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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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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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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 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).

Literature review

We reviewed case reports and papers on HHD obtained from searches of the NCBI PubMed (September 2016) and the Chinese Biological Medicine Database.

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

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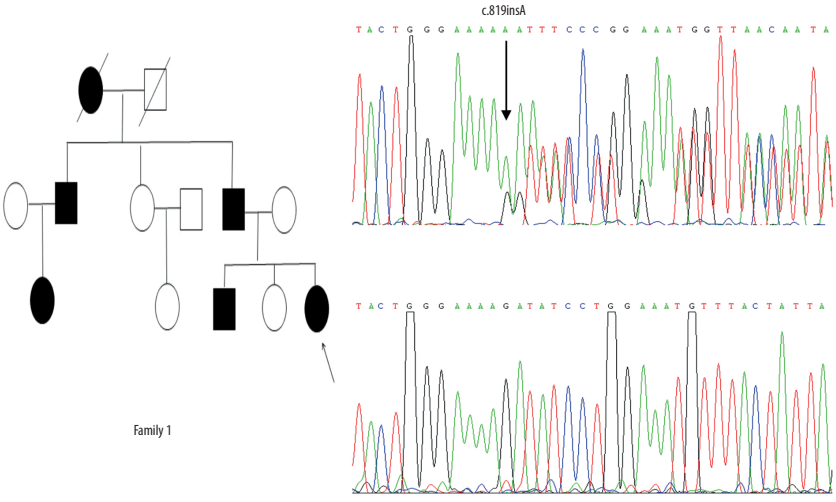
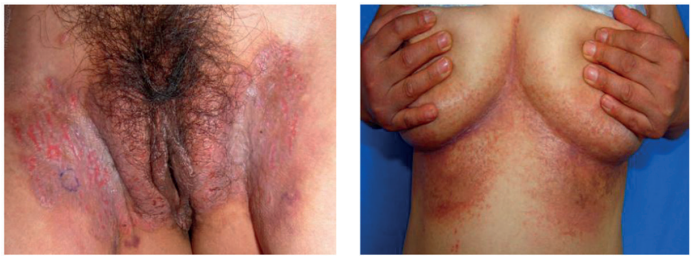
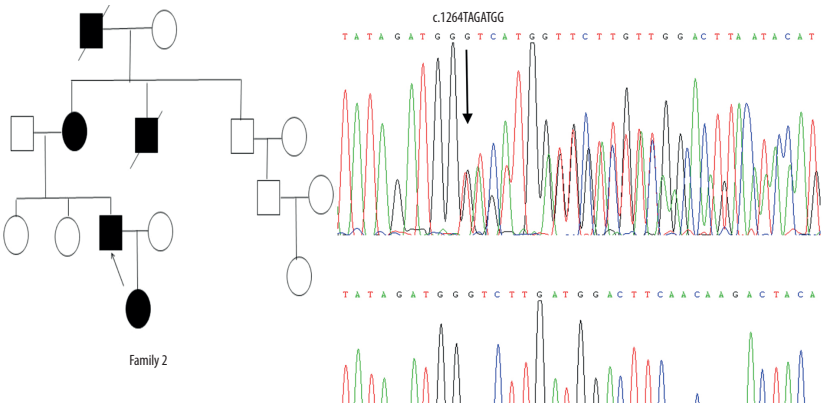
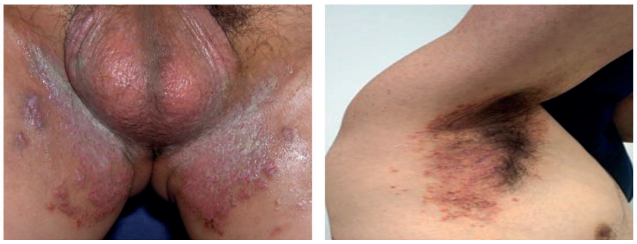
A









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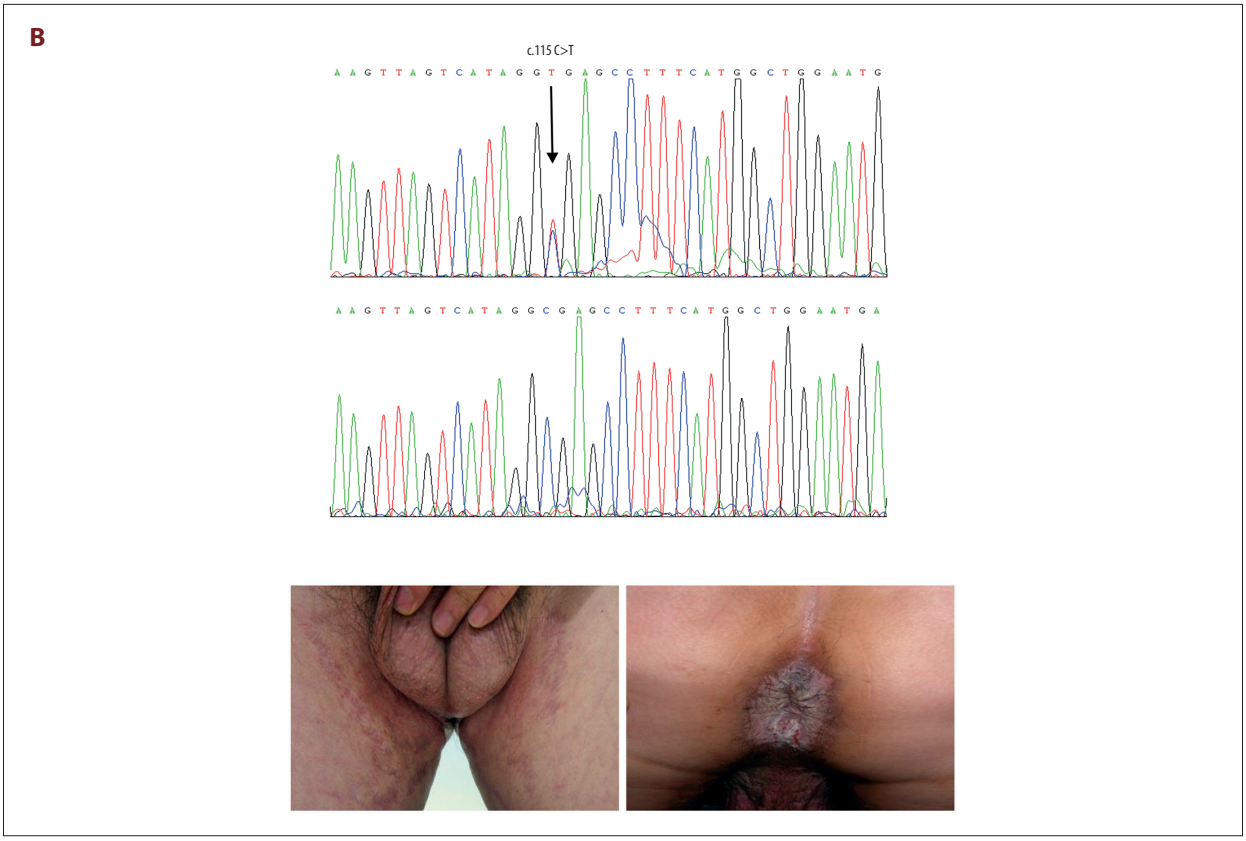
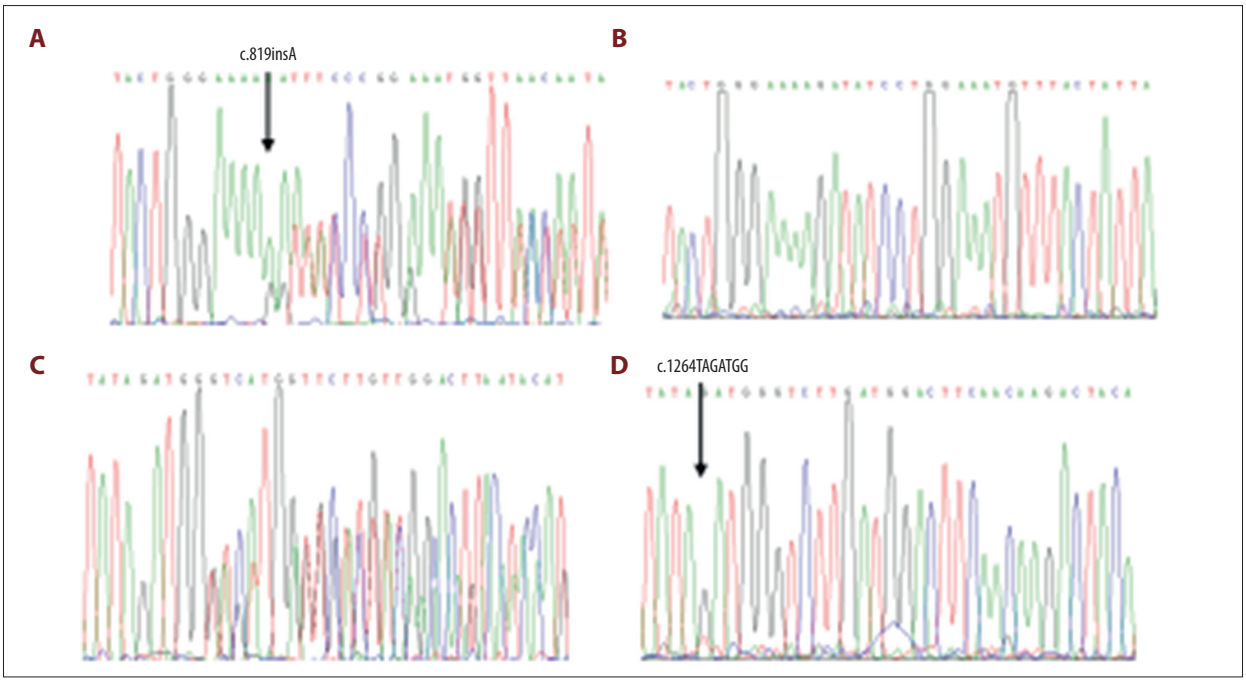


Figure 1. Pedigree chart and clinical features of Hailey-Hailey disease in this study. (**A**) Pedigrees of 2 families with Hailey-Hailey disease. Filled symbols represent individuals affected with HHD. The black arrow indicates the index subject; (**B**) Clinical features of Hailey-Hailey disease in the proband of family 2. This man showed symptoms such as demarcated erythema, vesicopustules, and crusted erosions in his right axillae, groin, and scrotum.



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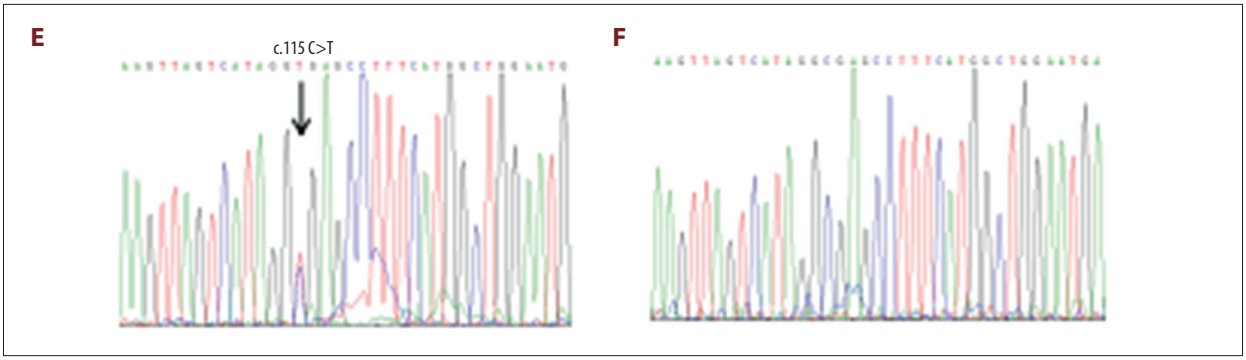

Figure 2. Mutation analysis of the ATP2C1 gene in patients with Hailey-Hailey disease in this study. (**A**) A frameshift mutation c.819insA (arrow) in family 1; (**C**) a frameshift mutation c.1264TAGATGG (arrow) in family 2; (**E**) a nonsense mutation c.115C>T(arrow) in sporadic case 1; (**B, D, F**) sequence of the normal persons.

Table 1. Summary of ATP2C1 gene mutations in the Han population.

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 F	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 S F S F	Exon 3	c.163C>T	Nonsense	5	PTC	N-ter/s 1	40 36 – –	Neck, axillae, groin groin, navel – –	[13] This study [23] [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	–	M1	45 34	Axilla, groin perianal	[16] [17]
10	F	Intron 5	c.361-2A>G	Acceptor splice	1	PTC/loss exon 6	M2	–	Neck, axillae, groin, perianal	[18]
11	F	Exon 6	c.366T>A	Nonsense	1	PTC	M2	29	Back, axilla, groin	[19]
12	S F	Exon 7	c.457C>T	Nonsense	2	PTC	A	19 29	– Neck, axillae, groin, scrotum	[20] [21]
13	S	Exon 7	c.478_479insA	Insertion	1	PTC	P	–	Groin	[22]
14	F	Intron 7	c.531+2T>Ad	Donor splice	1	–	A	–	Neck, axillae, groin	[23]
15	S	Exon 8	c.635C>A	Nonsense	1	PTC	A	58	–	[11]
16	F	Exon 8	c.661A>Cd	Missense	1	–	A	38	Axillae, groin, submammary	[16]

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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.888_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, perianal, neck	[28]
25	F	Exon 12	c.935T>C	Missense	1	–	M4	50	Axillae, groin	[27]
26	-	Exon 12	c.923_925delAAG	Deletion	1	PTC	M4	–	–	[15]
27	S	Exon 12	c.932_952del21bpd	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.1042T>C	Missense	1	–	P	31	vulva, axillae, neck	[19]
30	F	Exon 13	c.1049A>T	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	-	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	-	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>C	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.l462deld,o	Deletion	1	–	N	–	Groin, axillae, anus, neck	[18]

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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.1508delCTCAd	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	[34]
59	S	Exon 21	c.1934G>Td	Missense	1	–	S5	28	Intertriginous 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		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	–	M5	– 32	– Axillae, groin, perianal	[25] [15]
69	-	Intron 22	c.2127+1G>Ad	Donor Splice	1	Skip exon 23(?)	M5	–	–	[15]
70	F	Intron 22	c.2126(+5G>A)d	Donor Splice	1	PTC	M5	–	–	[10]
71	F	Exon 23	c.2132T>G	Missense	1	–	M5	29	Head, submammary, perianal, periocular	[13]
72	F	Exon 23	c.2132T>Cd	Missense	1	–	M5	–	–	[24]

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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 F S	Exon 24	c.2374delTTTG	Deletion	3	PTC	M7	24 28 26	Groin, axillae – Axillae, navel, abdomen	[13] [35] [40]
80	S F	Exon 24	c.2375delTTGT	Deletion	2	PTC	M7	27 –	Axillae, wrist neck, perianal	[17] [18]
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 F F	Exon 25	c.2395C>T	nonsense	3	PTC	I4	– 37 38	Groin, neck Groin, submammary Groin, wrist, perianal	[13] [23] [32]
84	S	Exon 25	c.2454delT	Deletion	1	PTC	M8	44	Groin, submammary	[13]
85	-	Exon 25	c.2454dupT	Insertion	1	PTC	M8	–	Groin, submammary	[15]
86	F S	Exon 25	c.2468C>Ad	Missense	2		M8	–	–	[10]
87	F	Exon 26	c.2558del10	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]

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).

a termination codon UAG at the site of the first downstream insertion. 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

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patients, with exon 21 detected 9 times. Furthermore, 11 redundant regions (c.1049A>T, c.115C>T, c.2374_2377delTTTG, c.2375_2378delTTGT, c.2395C>T, c.118-1G>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.

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