyr-Tyr”, and a premature UUG termination codon downstream of the insertion site (273LfsX). Patients in family 2 had an insertion mutation c.1264insTAGATGG. This gave rise to a frameshift mutation in the open reading frame and produced
Figure 1. Pedigree chart and clinical features of Hailey-Hailey disease in this study. (A) Pedigrees of 2 families with Hailey-Hailey disease. Filled symbols represent individuals affected with HHD. The black arrow indicates the index subject; (B) Clinical features of Hailey-Hailey disease in the proband of family 2. This man showed symptoms such as demarcated erythema, vesicopustules, and crusted erosions in his right axillae, groin, and scrotum.
| No. | Incidence | Exon/ intron | Nucleotide change | Mutation | Freq | Effect | Domain | Age of onset | Skin lesions influenced | References |
|-----|-----------|--------------|------------------|----------|------|--------|--------|-------------|------------------------|------------|
| 1   | S         | Intron 2     | c.117+2T>G       | Donor splice | 1    | PTC(?) | N-ter/s 1 | --          | --                     | [8]        |
| 2   | S         | Intron 2     | c.118-1G>A       | Acceptor splice | 2    | --     | N-ter/s 1 | 30          | --                     | [9] [10]   |
| 3   | F         | Intron 2     | c.118-2A>G       | Acceptor splice | 1    | PTC    | N-ter/s 1 | 35          | Axilla, groin and navel | [11]       |
| 4   | F         | Exon 2       | c.134delG        | Deletion   | 1    | PTC    | N-ter/s 1 | 28          | Axilla, groin and navel | [12]       |
| 5   | F         | Exon 3       | c.163C>T         | Nonsense   | 5    | --     | --      | 36          | --                     | [13]       |
|     | S         |              |                  |           |      |        | 40      | Axilla, groin, navel | This study  |
|     | F         |              |                  |           |      |        |        | --          | --                     | [14]       |
| 6   | F         | Exon 3       | c.168delC        | Deletion   | 1    | PTC    | N-ter/s 1 | 42          | Axilla, groin          | [13]       |
| 7   | F         | Exon 3       | c.185_188delAGTT | Deletion   | 1    | PTC    | N-ter/s 1 | --          | --                     | [15]       |
| 8   | F         | Exon 3       | c.180G>Ad        | Nonsense   | 1    | PTC    | N-ter/s 1 | --          | --                     | [10]       |
| 9   | F         | Intron 3     | c.235-2A>G       | Acceptor splice | 2    | PTC    | M1      | 45          | Axilla, groin perianal | [16] [17] |
| 10  | F         | Intron 5     | c.361-2A>G       | Acceptor splice | 1    | PTC/loss exon 6 | M2 | -- | Neck, axilla, groin, perianal | [18] |
|     |           |              |                  |           |      |        |        |             |                       |            |
| 11  | F         | Exon 6       | c.366T>A         | Nonsense   | 1    | PTC    | M2      | 29          | Back, axilla, groin    | [19]       |
| 12  | S         | Exon 7       | c.457C>T         | Nonsense   | 2    | PTC    | A       | 19          | --                     | [20] [21] |
|     | F         |              |                  |           |      |        | 29      | Neck, axilla, groin, scrotum |            |
| 13  | S         | Exon 7       | c.478_479insA    | Insertion  | 1    | PTC    | P       | --          | Groin                  | [22]       |
| 14  | F         | Intron 7     | c.531+2T>Ad      | Donor splice | 1    | PTC    | A       | --          | Neck, axilla, groin    | [23]       |
| 15  | S         | Exon 8       | c.635C>T         | Nonsense   | 1    | PTC    | A       | 58          | --                     | [11]       |
| 16  | F         | Exon 8       | c.661A>Cd        | Missense   | 1    | --     | A       | 38          | Axilla, groin, submammary | [16]       |
| No. | Incidence | Exon/ intron | Nucleotide change | Mutation | Freq | Effect | Domain | Age of onset | Skin lesions influenced | References |
|-----|-----------|--------------|-------------------|----------|------|--------|---------|-------------|------------------------|------------|
| 17  | S         | Exon 9       | c.689G>A          | Missense | 1    | –      | A       | 56          | Groin, perianal        | [25]       |
| 18  | S         | Exon 9       | c.705delA         | Deletion  | 1    | PTC    | A       | 1 month     | Neck, axillae, groin   | [26]       |
| 19  | S         | Exon 10      | c.775C>T          | Nonsense  | 1    | PTC    | S3      | 35          | Neck, axillae, groin, navel | [19]       |
| 20  | F         | Exon 10      | c.806T>G          | Missense  | 1    | –      | M3      | 41          | Axillae, groin, perianal, abdomen | [19]       |
| 21  | F         | Exon 10      | c.819insA         | Insertion | 1    | –      | M3      | 35          | Submammary fold, groin, and vulva | This study |
| 22  | F         | Exon 11      | c.885_889insT     | Insertion | 1    | PTC    | P       | –           | Groin                  | [22]       |
| 23  | F         | Exon 11      | c.854G>A          | Nonsense  | 1    | PTC    | I2      | 45          | Groin                  | [8]        |
| 24  | F         | Exon 12      | c.920C>T          | Missense  | 1    | –      | M4      | –           | Axillae, groin          | [28]       |
| 25  | F         | Exon 12      | c.935C>T          | Missense  | 1    | –      | M4      | 50          | Axillae, groin          | [27]       |
| 26  | F         | Exon 12      | c.923_925delAAG   | Deletion  | 1    | PTC    | M4      | –           | –                      | [15]       |
| 27  | S         | Exon 12      | c.932_952del21bp  | Deletion  | 1    | –      | M4      | –           | Axillae, groin          | [23]       |
| 28  | F         | Exon 12      | c.1004T>C         | Missense  | 1    | –      | S4      | 27          | Axillae, groin          | [15]       |
| 29  | S         | Exon 13      | c.1042C>T         | Missense  | 1    | –      | P       | 31          | Vulva, axillae, neck   | [19]       |
| 30  | F         | Exon 13      | c.1049A>G         | Missense  | 3    | –      | P       | –           | –                      | [15]       |
| 31  | F         | Exon 13      | c.1055C>Td        | Missense  | 1    | –      | P       | 12          | Vulva, groin, axillae, neck | [29]       |
| 32  | S         | Exon 13      | c.1058G>Td        | Missense  | 1    | –      | P       | 40          | –                      | [30]       |
| 33  | S         | Exon 13      | c.1067delC        | Deletion  | 1    | PTC    | P       | 18          | –                      | [11]       |
| 34  | F         | Exon 13      | c.1068del16bp     | Deletion  | 1    | PTC    | P       | 17          | Axillae, groin, wrist  | [31]       |
| 35  | F         | Exon 13      | c.1089delTCAC     | Deletion  | 1    | PTC    | P       | –           | –                      | [15]       |
| 36  | F         | Exon 15      | c.1264insTAGATGG  | Insertion | 1    | –      | P       | 26          | Axillae, groin, and scrotum | This study |
| 37  | F         | Exon 16      | c.1250G>Ad        | Missense  | 1    | –      | P       | 26          | Axillae, groin, popliteal | [32]       |
| 38  | F         | Exon 16      | c.1330delC        | Deletion  | 1    | PTC    | P       | 21          | Axilla, chelidon, wrist | [22]       |
| 39  | F         | Exon 16      | c.1402C>T         | Nonsense  | 1    | PTC    | P       | –           | –                      | [15]       |
| 40  | F         | Exon 16      | c.1413G>C         | Missense  | 1    | –      | ?       | 30          | Axillae, groin          | [27]       |
| 41  | F         | Exon 17      | c.1413del28bpn    | Deletion  | 1    | PTC    | ?       | 45          | Scalp, axillae, groin, | [33]       |
| 42  | F         | Intron 16    | c.1415-2A>G       | Acceptor splice | 1    | PTC    | ?       | –           | Groin, axillae, neck, anus | [18]       |
| 43  | F         | Exon 17      | c.1431T>A         | Nonsense  | 1    | PTC    | ?       | 31          | –                      | [34]       |
| 44  | F         | Exon 17      | c.1455delAd       | Deletion  | 1    | PTC    | N?      | 30          | Groin, axillae, anus   | [35]       |
| 45  | F         | Exon 17      | c.462delO         | Deletion  | 1    | –      | N       | –           | Groin, axillae, anus, neck | [18]       |
| No. | Incidence | Exon/intron | Nucleotide change | Mutation | Freq | Effect | Domain | Age of onset | Skin lesions influenced | References |
|-----|-----------|-------------|-------------------|----------|------|--------|---------|--------------|------------------------|------------|
| 46  | F         | Exon 17    | c.1516C>T        | Nonsense | 1    | PTC    | N       | 37           | Groin, axillae, anus, neck | [30]       |
| 47  | S         | Exon 17    | c.1508delCTCAAd  | Deletion | 1    | PTC    | N       | ~            | Groin, axillae           | [23]       |
| 48  | S, F      | Exon 17    | c.1523delAT      | Deletion | 2    | PTC    | N–      | ~            | Groin, axillae, anus, neck | [10], [18] |
| 49  | F         | Exon 18    | c.1588G>C        | Missense | 1    | –      | N       | ~            | ~                      | [8]        |
| 50  |           | Exon 18    | c.1685C>G        | Missense | 1    | PTC    | N       | ~            | ~                      | [15]       |
| 51  | F         | Exon 18    | c.1720C>T        | Nonsense | 1    | –      | P       | ~            | ~                      | [22]       |
| 52  | F         | Exon 18    | c.1738A>G        | Missense | 1    | –      | N       | 25           | Submammary, groin        | [13]       |
| 53  | S         | Exon 20    | c.1854G>Ad       | Missense | 1    | –      | N       | ~            | ~                      | [24]       |
| 54  | F         | Intron 19  | c.1891-1G>T      | Acceptor splice | 1    | –      | S5      | 23           | Axillae, groin and perineum | [12]       |
| 55  | F         | Intron 20  | c.1890+1delGTGAG | Donor splice | 1    | –      | S5      | 27           | ~                      | [9]        |
| 56  | F         | Exon 21    | c.1897C>T        | Nonsense | 1    | PTC    | S5      | 10           | Neck, axillae, groin, submammary | [36]       |
| 57  | F         | Exon 21    | c.1914del/insd   | Deletion/insertion | 1    | PTC    | S5      | 20           | Axillae, groin, perianal  | [37]       |
| 58  | S         | Exon 21    | c.1931A>G        | Missense | 1    | –      | S5      | 27           | Axillae, groin, perianal, wrist | [54]       |
| 59  | S         | Exon 21    | c.1934G>Td       | Missense | 1    | –      | S5      | 28           | Intertiginous areas       | [38]       |
| 60  | F         | Exon 21    | c.1942G>T        | Missense | 1    | –      | S5      | ~            | Axillae, groin, perianal, neck | [18]       |
| 61  | S         | Exon 21    | c.1952C>A        | Missense | 1    | –      | S5      | 29           | Groin, chest, popliteal   | [19]       |
| 62  | F         | Exon 21    | c.1982T>G        | Missense | 1    | –      | S5      | 17           | Axillae, groin, back, neck | [31]       |
| 63  | F         | Exon 21    | c.2023delAd      | Deletion | 1    | PTC    | S5      | ~            | Groin, neck              | [23]       |
| 64  | S         | Exon 21    | c.2025delG       | Deletion | 1    | PTC    | S5      | 25           | Groin, abdomen            | [19]       |
| 65  | S         | Intron 21  | c.2058(-17C>T) d | Acceptor splice | 1    | PTC    | S5      | ~            | ~                      | [10]       |
| 66  |           | Intron 21  | c.2058-1G>Cd     | Acceptor splice | 1    | –      | S5      | ~            | ~                      | [15]       |
| 67  | F         | Exon 22    | c.2068G>T        | Nonsense | 1    | PTC    | S5      | 19           | ~                        | [27]       |
| 68  | F         | Exon 22    | c.2126C>T        | Missense | 2    | –      | MS      | ~            | ~                      | [25], [15] |
| 69  |           | Intron 22  | c.2127+1G>Ad     | Donor splice | 1    | Skip exon 23(?) | MS | ~           | ~                      | [15]       |
| 70  | F         | Intron 22  | c.2126(+5G>A)d   | Donor splice | 1    | PTC    | MS      | ~            | ~                      | [10]       |
| 71  | F         | Exon 23    | c.2132T>G        | Missense | 1    | –      | MS      | 29           | Head, submammary, perianal, periocular | [13]       |
| 72  | F         | Exon 23    | c.2132T>Cd       | Missense | 1    | –      | MS      | ~            | ~                      | [24]       |
| No. | Incidence | Exon/ intron | Nucleotide change   | Mutation | Freq | Effect | Domain | Age of onset | Skin lesions influenced | References |
|-----|-----------|--------------|---------------------|----------|------|--------|--------|-------------|------------------------|------------|
| 73  | F         | Exon 23     | c.2164insACAT       | Insertion | 1    | PTC    | I3     | –           | –                      | [36]       |
| 74  | F         | Exon 23     | c.2198A>G           | Missense  | 1    | –      | M6     | 27          | Head, neck, groin, perianal | [13]       |
| 75  | F         | Exon 23     | c.2235insC          | Insertion | 1    | PTC    | M6     | 30          | Axillae, groin           | [25]       |
| 76  | F         | Exon 23     | c.2236G>Ad          | Missense  | 1    | –      | M6     | –           | Intertriginous areas     | [23]       |
| 77  | F         | Intron 24   | c.2243+2T>C         | Donor Splice | 1   | PTC    | M6     | –           | Neck, groin, perianal, axillae | [18]       |
| 78  | F         | Exon 24     | c.2251delGT         | Deletion  | 1    | PTC    | S6     | 37          | Hypogastrium, groin, perianal, axillae | [39]       |
| 79  | F         | Exon 24     | c.2374delTTTG       | Deletion  | 3    | PTC    | M7     | 24          | Groin, axillae           | [13]       |
|     | F         |             |                     |          |      |        |        | 28          | –                      | [35]       |
|     | S         |             |                     |          |      |        |        | 26          | Axillae, navel, abdomen  | [40]       |
| 80  | S         | Exon 24     | c.2375delTTGT       | Deletion  | 2    | PTC    | M7     | 27          | Axillae, wrist neck, perianal | [17]       |
| 81  | S         | Exon 24     | c.2384G>A           | Nonsense  | 1    | PTC    | I4     | 24          | –                      | [9]        |
| 82  | F         | Exon 24     | c.2412delT          | Deletion  | 1    | PTC    | I4     | 20          | –                      | [17]       |
| 83  | F         | Exon 25     | c.2395C>T           | nonsense  | 3    | PTC    | I4     | –           | Axillae, groin            | [13]       |
|     | F         |             |                     |          |      |        |        | 37          | Groin, submammary         | [23]       |
|     | S         |             |                     |          |      |        |        | 38          | Groin, wrist, perianal    | [32]       |
| 84  | S         | Exon 25     | c.2454delT          | Deletion  | 1    | PTC    | M8     | 44          | Groin, submammary        | [13]       |
| 85  | S         | Exon 25     | c.2454dupT          | Insertion | 1   | PTC    | M8     | –           | Groin, submammary       | [15]       |
| 86  | F         | Exon 25     | c.2468C>Ad          | Missense  | 2    | PTC    | M8     | –           | –                      | [10]       |
| 87  | F         | Exon 26     | c.2558delT10        | Deletion  | 1    | PTC    | M9     | 25          | Axillae, waist           | [13]       |
| 88  | F         | Exon 26     | c.2593C>T*          | Nonsense  | 1    | PTC    | I5     | 25          | Axillae, groin           | [18]       |
| 89  | F         | Exon 27     | c.2597A>C          | Missense  | 1    | –      | I5     | 25          | –                      | [11]       |
| 90  | S         | Exon 27     | c.2660C>A          | Nonsense  | 1    | PTC    | M10    | 22          | –                      | [9]        |

**References**

F – familial; S – sporadic; ‘–’ – not mentioned; Freq. – frequency. Descriptions were collated according to the reported cDNA reference sequence (GenBank accession No. NM_AF181120) using the running correct coding sequence and relative reading frame of the ATP2C1 gene (Ref. NG_007379.1).

Protein translation was expected to produce a premature termination codon, leading to subsequent protein destabilization and degradation. In the sporadic case 1, the nonsense mutation C>T at nucleotide 115 in exon 3 was identified, causing a premature termination codon at position 39(R39X).

We systematically searched the NCBI PubMed database (September 2016) and the Chinese Biological Medicine Database for previous case reports or literature on ATP2C1 mutations of HHD in China. In Table 1, all reported mutations to date are summarized, including their localization in the gene sequence, the type of mutation, the resulting amino acid change, and clinical features of HHD. To the best of our knowledge, a total of 90 different mutations (including our current results) have been reported in the literature. All of these occurred in the Han Chinese population, except for 1 in a Uygur with no findings. Similar to initial outcomes elsewhere [5], the majority of the mutations were deletion/insertion mutations (n=31, 34%) and missense mutations (n=28, 31%). Over 55% of the variants generate a premature termination codon (PTC), supporting the theory of ATP2C1 haploinsufficiency as a mechanism for HHD. Exons 7, 13, and 21 appear to be more frequent locations for mutations in Chinese
patients, with exon 21 detected 9 times. Furthermore, 11 redundant regions (c.1049A>T, c.115C>T, c.2374_2377delTTTG, c.2375_2378delITGTG, c.2395C>T, c.1181G>A, c.235-2A>G, c.457C>T, c.1523_1524delAT, c.2126C>T, and c.2468C>T) were identified, with c.115C>T being the most frequently mutated, occurring 5 times in our study. Our analysis suggests the mutated areas mentioned above may be unique to the Chinese Han population. In addition, our summary indicates there is no correlation between genotype and phenotype; the age of onset, severity, location, and disease progression varied between individuals within the same and different families, even if patients shared the same mutation.

Conclusions

We identified 3 genetic mutations in the ATP2C1 gene that cause HHD. Two of these mutations are novel, while the third has previously been reported. These 2 novel mutations possibly add to the existing list of ATP2C1 mutations and may be useful during prenatal examinations in affected family members. In addition, the reported mutations of ATP2C1 not only provide a detailed summary of the known variations, but also give insight into mutations associated with the Chinese Han population. Extensive functional experiments are still necessary to confirm the relevance of our recent findings.

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Conflict of interests

None.

References:

1. Sudbrak R, Brown J, Dobson-Stone C et al: Hailey-Hailey disease is caused by mutations in ATP2C1 encoding a novel Ca2+ pump. Hum Mol Genet, 2000; 9(7): 1131–40
2. Mizuno K, Hamada T, Hashimoto T, Okamoto H: Successful treatment with narrow-band UVB therapy for a case of generalized Hailey-Hailey disease with a novel splice-site mutation in ATP2C1 gene. Dermatol Ther, 2014; 27(4): 233–35
3. Surge SM: Hailey-Hailey disease: The clinical features, response to treatment and prognosis. Br J Dermatol, 1992; 126(3): 275–82
4. Behne MJ, Tu CL, Aronchik I et al: Human keratinocyte ATP2C1 localizes to the Golgi and controls Golgi Ca2+ stores. J Invest Dermatol, 2003; 121(4): 688–94
5. Micaroni M, Giaclgetti G, Plebani R et al: ATP2C1 gene mutations in Hailey-Hailey disease and possible roles of SPCA1 isoforms in membrane trafficking. Cell Death Dis, 2016; 7(6): e2259
6. Micaroni M, Perinetti G, Berrie CP, Mironov AA: The SPCA1 Ca2+ pump and intracellular membrane trafficking. Traffic, 2010; 11(10): 1315–33
7. Aberg KM, Racz E, Behne MJ, Mauro TM: Involucrin expression is decreased in Hailey-Hailey keratinocytes owing to increased involucrin mRNA degradation. J Invest Dermatol, 2007; 127(8): 1973–79
8. Zhang ZZ, Liang YH, Quan C et al: Three novel ATP2C1 mutations in Chinese patients with Hailey-Hailey disease. Br J Dermatol, 2008; 158(4): 831–33
9. Li H, Sun HK, Zhu XL: Four novel mutations in ATP2C1 found in Chinese patients with Hailey-Hailey disease. Br J Dermatol, 2003; 149(3): 471–74
10. Tian H, Chen L, Mei A et al: Four novel ATP2C1 mutations in Chinese patients with Hailey-Hailey disease. Indian J Dermatol Venereol Leprol, 2013; 79(2): 42–47
11. Li X, Zhang D, Xiao S, Peng Z: Four novel mutations of the ATP2C1 gene in Chinese patients are associated with familial benign chronic pemphigus. Clin Exp Dermatol, 2012; 37(7): 797–99
12. Shi BJ, Xiao S, Zhang Z et al: The ATP2C1 gene in Hailey-Hailey disease patients: one novel deletion and one novel splicing mutation. J Eur Acad Dermatol Venereol, 2015; 29(12): 2495–97
13. Zhang HZ, Tian HQ, Du DH et al: Analysis of ATP2C1 gene mutations in Chinese patients with Hailey-Hailey disease. Clin Exp Dermatol, 2012; 37(2): 190–93
14. Zhang GL, Sun Y, Shi HJ et al: [Mutation analysis of ATP2C1 gene in a Chinese family with Hailey-Hailey disease.] Zhonghua Yi Xue Ke Xue Yuan Xue Bao, 2010; 29(4): 414–16 [in Chinese]
15. 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(10): 1202–6
16. Zhang ZZ, Li W, Zhou FS et al: [Identification of a novel mutation in the ATP2C1 gene in a Chinese pedigree with Hailey-Hailey disease.] Zhongguo Yi Xue Ke Xue Yuan Xue Bao, 2007; 29(2): 163–66 [in Chinese]
17. Zhang ZZ, Quan C, Mu YZ et al: Study on the mutations of ATP2C1 gene in six cases with familial benign chronic pemphigus. Chin J Dermatol, 2014; 28: 441–43
18. Zhang F, Yan X, Jiang D et al: Eight novel mutations of ATP2C1 identified in 17 Chinese families with Hailey-Hailey disease. Dermatology, 2007; 215(4): 277–83
19. Tian H, Yan X, Liu H et al: Six novel mutations identified in Chinese patients with Hailey-Hailey disease. J Dermatol Sci, 2010; 58(1): 80–82
20. Chang HQ, Xiao FL, Zhou FS et al: Mutation detection of the ATP2C1 gene in a Chinese family with Hailey-Hailey disease. Acta Univer Med Anhui, 2008; 43: 212–14
21. Hu Z, Bonifas JM, Beech J et al: Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. Nat Genet, 2000; 24(3): 61–85
22. Li H, Chen L, Mei A et al: Four novel ATP2C1 mutations in Chinese patients with Hailey-Hailey disease. J Dermatol, 2016; 43(10): 1197–200
23. Chao SC, Tsai YM, Yang MH: Mutation analysis of ATP2C1 gene in Taiwanese patients with Hailey-Hailey disease. Br J Dermatol, 2002; 146(4): 595–600
24. Luo S, Ni H, Li Y et al: Novel clinical and molecular findings in Chinese families with Hailey-Hailey disease. Clin Exp Dermatol, 2011; 36(7): 814–16
25. Meng L, Gu Y, Du XF et al: Two novel ATP2C1 mutations in patients with Hailey-Hailey disease and a literature review of sequence variants reported in Chinese population. Genet Mol Res, 2015; 14(4): 19349–59
26. Xu Z, Zhang L, Xiao Y et al: A case of Hailey-Hailey disease in an infant with a new ATP2C1 gene mutation. Pediatric Dermatol, 2011; 28(2): 165–68
27. Xing XS, Wang Z, Liu S et al: Three novel mutations of the ATP2C1 gene in Chinese families with Hailey-Hailey disease. J Eur Acad Dermatol Venereol, 2016; 30(6): 1057–59
28. Ma YM, Zhang XL, Liang YH et al: Genetic diagnosis in a Chinese Hailey-Hailey disease pedigree with novel ATP2C1 mutation. Arch Dermatol Res, 2008; 300(4): 203–7
29. Cheng YL, Cheng YM, Zhao G et al: A novel missense mutation of the ATP2C1 gene in a Chinese patient with Hailey-Hailey disease. Biochem Biophys Res Commun, 2011; 406(3): 420–22
30. Zhang XQ, Wu HZ, Li BX et al: Mutations in the ATP2C1 gene in Chinese patients with Hailey-Hailey disease. J Eur Acad Dermatol Venereol, 2011; 35(5): 702–5
31. Ding TG, Fang H, Lao LM et al: Genetic diagnosis of Hailey-Hailey disease in two Chinese families: Novel mutations in the ATP2C1 gene. Clin Exp Dermatol, 2009; 34(8): e968–71

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32. Zhang D, Li X, Xiao S et al: Detection and comparison of two types of ATP2C1 gene mutations in Chinese patients with Hailey-Hailey disease. Arch Dermatol Res, 2012; 304(2): 163–70
33. Wang CC, Chao SC, Tsai TH: Hailey-Hailey disease: A novel mutation of the ATP2C1 gene in a Taiwanese family with divergent clinical presentation. J Eur Acad Dermatol Venereol, 2008; 22(9): 1145–46
34. Xu QQ, Cheng CZ, Huo J et al: Detection of ATP2C1 gene mutations in two Chinese families with Hailey-Hailey disease. Chin J Dermatol, 2012; 26: 475–76
35. Li XL, Peng ZH, Xiao SX et al: A novel deletion mutation of the ATP2C1 gene in Chinese patients with Hailey-Hailey disease. J Eur Acad Dermatol Venereol, 2008; 22(2): 253–54
36. Zhu YG, Yang S, Gao M et al: Two novel mutations of the ATP2C1 gene in Chinese families with Hailey-Hailey disease. J Dermatol Sci, 2006; 42(2): 125–27
37. Yin CH, Wang BX, Ma DL: Gene mutations in a Chinese family with Hailey-Hailey disease. Chin J Dermatol, 2003; 36: 507–9
38. Li X, Xiao S, Peng Z et al: Two novel mutations of the ATP2C1 gene in Chinese patients with Hailey-Hailey disease. Arch Dermatol Res, 2007; 299(4): 209–11
39. Liu JZ, Yang T, Li X et al: A novel mutation in the ATP2C1 gene is associated with Hailey-Hailey disease in a Chinese family. Int J Dermatol, 2009; 48(1): 47–51
40. Chen SY, Huang CZ, Li JW: Mutation detection of ATP2C1 gene in a Chinese family with Hailey-Hailey disease. Chin J Dermatol, 2004; 37: 550