A novel missense mutation of the *ATP2C1* gene in a Chinese patient with papular acantholytic dermatosis of the anogenital area

Sir,

Papular acantholytic dermatosis of the anogenital and genitocrural area is a rare variant of focal acantholytic dermatosis which primarily occurs over the vulva. Most studies have classified it as a distinct entity. Recent research has revealed that mutations in the *ATP2C1* gene, which is typically seen in Hailey–Hailey disease, is also detected in papular acantholytic dermatosis of the anogenital area.[1,2] We report the results of direct nucleotide sequencing of the *ATP2C1* gene in a Chinese patient who sporadically developed papular acantholytic dermatosis of the anogenital area.

A 36-year-old woman presented with asymptomatic lesions over the genital area since eight months. Physical examination revealed multiple papules on the labia majora and perineum [Figure 1a]. They were confluent in distribution, flesh-coloured and slightly firm in consistency. Histopathological examination showed hyperkeratosis with irregular acanthosis, suprabasal clefts and diffuse acantholysis in the stratum spinosum giving a "dilapidated brick wall" appearance [Figure 1b]. Dyskeratosis with corps ronds and grains was also present [Figure 1c]. There were no deposits of immunoglobulin or complement on direct immunofluorescence examination.

Based on the above findings, we made a diagnosis of papular acantholytic dermatosis of the anogenital area. We collected peripheral blood from the patient, her healthy parents and one hundred unrelated controls after taking informed consent. Genomic deoxyribonucleic acid was extracted to amplify all exons of the *ATP2C1* gene with intronic flanking sequences using polymerase chain reaction.[3] The polymerase chain reaction products were purified using the QIAquick polymerase chain reaction purification kit and were sequenced using an ABI Prism 3730 automated sequencer. We detected a heterozygous missense c. 1748G > A mutation in exon 18 of the *ATP2C1* gene in our patient [Figure 2a]. The mutation changed the codon AGA at position

583 to AAA, which substituted arginine with lysine (p.R583K). The mutation was not found in the parents or any of the controls [Figure 2b]. It was also not found in the national center for biotechnology information single-nucleotide polymorphism database, the 1000 genomes database or the exome aggregation consortium browser. This supports the idea that this is a *de novo* causative mutation rather than a polymorphism.

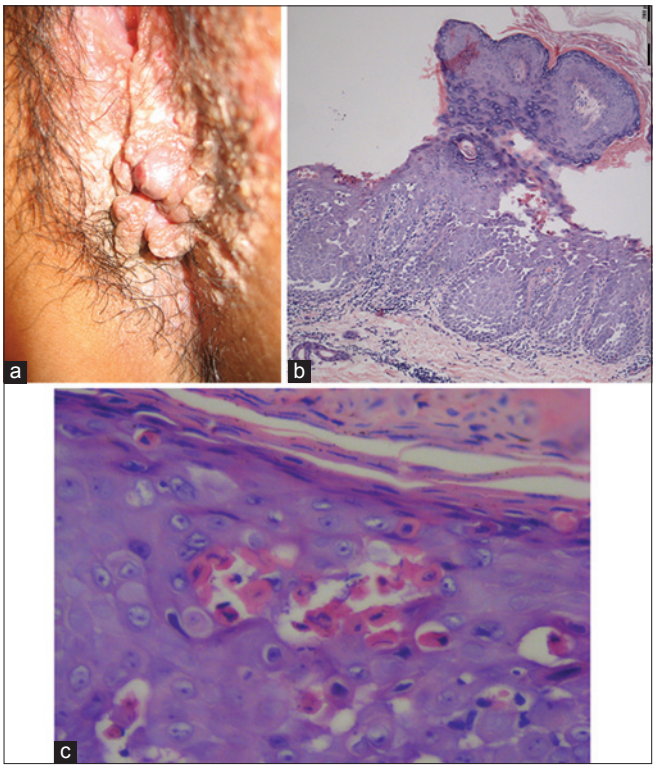

Figure 1: (a) Multiple confluent, flesh-coloured and slightly firm papules on the labia majora. (b) Hyperkeratosis with irregular acanthosis, suprabasal clefts and diffuse acantholysis in the spinous layer giving the appearance of a dilapidated brick wall (H and E, ×100). (c) Dyskeratosis with corps ronds and grains (H and E, ×400)

Papular acantholytic dermatosis of the anogenital area is characterized by variably pruritic, 0.1–0.5 mm sized, isolated or grouped, smooth papules confined to the this area. Lesions are usually present for a long duration with no antecedent family history. Females are usually affected with the labia majora being the most common site involved. Only a few cases have been reported in males.[4] Histopathology shows features of acantholysis accompanied by varying degrees of dyskeratosis. Almost all immunofluorescence studies were negative. The lack of skin changes in areas such as the neck, axillary folds, or inframammary regions helps to distinguish this condition from Hailey–Hailey disease. Although Hailey–Hailey disease localized to the genital area has been described, such patients always have a positive family history and clinical features characteristic of Hailey–Hailey disease are observed. Interestingly, three recent cases of papular acantholytic dermatosis of the anogenital areas have reported two distinct mutations within the *ATP2C1*

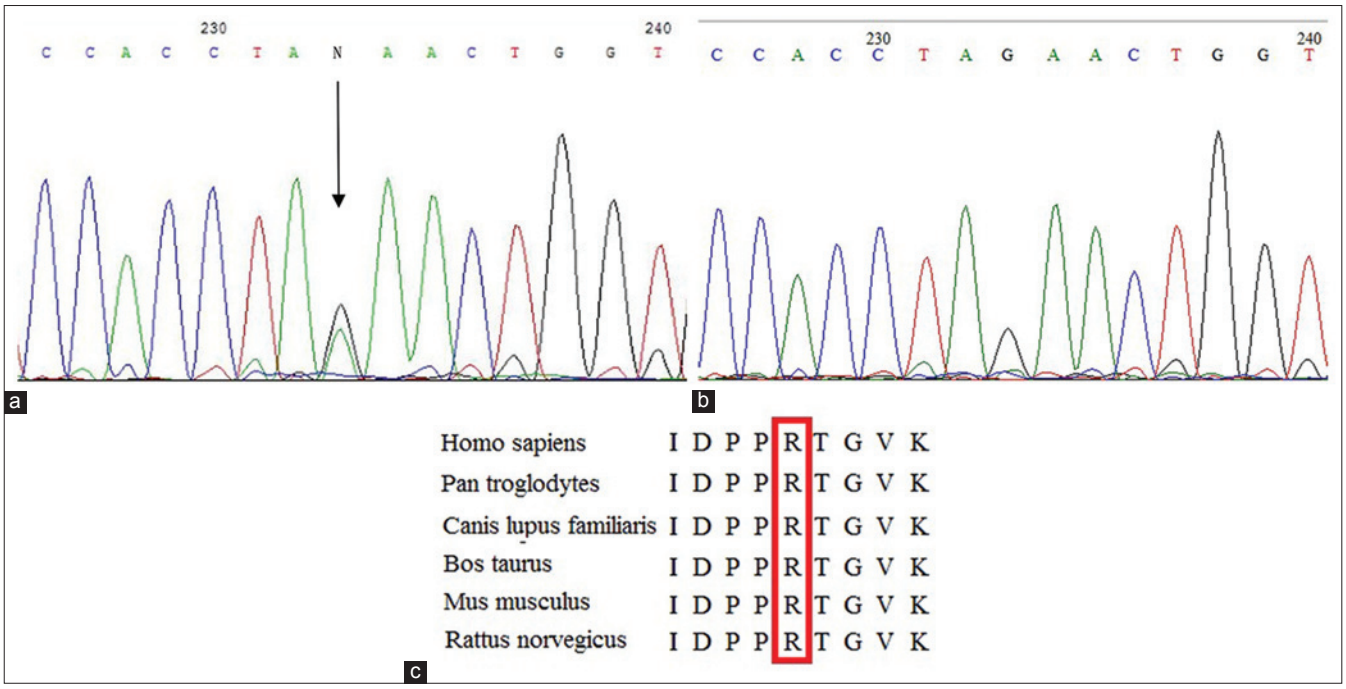

Figure 2: (a) Heterozygous c. 1748G > A (p.R583K) mutation in exon 18 of the *ATP2C1* gene. (b) The equivalent *ATP2C1* genomic sequence in a normal individual. (c) Relative protein positions of the mutation. Residue R at position 583 is conserved in all species of *Eutheria*

gene (c. 2375delTTGT and c. 360 + 2T > A). This, along with the fact that the condition can evolve into typical Hailey–Hailey disease after many years, implies that the two diseases may belong to the same clinico-pathologic spectrum.[1,2]

The *ATP2C1* gene encodes human secretory pathway calcium ATPase protein 1, a Ca^{2+}-ATPase responsible for pumping calcium from the cytoplasm to the Golgi apparatus. Fairclough *et al*. investigated missense mutations of the *ATP2C1* gene including L341P, C344Y, C411R, T570I and G789R. They found low levels of expression in keratinocytes despite normal levels of mRNA and correct targeting to the Golgi apparatus. This suggests instability or abnormal folding of the mutated human secretory pathway calcium ATPase protein 1 polypeptides.[5] We also searched relative protein positions of the mutation in GenBank, and found that Arg583 is conserved in all species of *Eutheria* [Figure 2c]. Consequently, the novel mutation results in calcium transport dysfunction and may account for the pathogenesis of this condition. The experimental program Polymorphism phenotyping v2 (http://genetics.bwh.harvard.edu/pph2/), predicted that this mutation is "benign" with a score of 0.012., whereas the five missense mutations in Hailey–Hailey disease were predicted to be "probably damaging." These results may explain why the novel mutation caused a relatively mild phenotype of papular acantholytic dermatosis of the anogenital area rather than classic Hailey–Hailey disease.

To summarize, our report provides evidence that the *ATP2C1* gene is the pathogenic gene in papular acantholytic dermatosis of the anogenital areas. We were unable to find any previous reports of the condition with a missense mutation in *ATP2C1*. Taking both clinicopathological and genetic overlap with Hailey–Hailey disease into account, we propose that papular acantholytic dermatosis of the anogenital area may be considered as a mild variant of Hailey–Hailey disease. These two phenotypes may be a part of the same disease spectrum.

Acknowledgment

We are most grateful to all members of the PAD family for taking part in our study.

Financial support and sponsorship

This work was funded by grants from Foundation of PUMC innovation team, National Natural Science Foundation of China (81472872) and Peking Union Medical College Youth Research Fund (33320140048).

Conflicts of interest

There are no conflicts of interest.

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Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.181206

How to cite this article: Xiao X, Chen L, Wang B, Li C. A novel missense mutation of the *ATP2C1* gene in a Chinese patient with papular acantholytic dermatosis of the anogenital area. Indian J Dermatol Venereol Leprol 2016;82:429-31.

Received: April, 2015. **Accepted:** November, 2015.