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ORIGINAL RESEARCH

Two Novel and a Recurrent *ATP2C1* Mutations in Chinese Population with Hailey–Hailey Disease

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Purpose: Hailey–Hailey disease (HHD), also known as familial benign chronic pemphigus, is a rare autosomal dominant inherited blistering dermatosis. Pathogenic variants in *ATP2C1* have been associated with HHD since 2000. This study aimed to identify the mutations in the *ATP2C1* gene in two Chinese pedigrees and two sporadic cases with HHD.

Patients and Methods: Two Chinese pedigrees and two sporadic cases were included in this study. Whole-exome sequencing and Sanger sequencing were performed to detect the mutation of the *ATP2C1* gene. Predictions of protein structure and function were performed using bioinformatics tools, including Mutation Taster, Polyphen-2, SIFT, and Swiss-Model.

Results: In this study, we detected three heterozygous mutations, including novel compound mutations of (c.1840–4delA and c.1840_1844delGTTGC), splice site mutation of c.1570+3A>C, and a previously known nonsense mutation c.1402C>T in the *ATP2C1* gene. Combined with our previous study, ten patients with c.1402C>T mutation in the *ATP2C1* gene have been identified, and all these patients originated from Jiangxi Province.

Conclusion: c.1402C>T mutation in the *ATP2C1* gene was considered a regional highly prevalent mutation in the Chinese population with HHD. The results added new variants to the database of *ATP2C1* mutations associated with HHD.

Keywords: Hailey–Hailey disease, novel mutation, *ATP2C1*, Chinese pedigree, Sanger sequencing

Introduction

Hailey–Hailey disease (HHD; Online Mendelian Inheritance in Man no. 169600), also known as familial benign chronic pemphigus, is a rare autosomal dominant inherited blistering dermatosis. It is characterized by recurrent blisters, erythema, and vesicles predominantly located in the neck, axilla, groin, and breast folds.[1] Histopathologically, HHD is characterized by extensive epidermal suprabasilar acantholysis, known as the "dilapidated brick wall".[2]

In 2000, mutations in ATPase calcium-transporting type 2C member 1 (*ATP2C1*) gene on chromosome 3q22.1 encoding the secretory pathway Ca^{2+}/Mn^{2+}-ATPase (SPCA1) were reported to be the causative gene for HHD.[3] So far, more than 200 mutations in the *ATP2C1* have been found. In the recent study done by Xiao et al,[4] two novel mutations (c.1673_1674insGTTG and c.2225A>G) and one previously reported nonsense mutation (c.1402C>T) were identified in three pedigrees and four sporadic cases with HHD from Jiangxi province, China. To further understand the *ATP2C1* mutation spectrum, we performed mutation analysis of the *ATP2C1* gene in two pedigrees and two sporadic cases with HHD.

Materials and Methods

Study Cases

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, China. All procedures in this study were performed according to the principles of the Declaration of Helsinki. Four unrelated

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patients were recruited for this study. About 2 mL of peripheral blood was collected from the participants who signed informed consent.

Sanger Sequencing

Genomic DNA was extracted from peripheral blood using a Flexigene DNA Kit according to the manufacturer's instructions (Qiagen, Düsseldorf, Germany). All 28 exons of the *ATP2C1* gene and their flanking intron sequences were amplified by polymerase chain reaction (PCR) using primers designed by Primer3 (http://bioinfo.ut.ee/primer3–0.4.0/). Primer sequences and PCR conditions are available upon request. The PCR products were purified using SAP (Promega, Madison, WI, USA) and Exo I (Epicentre, Madison, WI, USA). The purified PCR products were sequenced using dye terminator chemistry BigDye3.1 (Applied Biosystems, Foster City, CA, USA). Sequencing reactions were run on 3730xl genetic analyzer (Applied Biosystems). Sequence comparisons and analysis were performed using PolyPhred Analysis Software.[5]

Whole-Exome Sequencing

Genomic DNA was extracted from the peripheral blood samples. The Illumina Truseq Exome Enrichment Kit V6 (Illumina, San Diego, CA, USA) was applied to construct the whole-exome library. Then, 2 × 150 bp paired-end massively parallel sequencing was performed using a HiSeq 2500 Sequencing System (Illumina, San Diego, CA, USA).

Results

Clinical Manifestation

Patient 1 (P1) was a 49-year-old Chinese female patient with ten-year history of recurrent erosions, pruritus, and crust, involving bilateral axillae and groin. The lesions were well demarcated and symmetrically distributed (Supplementary Figure 1A). Symptoms were relieved after using topical glucocorticoids. Patient 2 (P2) was a 58-year-old Chinese male with 30 years of recurrent erythema and blisters in the axillae, neck, elbow, and groin (Supplementary Figure 1B). The lesions were aggravated by heat and sweating. Similar lesions were also observed on the body of his son. Patient 3 (P3) is a 45-year-old Chinese male presenting with erythema, blisters, and erosions. The lesions initially appeared on the neck when he was 25 and then extended gradually to bilateral axillae and groin over the years (Supplementary Figure 1C). He was treated with glucoside tripterygium total and compound glycyrrhizin capsules with significant clinical improvement. Patient 4 (P4) is a 58-year-old male who developed erythema, erosions with pain in the bilateral groins 20 years ago (Supplementary Figure 1D). Recurrent symptoms were improved with topical glucocorticoids. His son presented with mild erythema on his groin. Histological examination of these patients disclosed acantholysis with a dilapidated brick wall appearance in the epidermis.

ATP2C1 Variants in HHD Patients

Sanger sequencing of genomic DNA from P1 revealed novel compound mutations of c.1840–4delA and c.1840_1844delGTTGC (Supplementary Figure 2A). Sanger sequencing of genomic DNA from P2 revealed a previously known nonsense mutation, c.1402C>T in exon 16 (Supplementary Figure 2B). Whole-exome sequencing of P3 revealed the same mutation as P2 (Supplementary Figure 3). Sanger sequencing of genomic DNA from P4 revealed splice site mutation of c.1570+3A>C in intron 17 (Supplementary Figure 2C).

Review of the C.1402C >T Mutation in ATP2C1 in Jiangxi Province

Combined with our previous study, ten patients with c.1402C>T mutation in the *ATP2C1* have been identified so far. They were from four pedigrees and one sporadic patient (P3), including six males and four females. The age of onset was between 25 and 37 years. All of these cases originated from the northern region of Jiangxi Province and had no known relationship in recent generations. Detailed information was shown in Table 1.

Table 1 Clinical Characteristics of Patients with c.1402C>T Mutation of ATP2C1 in Jiangxi Province

Reference		Patient	Gender	Age	Age at Onset	Place of Residence	Affected Skin Lesions		
							Neck	Axilla	Groins
Xiao et al[4]	Pedigree 1	P5	Female	41 y	27 y	Xiushui County	–	+	+
		P5 mother	Female	63 y	26 y	Xiushui County	+	+	+
		P5 sister	Female	38 y	31 y	Xiushui County	–	+	–
		P5 son	Male	12 y	–	Xiushui County	–	–	–
		P5 nephew	Male	6 y	–	Xiushui County	–	–	–
	Pedigree 2	P6	Male	42 y	32 y	Poyang County	+	+	+
	Pedigree 3	P7	Female	47 y	37 y	Yanshan County	+	+	+
		P7 son	Male	24 y	–	Yanshan County	–	–	–
Present study	Pedigree 4	P2	Male	58 y	28 y	Fengcheng City	+	+	+
	Sporadic 1	P3	Male	45 y	25 y	Jinxian County	+	+	+

Bioinformatic Analysis of the Variants

To predict the likelihood of pathogenicity, three online tools (MutationTaster http://www.mutationtaster.org, PolyPhen-2 http://genetics.bwh.harvard.edu/pph2, SIFT http://sift.bii.astar.edu.sg) were employed. c.1840–4delA and c.1840_1844delGTTGC were predicted to be "deleterious" (score = 0.02) in SIFT, "possibly damaging" (score = 0.869) in PolyPhen2, an "disease-causing" (p = 1) in Mutation Taster. c.1402C>T was also predicted to deleterious: Mutation Taster (disease-causing, p = 1). In addition, the splice site variant (c.1570+3A>C) was predicted as "most probably affecting splicing" by Human Splicing Finder (http://www.umd.be/HSF3/). The 3D models of wild-type proteins and the mutant proteins c.1840_1844delGTTGC (p. Val614Ser) and c.1402C>T (p. Arg468X) were constructed using Swiss-Model (http://swissmodel.expasy.org) (Supplementary Figure 4). This analysis suggested that substituted amino acids cause protein translation termination.

Discussion

In our study, novel compound mutations of c.1840–4delA and c.1840_1844delGTTGC in the *ATP2C1* gene were identified in P1. The c.1840–4delA mutation identified in intron 19 probably affects the complete splicing of exon 20. The c.1840_1844delGTTGC mutation was located at the N-domain coding areas, and the mutation can cause the introduction of a premature termination codon (PTC) 6 codons downstream of the deletion site, leading to amino acid sequence change based on Mutation Taster assessment. The other novel mutation (c.1570+3A>C) located at the splice acceptor site of intron 17 and affected the canonical splice sequences of exon 17. In addition, a previously reported nonsense mutation, c.1402C>T of *ATP2C1*, was identified in P2 and P3. This transition resulted in a nonsense mutation of arginine codon (CGA) to a stop codon (TGA) at amino acid residue 468 in the hSPCA1 and premature translation termination (p. Arg468X). So far, this mutation has been found in ten patients from four pedigrees and one sporadic patient in Jiangxi Province, but seems very rare worldwide. According to the GnomAD database, this mutation was only reported in 1 out of 18,288 in an East Asian population. Hence, we conclude that this highly prevalent mutation in our cases with HHD is very rare in the worldwide population.

Wang et al[6] reviewed all of the reported mutations of HHD in a Chinese Han population but failed to find any specific relationships between genotypes and phenotypes. Additionally, the skin lesions may be influenced by extrinsic factors, such as infection, heat, sweating, and mechanical trauma.

Conclusion

In conclusion, we identified two novel mutations (c.1840_1844delGTTGC, c.1840–4delA) and (c.1570+3A>C), as well as a previously reported mutation (c.1402C>T). Meanwhile, our study revealed a highly recurrent prevalent mutation in this local population. Further studies will focus on elucidating the molecular mechanisms of *ATP2C1* involved in HHD pathogenesis.

Data Sharing Statement

The sequencing data has been submitted to ClinVar database (accession number: SCV002818467, SCV002818462, SCV002818461, SCV002818460, https://www.ncbi.nlm.nih.gov/clinvar/). All datasets generated for this study are included in the article/ Supplementary Material, and further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study.

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Disclosure

The authors report no conflicts of interest in this work.

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