Hailey-Hailey Disease Masquerading as Condyloma Acuminatum
- Case Report and Novel Mutation Analysis

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Familial benign chronic pemphigus, (Hailey-Hailey disease, HHD, OMIM 169600), first described by Hailey brothers, is an autosomal dominant inherited skin disorder characterized by recurrent blistering predominantly over neck, groin and axillary areas. Histopathologically, defects in cell-to-cell adhesion in suprabasal layers of the epidermis (acantholysis) are characterized. Mutation in ATP2C1, the gene encoding a novel P-type Ca²⁺-transport ATPase, was recently found to cause Hailey-Hailey disease.

Here we presented a 29-year-old male patient who suffered a verrucous plaque over anal orifice and perianal area with pruritus and mild painful sensation for more than one year. Condyloma acuminata was diagnosed at private clinics and different kinds of therapies were applied but in vain. Histopathology showed suprabasal cleft with extensive acantholysis, indicating Hailey-Hailey disease. No other skin lesions and no family history were contributed. Mutation analysis of ATP2C1 gene revealed a novel insertion mutation (1230insACACA). (Dermatol Sinica 23: 101-104, 2005)

Key words: Hailey-Hailey disease (HHD), Familial benign chronic pemphigus, ATP2C1 gene, Condyloma
INTRODUCTION

Familial benign chronic pemphigus, or Hailey-Hailey disease (HHD, OMIM 169600), was first described by Hailey brothers. It is an autosomal dominant disease characterized by recurrent vesicles and erosions, particularly involving intertriginous areas such as axillae, groin and neck and occurring after puberty or in middle age. Both sexes are equally affected and family history is positive in 70% of the patients. Histopathologically, HHD shows intraepidermal vesicles with prominent acantholysis and cleft above the basal cell layer revealing a characteristic “dilapidated brick wall” picture. Recent studies have revealed that HHD is caused by mutations in ATP2C1 encoding a novel Ca\textsuperscript{2+} pump.\textsuperscript{2,3} We reported a case manifesting anal orifice and perianal lesions, which was misdiagnosed as condyloma acuminate first.

CASE REPORT

HISTORY & CLINICAL MANIFESTATION

This 29-year-old heterosexual man suffered from pruritus and mild painful over anal orifice and perianal area for more than 1 year. He visited private clinics for help and condyloma acuminata was diagnosed. He received cryotherapy several times and topical podophyllin therapy for a long time but there were no obvious improvement. On examination, a solitary macerated verrucous plaque with erythematous base was found over anal orifice and perianal area. (Fig. 1) There was no any other skin lesion. No other family members were affected.

MICROSCOPIC FINDING

A skin biopsy was performed and histopathology revealed hyperkeratosis and focal parakeratosis with psoriasiform epidermal hyperplasia and extensive acantholysis of spinous cells with suprabasal cleavage and scattered dyskeratotic cell in the epidermis. The appearance has been likened to that of a “dilapidated brick wall” (Fig. 2). A perivascular lymphocytic infiltrate was present in upper dermis. Electron microscopy revealed changes consistent with a defect of desmosomal adhesion: there is separation of tonofilaments from desmosomes and a reduction of visible desmosomes on the cell surface; electron-dense material is noticed around nucleus.

GENE ANALYSIS

Due to unusual clinical manifestation and family history, gene mutation analysis was performed with PCR amplification and automated sequencing.

Genomic DNA was extracted from periph-
eral blood of the patient and his parents, respectively, with informed consent. DNA sample was then subjected to mutation screening by amplification of segments of ATP2C1 gene spanning all 27 exons of the gene using primers synthesized on the basis of intronic sequences.

For PCR amplification, approximately 200 ng of genomic DNA, 12.8 pmol of each primer, 10 μmole dNTP and 1.25 U of AmpliTaq Gold (Perkin Elmer, Roche Molecular Systems, Inc., Branchburg, New Jersey, USA) were used in a total volume of 50 μl. The oligonucleotide primers were designed to amplify the mutation in exon 14 and 15 of the ATP2C1 gene are: forward primer, 5’ — GTCTTGTCACCACCAAGTGT — 3’; reverse primer 5’ — GTGAGGGCAGTGTCTCAAT — 3’.

The product size should be 384 bp normally. The amplification conditions were 94°C for 5 min, followed by 35 cycles of 94°C for 45 second, annealing temperature (50°C) for 45 second and 72°C for 45 second, and extension at 72°C for 10 min. The PCR products were examined on 2% agarose gel. The PCR product was subjected to direct automated sequencing (377 ABI Advanced Biotechnologies, Columbia, Md.).

DNA sequencing of the exon 15 from the proband showed a 5 bp insertion mutation (1230insACACA), which causes frameshift and premature stop codon (PTC+6aa) (Fig. 3).

**DISCUSSION**

HHD usually occurs in the third and fourth decade and affects mainly the flexural areas, especially the intertriginous area such as neck, axillae and groin. Mucosal involvement is rare and asymptomatic longitudinal white lines on fingernail are noticed in some patients. HHD manifests recurrent vesicular lesions, crusted erosions and warty papules. Lesions are often induced or exacerbated by external factor such as sweating, friction and cutaneous infection.

HHD is an autosomal dominant genodermatosis and caused by mutations of ATP2C1 gene, a ATP-powered Ca²⁺ pump, located at chromosome 3q21-q24. The ATP2C1 is localized to the Golgi apparatus in human keratinocytes, similar to its localized in yeast and *Caenorhabditis elegans*. Human ATP2C1 protein approximated 115 kDa in size. Extracellular Ca²⁺ plays a critical role in regulating differentiation and adhesion of cultured keratinocytes. The human ATP2C1 controls a significant Ca²⁺ store. HHD keratinocytes display elevated resting cytosolic Ca²⁺ concentrations, abnormally low Golgi Ca²⁺ levels, and impaired regulation of excess cytosolic Ca²⁺ in vitro. Elevated cytosolic Ca²⁺ could influence gene expression or alter posttranslational modification of target proteins (activation of protein kinase C). Alternatively, low Ca²⁺ concentrations in the Golgi lumen could impair post-translational modifications (proteolytic processing, glycosylation, trafficking or sorting) of membrane associated proteins important in epidermal cell-to-cell adhesion, such as desmosomal components. This may impair desmosome formation and/or stability, leading to the acantholysis characteristic of HHD.

Misdiagnosis is commonly due to wide phenotypic variation. HHD should be distinguished clinically from pemphigus vulgaris or vegetans, and intertrigo. HHD located exclusively in the perineal or perianal area is rare.

**Fig. 3**

Automatic sequencing of the exon 15 of ATP2C1 gene. (A) Normal sequence; (B) subcloning showed 5 bp (ACACA) insertion and frameshift with premature stop codon (TAA, PTC+6aa); (C) the normal and mutant alleles whose superimposition by the 5 bp insertion (1230insACACA) are displayed.
The localization solely to genital area, a negative family history, and the absence of vesicles or crusting explain the common misdiagnosis of verrucoid HHD as genital warts. Biopsy for histopathological examination is important.

To date, more than 62 ATP2C1 gene mutations had been reported in the literature (http://uwcmml1s.uwcm.ac.uk/uwcm/mg/search/10796903.html). In this report, we detected a novel mutation with 5 bp insertions (1230insACACA) which resulted in frameshift and premature stop codon (TAA, PTC+6aa).

Although we find a rare clinical manifestation with a novel mutation in this case, no clear genotype-phenotype correlation is observed in the group of patient for whom clinical information is available in previous studies. Neither age of onset, pattern of outbreak, severity, nor progression of disease can be attributed to mutation type or location in the putative protein structure. Clinical phenotype might simply be influenced by other intrinsic and extrinsic factors such as expression levels of ATP2C1 in each patient, ultraviolet irradiation, high environmental temperature, minor mechanical stimuli in daily life and the presence of pathogens, etc. We speculate that clinical phenotype might not relate to the types of mutation in ATP2C1.

**CONCLUSION**

Due to extensive phenotypic variation, misdiagnosis was common and biopsy for definite diagnosis is indicated, especially if the lesions have been present for many months or persist despite treatment. A novel insertion mutation of ATP2C1 was found in this study for further emphasized the variation of the genotype of HHD.

**REFERENCES**