

CASE REPORT

Two Novel ATP2C1 Mutations in Portuguese Patients with Hailey-Hailey Disease

Duas Novas Mutações do Gene ATP2C1 em Doentes Portuguesas com Doença de Hailey-Hailey

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ABSTRACT – Hailey-Hailey disease (HHD) is a rare autosomal dominant acantholytic dermatosis. It is characterized by a recurrent eruption of vesicles, erosions, and scaly erythematous plaques involving intertriginous areas and first occurring after puberty, mostly in the third or fourth decade. In 2000, mutations in the ATP2C1 gene on band 3q22.1, encoding the secretory pathway Ca²⁺/Mn²⁺-ATPase protein 1 (hSPCA1), have been identified as the cause of HHD. We report the identification of two novel mutations of ATP2C1 gene in two Portuguese patients, which expands the spectrum of ATP2C1 mutations underlying HHD and provides useful information for genetic counseling.

KEYWORDS – Calcium-Transporting ATPases/genetics; Frameshift Mutation; Mutation; Pemphigus, Benign Familiar/diagnosis; Pemphigus, Benign Familiar/genetics.

RESUMO – A doença de Hailey-Hailey (DHH) é uma dermatose acantolítica autossômica dominante rara. Clinicamente, caracteriza-se por episódios recorrentes de vesículas, erosões e placas eritematosas descamativas envolvendo áreas intertriginosas, com início após a puberdade, geralmente na terceira ou quarta década de vida. Em 2000, mutações no gene ATP2C1, no cromossoma 3q22.1, que codifica a proteína 1 da via secretora humana Ca²⁺/Mn²⁺-ATPase (hSPCA1), foram identificadas como a causa da DHH. Relatamos a identificação de duas novas mutações do gene ATP2C1 em duas doentes portuguesas, expandido o espectro de mutações ATP2C1 subjacentes à DHH e fornecendo informações úteis para o aconselhamento genético.

PALAVRAS-CHAVE – ATPases Transportadoras de Cálcio/genética; Mutação; Mutação da Fase de Leitura; Pênfigo Familiar Benigno/diagnóstico; Pênfigo Familiar Benigno/genética.

INTRODUCTION

Hailey-Hailey disease (HHD, OMIM 169600), also known as familial benign chronic pemphigus, was first described by the Hailey brothers in 1939.¹ It is a rare autosomal dominant inherited disorder with an incidence of approximately 1 in 50 000 individuals.² HHD first occurs after puberty, mostly in the third or fourth decade, with no sex or ethnic group predilection.^{2,3} Clinically, it presents as recurrent pruritic vesicles, painful erosions, and scaly erythematous plaques involving intertriginous areas and first occurring after puberty, mostly in the third or fourth decade.^{2,3} Histopathologically, it is characterized by an intercellular split of the epidermal suprabasal layers (acantholysis) resulting from the disruption of cell-cell contacts.^{2,3} Mutations in the ATP2C1 gene on band 3q22.1, encoding the secretory pathway Ca²⁺/Mn²⁺-ATPase protein 1 (hSPCA1), have been identified as the cause of HHD.⁴ In human keratinocytes, hSPCA1 plays a significant role in maintaining calcium homeostasis between the cytoplasm and the Golgi apparatus, which is fundamental for maintaining desmosomal integrity.² Mutation in ATP2C1 might affect Ca²⁺ signaling in keratinocytes, altering the sorting of desmosomal proteins or their

glycosylation, and resulting in the epidermal defects seen in skin lesions.² Herein, we report the identification of two novel mutations of the ATP2C1 gene in two Portuguese patients.

CASE REPORTS

Case 1

Patient 1 was a 56-year-old Portuguese Caucasian woman with a 2-year history of pruritic erythematous plaques on the groins and vulva, without previous diagnosis of HHD. Treatments with topical corticosteroid and fusidic acid, oral flucloxacillin and valaciclovir were used without any improvement of the skin lesions. Her mother had a history of similar skin lesions. Cutaneous examination revealed symmetrically distributed erythematous plaques with erosions and fissures on the groins and vulvar region (Fig. 1-A). Skin biopsy showed suprabasal keratinocyte acantholysis with mild dyskeratosis (Fig. 1-B). Accordingly, a diagnosis of HHD was established, and the patient was successfully treated with oral acitretin 10 mg/day and topical corticosteroid, with total regression of the lesions within 5 months.

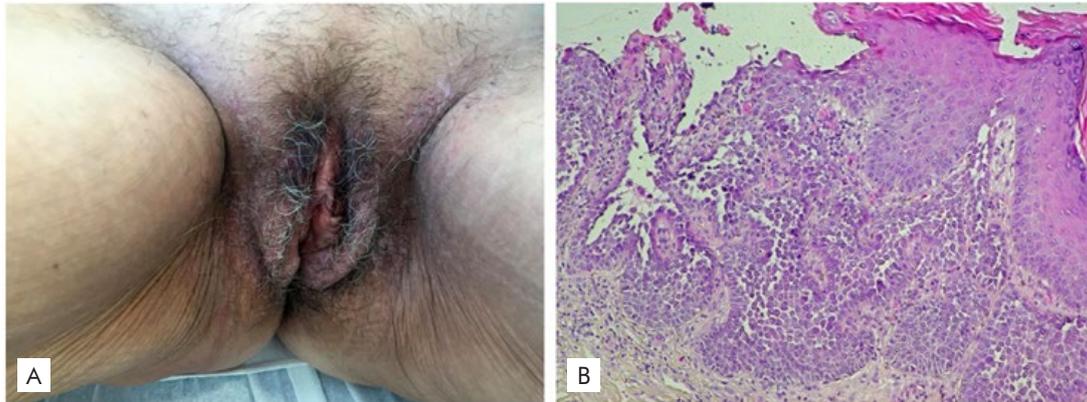


Figure 1 - Patient 1 (A) Clinical picture showing erythematous plaques with erosions and fissurations on the groins and vulvar region. (B) Histological examination showing suprabasal keratinocyte acantholysis with mild dyskeratosis (Hematoxylin and eosin, original magnification $\times 100$).

Case 2

Patient 2 was a 60-year-old Portuguese Caucasian woman with a 18-year history of typical skin lesions of HHD, mostly involving inframammary regions and groins (Fig. 2-A,B). The diagnosis of HHD was previously confirmed by histopathological study (Fig. 2-C,D). She reported 6 affected family members: the father, an uncle, a brother, a cousin, a niece and her son. The patient was admitted to the inpatient Dermatology Department for a clinical exacerbation of the skin lesions, already treated in the domicile with oral minocycline 100mg/day and betamethasone ointment, with minimal response. Bacterial culture from inguinal fold showed

growth of *Streptococcus pyogenes*. The patient was treated with oral clarithromycin, oral acitretin 10 mg/day and zinc oxide ointment, with significant clinical improvement within 2 months.

Genetic tests

After informed consent, genomic DNA was extracted from the patients' peripheral blood using a standard in-house salting-out method.

A whole exome library was prepared using the Twist human core exome kit (Twist Bioscience). Target regions were sequenced (paired-end) on an Illumina platform (NovaSeq 6000) with 150

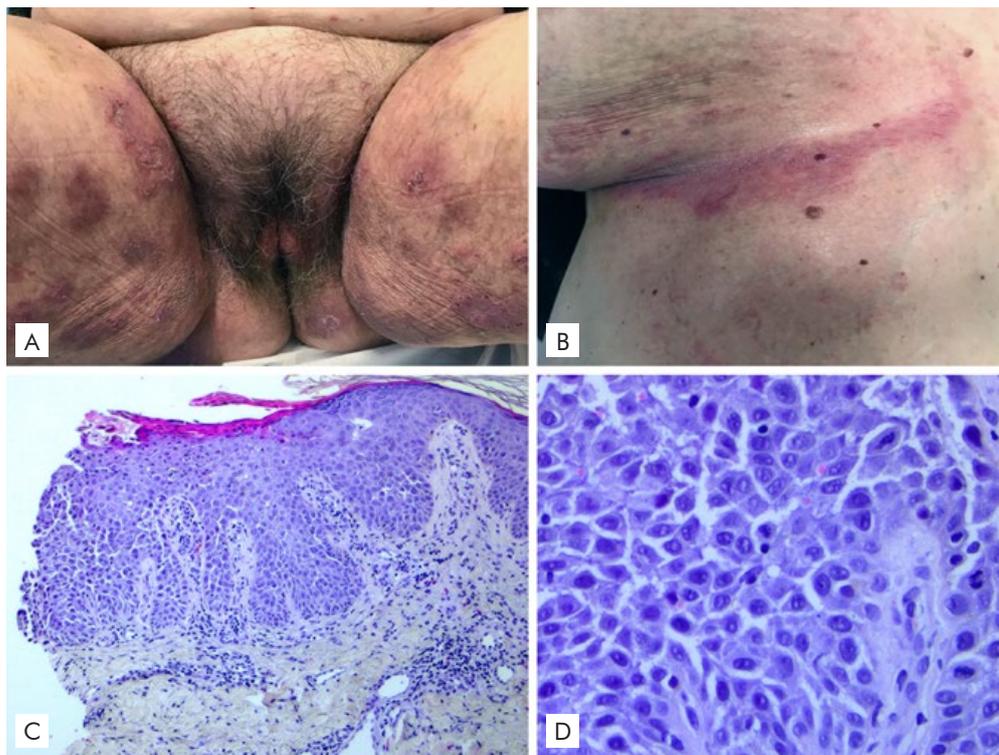


Figure 2 - Patient 2 (A,B) Clinical picture showing erythematous eroded involving the groins, perineum and inframammary folds. (C,D) Histological examination showing focal acantholysis beginning in the suprabasal area and extending throughout the epidermis. (Hematoxylin and eosin, original magnification $\times 100$, $\times 400$).

base read length, with a medium read depth of at least 60x. All the exonic and splice-site regions of the ATP2C1 gene were analyzed. To assess the potential functional consequences of detected variants and predict the clinical impact, bioinformatic data analysis was performed using well-established computational methods based on evolutionary conservation, protein structure and/or sequence homology.

Two heterozygous mutations of the ATP2C1 gene were identified in these patients with HHD (Table 1). In **patient 1**, a donor splice site G>T transition at nucleotide 1741+1 (c.1741+1G>T) was found in intron 18 of ATP2C1 (Fig. 3-A). In **patient 2**, a duplication of an A at nucleotide 1669 was found in exon 18 of ATP2C1 (c.1669dupA), which altered the coding sense from Threonine to Asparagine at position 557, and creating a premature stop codon at position 65 [p.(Thr557Asnfs*65)] (Fig. 3-B). These two mutations were absent in public databases. They were classified according to the American College of Medical Genetics and Genomics guidelines as likely pathogenic.⁵

Table 1 - Two novel mutations of ATP2C1 gene identified.

Patient	Location	Nucleotide substitution	Aminoacid substitution	Mutation type
1	Intron 18	c.1741+1 G>T	-	Donor splice site
2	Exon 18	c.1669dupA	p.Thr557 Asnfs*65	Frameshift

DISCUSSION

Since ATP2C1 was first reported as the causative gene for HHD in 2000, at least 185 ATP2C1 gene mutations have been discovered worldwide.⁶ These mutations are scattered throughout the ATP2C1 gene, distributed all over the encoded sequence (27 exons) and in the

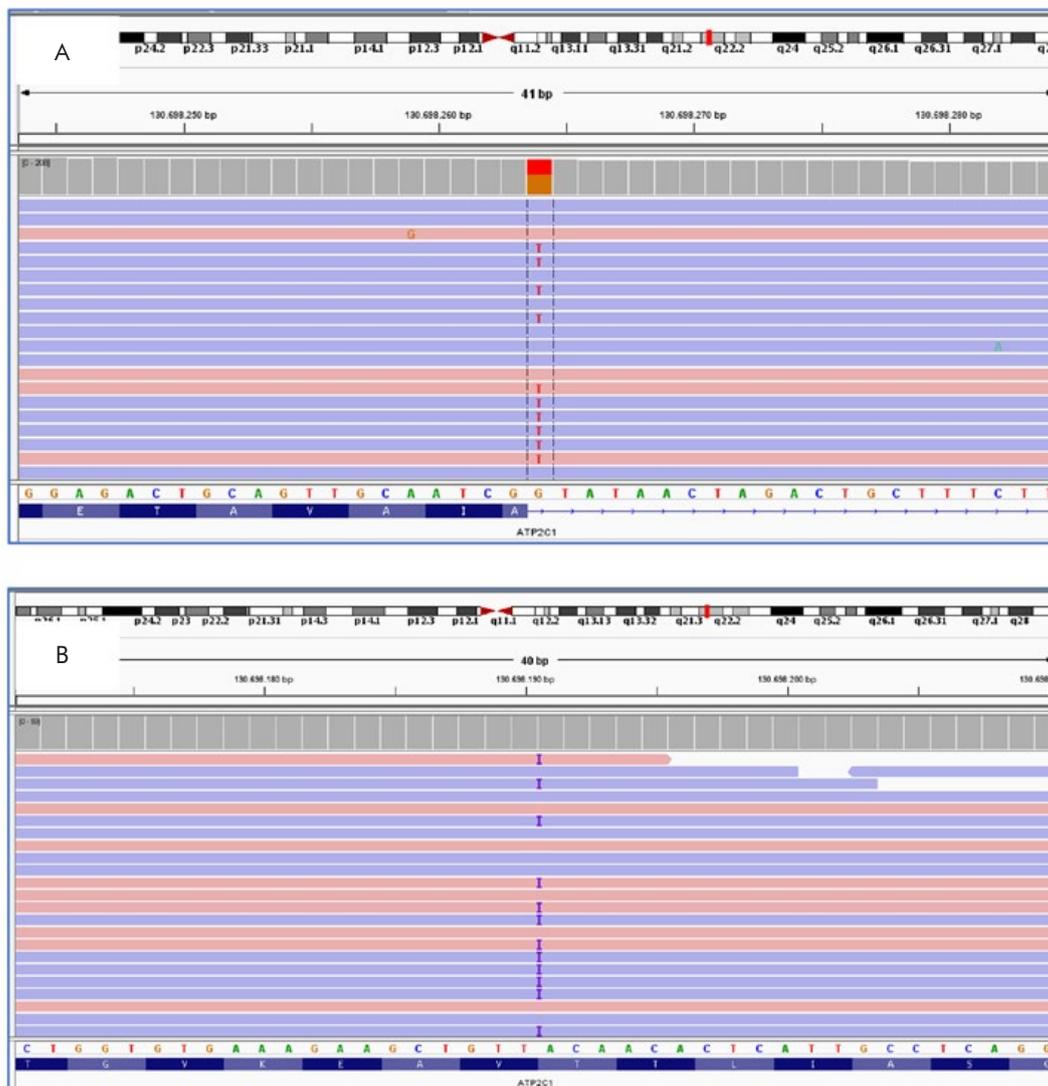


Figure 3 - ATP2C1 gene analysis of genomic DNA. (A) Patient 1, c.1741+1G>T. G>T transversion at the splice acceptor site of intron 18 of the ATP2C1 gene. (B) Patient 2, c.1669dupA. Duplication of A at nucleotide 1669 in exon 18.

intron splice sites, with no hotspots or clusters.⁷ They result in conformational defects and decreased levels of hSPCA1, leading to Golgi apparatus fragmentation, impaired cell proliferation, and defective sorting of proteins.⁶

No clear correlation between the genotype and phenotype was reported so far.^{7,8} Age of onset, severity, or progression could not be attributed to the mutation location or type in the putative protein structure.⁸ Modifying genes and environmental factors may greatly influence clinical features of the disease.⁸

In summary, we identified two novel heterozygous mutations in the ATP2C1 gene in Portuguese patients with HHD. This result expands the repertoire of ATP2C1 mutations associated with HHD and provides useful information for genetic counseling for HHD patients and families. Further research is required to clarify the genotype-phenotype correlation.

Apresentações/Presentations

A paciente 1 foi apresentada em poster no 1º Congresso Virtual de Dermatologia e Venereologia, realizado de 21 a 22 de novembro de 2020, vencedor do prémio de melhor poster.

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