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# Somatic *ATP2A2* Mutation in a Case of Papular Acantholytic Dyskeratosis: Mosaic Darier Disease

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## Abstract

Papular acantholytic dyskeratosis (PAD), also known as acantholytic dermatosis of the vulvocrural (or anogenital) area, is an uncommon eruption reported predominantly in women. This entity manifests with pruritic papules in the groin/anogenital area and less commonly on the chest. The pathobiology of PAD is uncertain. A 62-year old woman presented with multiple verrucous-appearing lesions in the groin and on the chest showing acantholytic dyskeratosis on histopathology. Given histological similarity of these PAD lesions to Darier disease (DD) due to inherited *ATP2A2* mutation, we screened affected and normal tissue and peripheral blood in our patient for mutations in *ATP2A2*. We found an identical *ATP2A2* p.706D>N mutation in multiple independent PAD lesions that was not present in uninvolved skin or peripheral blood DNA. These findings establish somatic mosaicism of *ATP2A2* mutations as a genetic cause for PAD.

## Introduction

Papular acantholytic dyskeratosis (PAD), also known as acantholytic dermatosis of the vulvocrural (or anogenital) area is an uncommon and frequently misdiagnosed eruption seen more commonly in women than in men. Typically, patients present as adults with pruritic papules in the groin area; some patients also report lesions on the chest. Many are diagnosed on clinical grounds as having genital warts; due to inconsistent history and/or failure to respond appropriately to treatment, a biopsy leads to the alternative diagnosis of PAD. Although there has been speculation about a possible relationship to the autosomal dominant genodermatoses of DD and Hailey-Hailey disease (HHD), comprehensive genetic testing of affected and unaffected tissue in addition to blood has not previously been performed in a patient with PAD.

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## Report of a Patient

A 62 year-old woman reported a greater than five-year history of itchy bumps in the groin. A family history was negative for similar lesions. On examination she had multiple, bilateral, skin-coloured papules on the mons pubis, external labia, inguinal folds and upper medial thighs with fewer, similar papules on the central chest and inframammary areas (Fig. 1). The papules were scattered and focally aggregated, but were not arrayed in a linear or Blaschkoid pattern. The remainder of the exam was normal, including nails, mucosae, palms and soles. Initial biopsies taken for diagnosis from the groin showed acantholytic dyskeratosis. Human papilloma virus (HPV) was not detected by *in situ* hybridization with a panel of common HPV types.

## Materials and Methods

Under a protocol approved by the Yale University Human Research Protection Program, seven biopsies of separate verrucous papules from the groin (including labia majora, inguinal crease, upper thigh) and one from the chest were obtained; a biopsy of normal skin was taken from the low abdomen/mons pubis. The chest sample was formalin-fixed, paraffin-embedded; the remaining eight biopsies were snap-frozen and embedded in Optimal Cutting Temperature compound. All samples were evaluated by light microscopy. Six samples with the most marked histopathological changes were selected for laser-dissection of affected epidermis and a portion of dermis as a control; epidermis was also laser-dissected from the biopsy of normal skin. DNA was prepared from these samples, whole genome amplification performed, followed by PCR and sequencing of the *ATP2A2* gene in parallel with DNA from blood.

## Results

Evaluation by light microscopy of the papular lesions from the groin and chest revealed epidermal acanthosis with patchy acantholysis and scattered dyskeratotic cells (Fig. 1). No epidermal abnormalities were seen in the biopsy of normal skin.

Sequencing of six samples of lesional tissue revealed a missense mutation in exon 15 of *ATP2A2* not present in peripheral blood or normal tissue (c.2116G>A, p.706D>N) (Fig. 1). This mutation occurs at a residue which is 100% conserved in vertebrates.

## Discussion

PAD is an under-recognized entity easily mistaken for condyloma because of its verrucous appearance and predilection for the genital area.[1] Misdiagnosis can cause significant patient distress.

There are at least 16 reports of compatible cases in adult female patients,[1–16] in which multiple lesions were reported as showing both acantholysis and dyskeratosis. In an additional 8 women, the lesions were solitary and therefore are of uncertain relevance.[5, 17, 18] One report described positive direct immunofluorescence, in contrast to other published cases.[19] There are also 6 similar reports in men,[20–23] and 3 in children.[24–26]

None of these reports indicated a positive family history. These cases have been published under various names, many as papular acantholytic dyskeratosis/dermatosis, others as acantholytic dermatosis of the vulvocrural/anogenital area; some cases have been published under the names of histopathologically similar entities such as multiple warty dyskeratomas,[11] with subsequent commentary suggesting reclassification into the PAD spectrum.[12] Lesions have been reported on the genital mucosa, external genitalia, and surrounding skin of the groin and upper thigh. Two reports also involved the chest,[6, 7] prompting the suggested alternate terminology "intertriginous acantholytic dermatosis,"[7] although this name has not been adopted. The findings in our patient were similar to these latter reports, with papules both in the groin and on the chest. Although a relationship to DD and HHD has been proposed, comprehensive testing of affected and unaffected tissue in addition to blood has not previously been performed. The results of this study indicate that somatic mosaic mutations in *ATP2A2*, the gene encoding the sarco-endoplasmic reticulum calcium-pumping ATPase (type 2) mutated in DD, can result in the clinical phenotype referred to as PAD.

The mutation identified in our patient was previously reported in an Italian patient with germline DD manifesting as acrokeratosis verruciformis (AKV) with nail changes.[27] There is evidence that AKV and DD are allelic disorders with variable expression of overlapping features.[28] Mutations in the same codon of *ATP2A2* have resulted in clinical phenotypes of AKV and DD in separate individuals.[29] The p.706D>N mutation falls within a domain regulating enzymatic phosphorylation required for calcium conductance and is known to reduce phosphorylation rate and calcium flux.[30] Aberrant calcium flux has been shown to cause loss of epidermal integrity, a hallmark of DD and PAD.

Mutations resulting in segmental disease occur spontaneously during embryogenesis. This study indicates that mosaic mutation in *ATP2A2* can cause PAD. Timing of the mutational event in embryogenesis likely determines the distribution and extent of tissue involvement. Study of a patient with segmental DD revealed that mutation in 37% of cells within a region of skin was sufficient to produce cutaneous manifestations; the minimum threshold is expected to be slightly less.[31] Our findings of variable percentages of mutated DNA within samples showing normal or affected histopathology correlate with this concept and may partly represent admixture with normal tissue given the sampling approach employed.

It is not established why there is a predilection for women and for the genital area in PAD; however, a moist, high-friction environment has been suggested as a predisposing factor.[5] It stands to reason that conditions known to exacerbate DD could promote expression of the disease in a mosaic patient. The age of PAD onset/manifestation reported in the literature is variable, with multiple examples in each decade of life, including patients in their 60s. Similarly, cases of late "onset" germline DD, including at 50 and 75 years of age[29, 32] have been reported.

Treatment of PAD is challenging. Topical and oral retinoids are favored in case reports.[5, 24, 33] This observation is supported by their known utility in DD. Ablative treatments including lasers have shown success;[5, 9, 14] this might be explained by preferential healing of treated areas with a predominance of wild-type keratinocytes.

There are reports where a relationship to HHD has been favored over DD.[33–35] Predominantly HHD-like histopathology has been seen in a minority of cases.[22, 35–38] Mutation in the *ATP2C1* gene (affected in HHD) has been demonstrated in tissue from a patient with an extensive vulvocrural eruption showing HHD-like pathology; however sequencing of blood was not performed, therefore, it is not possible to exclude a constitutional mutation in this case.[33] Similarly, a mother and daughter each with adult onset of pruritic genitoperineal papules, were found to harbour identical heterozygous mutations in the *ATP2C1* gene, presumably germline mutations in both patients.[35] It remains possible, even probable, that mosaic forms of both DD and HHD (as well as formes frustes of these germline diseases) might eventuate in the clinical pattern currently recognized as PAD. The appearance of the pathology can help to guide the genetic evaluation of such cases.

We report a case of PAD demonstrating mosaic mutation of the gene affected in DD. Dermatologists and pathologists should be aware of this diagnosis and its genetic underpinnings. Histopathological examination of suggestive genital lesions is important to allow for appropriate patient counseling and treatment, including consideration that DD could be transmitted to offspring in whom the entire body could be affected..

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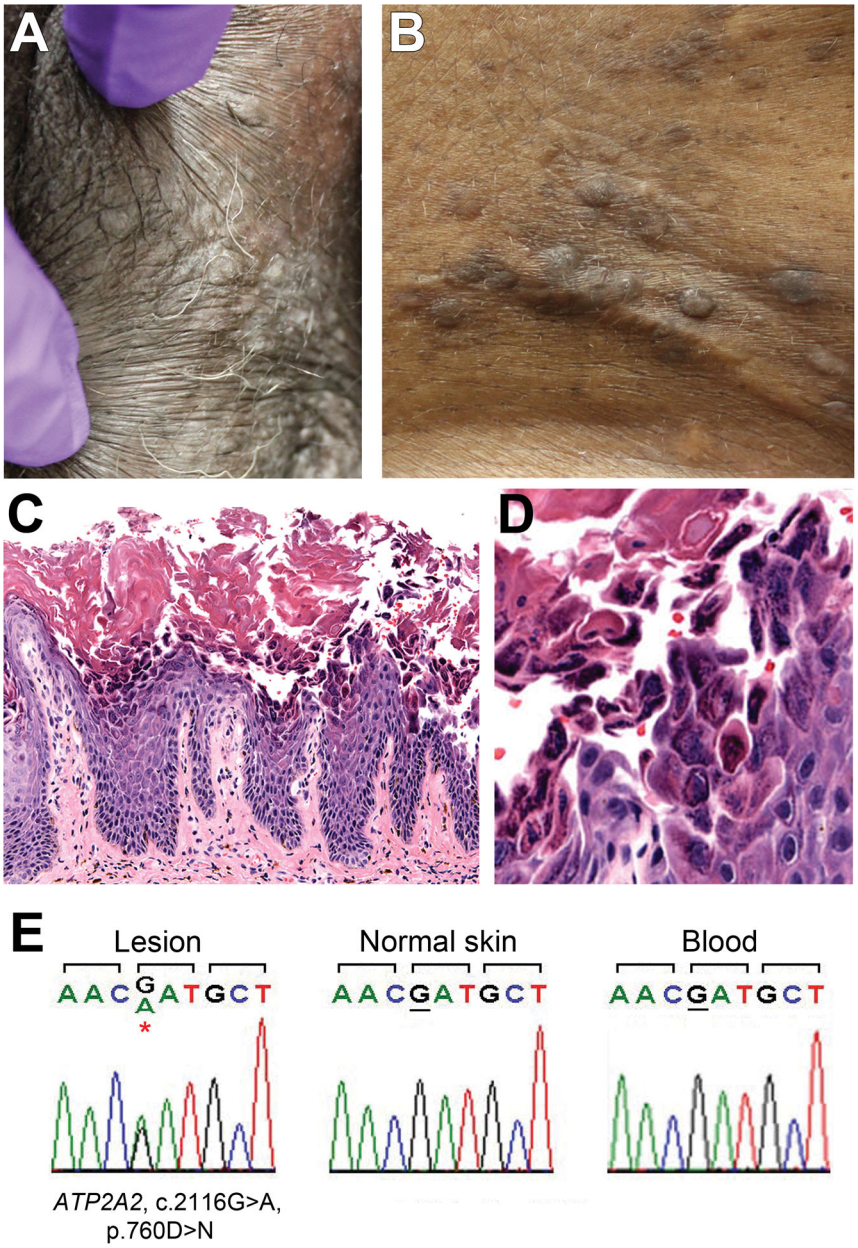


**Figure 1.**

Clinical, histopathological and sequencing findings.

*Top panel:* Skin-colored papules on the left external labia majora (a) and central chest (b). *Central panel:* Hematoxylin and eosin stains of lesional tissue at low power (c) and high power (d) show acanthosis and papillomatosis, with acantholysis and dyskeratosis of keratinocytes. *Lower panel:* Chromatograms (e) demonstrate mutation of *ATP2A2* in affected epidermis with wild-type sequence in unaffected epidermis and peripheral blood.