Papular acantholytic dyskeratosis of the anogenital area with novel ATP2C1 gene mutations

Xue-Min Xiao¹, Yi-Qun Jiang², Wei Tian¹, Cheng-Rang Li²

¹Department of Dermatology, The Union Hospital, Fujian Medical University, Fuzhou, Fujian 350001, China; ²Institute of Dermatology, Jiangsu Key Laboratory of Molecular Biology for Skin Diseases and Sexually Transmitted Infections, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu 210042, China.

To the Editor: Focal acantholytic dyskeratosis (FAD) is used to describe a group of diseases with diverse clinical manifestations but characteristic histological structures. In 1984, the first case of "papular acantholytic dyskeratosis (PAD) of the vulvocural area" was reported in a 23-year-old female with pathological manifestations of FAD and the researchers believed that it might be a new independent disease.[1] Recently, the relationship between PAD and Hailey-Hailey disease (HHD) as well as Darier disease (DD) is receiving increasing attention from scholars. We performed gene mutation screening in two patients with sporadic PAD and explored the nature of PAD.

Case 1 was a 39-year-old male presenting with itchy eruptions on the perianal area for 5 years. Clinical examination showed multiple skin-colored, dome-shaped, scattered or grouped, smooth papules and nodules around the anus [Figure 1A]. Histopathological examination of the perianal papules revealed extensive suprabasilar and intra-spinous acantholysis with few dyskeratotic cells and incomplete acantholysis in part of the epidermis, leading to a "dilapidated brick wall" appearance [Figure 1B and 1C]. Case 2 was a 60-year-old female who complained of itchy lesions on her genital area for 5 years. Clinically, scattered light red and flesh-colored, smooth papules were located on the right side of the labia majora. Histopathological examination of the labia majora papules showed typical acantholytic dyskeratotic cells and acantholysis in the upper stratum spinosum.[2] Other parts of the body were normal, and there was no family history of similar lesions in either parent. An acetowhite test and microscopic examination for fungi in both lesions were negative. Additionally, no human papillomavirus DNA was detected in either lesion, and no deposits of immunoglobulin or complement on direct immunofluorescence examination were detected. Based on the above findings, the two patients were diagnosed with PAD.

The study was approved by the institutional ethical review boards of the Peking Union Medical College (No. 2015-028). After obtaining informed consent, genomic DNA was extracted from the peripheral blood samples of the patients and their parents, and 100 unrelated healthy individuals served as controls. Skin lesion specimens were collected from the patients, fixed in 4% formaldehyde solution, dehydrated routinely, embedded in paraffin, and sliced into sections with a thickness of 3 μm, and DNA was extracted using the phenol-chloroform method. All exons of the adenosine triphosphatase (ATPase), calcium transporting, type 2C, member 1 (ATP2C1) and ATPase, calcium transporting, cardiac muscle, slow twitch 2 (ATP2A2) genes with intronic flanking sequences were amplified by polymerase chain reaction and subsequently sequenced.[3,4] In both the blood and skin specimens of case 1, a heterozygous missense mutation in exon 17 of ATP2C1 was identified (NM_014382.4: c.1468T>C, p. C490R) [Figure 1D]. Similarly, a heterozygous nonsense mutation in exon 25 of ATP2C1 was identified (c.2395C>T, p. R799X) in case 2 [Figure 1E]. These mutations were not detected in the parents of the two patients, 100 normal controls or the National Center for Biotechnology Information Single-nucleotide Polymorphism database [Figure 1F and 1G]. p.C490R is a novel mutation not documented in the Human Gene Mutation Database or PubMed database. No mutations in the ATP2A2 gene were found.

Clinically, PAD is characterized by multiple smooth skin-colored or white papules with a diameter of 1 to 5 mm and a hard texture; these papules can coalesce into plaques and may be accompanied by varying degrees of itching or burning. To date, only approximately 30 cases have been reported worldwide.[1] PAD usually occurs in middle-aged women; it is most common in the vulva, perineum, and...
Focal or segmental DDs are brown-gray keratinized papules and plaques with greasy crusts; they commonly occur in the trunk and limbs, often accompanied by changes in fingers and nails, though without reports in the genital area. DD generally involves a family history and is caused by mutations in the ATP2A2 gene. Hyperkeratosis and dyskeratosis are more pronounced in DD, and there is no extensive acantholysis similar to that found in PAD. Grover disease has a sudden onset, manifesting as pruritic red papulovesicles, which are common on the neck, trunk, and proximal limbs but have not been reported in the anogenital area. PAD is most likely to be confused with HHD, for which mutations in the ATP2C1 gene are responsible. Although HHD confined to the vulva has been reported, HHD confined to the vulva presents with the characteristic clinical manifestations, namely, painful blisters with...
exudates, erosion, a family history, and no dyskeratosis by histopathology.

In addition to our cases, genetic changes have been reported for six PAD cases. One patient carried a mosaic mutation in ATP2A2, and ATP2C1 mutations as the potential cause were described for other cases. Moreover, there are reports of PAD transforming into typical HHD after many years and of PAD combined with HHD, suggesting a relationship of PAD with HHD over DD. The nonsense mutation p.R799X has been confirmed to be a disease-causing mutation in a typical HHD family, indicating that the same ATP2C1 germline mutation can cause the two different clinical phenotypes PAD and HHD. Variable penetrance owing to the presence of genetic modifiers is a potential cause of the different clinical manifestations of PAD and HHD.

The ATP2C1 gene encodes a calcineurin called human secretory pathway Ca2+-ATPase pump type 1 (hSPCA1). This enzyme is mainly localized in the Golgi apparatus of keratinocytes and pumps Ca2+ from the cytoplasm into the Golgi, regulating the processing of desmosomal proteins, desmosome junctions, and intercellular adhesions.[4] The following facts confirm the pathogenicity of the mutations. First, this mutation was predicted to be “possibly damaging” by PolyPhen (http://genetics.bwh.harvard.edu/pph2/), “deleterious” by PROVEAN (http://provean.jci.org/), “damaging” by SIFT (http://sift.jcvi.org/), “disease causing” by MutationTaster (http://mutationtaster.org/) and “high functional impact” by MutationAssessor (http://mutationassessor.org/); the nonsense mutation p. R799X results in a truncated hSPCA1 protein of 798 amino acids but lacking the last 121 amino acids. Moreover, we searched for the relative protein positions of the mutations and found that they are conserved in mammals, which suggests that they play important roles in maintaining protein activity during long-term evolution. Furthermore, the amino acids encoded by the two ATP2C1 mutations (c.1468T>C and c.2395C>T) are located in the cytoplasmic region between transmembrane fragments 4 and 5 and in the lumen region between transmembrane fragments 7 and 8, respectively. We speculate that a structural change in hSPCA1 occurs when the cytoplasmic region and lumen region are mutated, which affects its calcium ion transport and storage functions, eventually destroying intercellular adhesions and causing disease.

In summary, we report two sporadic PAD patients, each harboring mutation in the ATP2C1 gene, which further confirms that ATP2C1 mutation can cause PAD. To our knowledge, we might be the first to identify a mutation in ATP2C1 in a male patient with PAD. Considering the similarities between PAD and HHD with regard to clinical pathology and molecular genetics, we believe that PAD may not be an independent disease but rather a forme fruste or restricted type of HHD, implicating common continuous disease spectrum with HHD.

Funding
This work was supported by grants from the National Natural Science Foundation of China (Nos. 81602785 and 81472872), the Natural Science Foundation of Fujian, China (No. 2017J05128), Fujian Provincial Health Technology Project (No. 2019-ZQN-47), and the Opening Foundation of Research Platform of Fujian University of Traditional Chinese Medicine (No. X2018018- Platform).

Conflicts of interest
None.

References
1. Haddadeen C, Theaker J, Rowen D, Lottery H. Acantholytic dyskeratosis of the vulva presenting with clinical features of vulval lichen sclerosus-a possible rare collision entity. J Cutan Pathol 2020;47:61–64. doi: 10.1111/cup.13360.
2. Xiao XM, Li CR, Wang BX, Jiang YQ. A case of papular acantholytic dyskeratosis of the vulvoocular area [in Chinese]. Chin J Dermatol 2014;47:662. doi: 10.3760/cma.j.issn.0412-4030.2014.09.016.
3. Knopp EA, Saraceni C, Moss J, McNiff JM, Choate KA. Somatic ATP2A2 mutation in a case of papular acantholytic dyskeratosis: mosaic Darier disease. J Cutan Pathol 2015;42:853–857. doi: 10.1111/cup.12551.
4. Vodo D, Malchin N, Farman M, Sarig O, Sprecher E. Identification of a recurrent mutation in ATP2C1 demonstrates that papular acantholytic dyskeratosis and Hailey-Hailey disease are allelic disorders. Br J Dermatol 2018;179:1001–1002. doi: 10.1111/bjd.16915.
5. Gümüş AT, Iklnur T, Pabaçuoğlu U, Lebe B, Altiner DD. Papular acantholytic dyskeratosis of the anogenital area with positive direct immunofluorescence results. Clin Exp Dermatol 2007;32:301–303. doi: 10.1111/j.1365-2230.2007.02385.x.
6. Xiao X, Chen L, Wang B, Li C. A novel missense mutation of the ATP2C1 gene in a Chinese patient with papular acantholytic dyskeratosis of the anogenital area. Indian J Dermatol Venereol Leprol 2016;82:429–431. doi: 10.4103/0378-6523.181206.

How to cite this article: Xiao XM, Jiang YQ, Tian W, Li CR. Papular acantholytic dyskeratosis of the anogenital area with novel ATP2C1 gene mutations. Chin. Med J. 2021;134(12). doi: 10.1097/CM9.000000000001443