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CASE REPORT

New Mutation in the Birt Hogg Dube Gene

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PALABRAS CLAVE

Fibrofolliculoma;
Acrocordón;
Síndrome Birt Hogg
Dubé;
Mutación

Abstract

Patients with Birt-Hogg-Dube syndrome have an increased risk of developing hamartomas of the pilosebaceous unit, renal tumors of various types, lung cysts, and spontaneous pneumothorax. We present the case of a 54-year-old woman with a long history of whitish papules in the central region of the face and a family history of similar lesions. Biopsy and genetic study revealed a new mutation of the gene involved in Birt-Hogg-Dube syndrome.

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Nueva mutación en el síndrome de Birt Hogg Dubé

Resumen

El Birt Hogg Dubé es un síndrome que predispone a la aparición de hamartomas del folículo pilosebáceo y a mayor riesgo de presentar tumores renales de diversa estirpe, quistes pulmonares y neumotórax espontáneos.

Presentamos el caso de una mujer de 54 años que presenta desde hace años pápulas blanquecinas centofaciales e historia familiar de esas mismas pápulas.

Tras biopsia y estudio genético de la paciente se detecta una nueva mutación en el gen implicado en este síndrome.

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Figure 1 Well-delimited, whitish papules on the cheeks and dorsum of the nose.



Figure 2 Whitish papules in the submandibular region and on the lateral aspect of the neck, similar in appearance to those on the face but in smaller numbers.

Introduction

Birt Hogg Dubé (BHD) syndrome is a genodermatosis with autosomal dominant inheritance. It was first described in 1977 as the association of 3 skin lesions-fibrofolliculomas, trichodiscomas, and acrochordons-that start to appear between the third and fourth decades of life. Interest in the syndrome increased some years later when it was found to have an association with renal tumors and lung cysts. It is now known that the syndrome is due to a germline mutation in the *BHD (FLCN)* gene, which codes for a protein called folliculin.^{1,2}

Fibrofolliculomas and trichodiscomas presents clinically as multiple, domed, skin-colored or whitish papules, usually on the face and neck and more rarely on the upper part of the trunk and proximal areas of the lower limbs. It is now believed that fibrofolliculomas and trichodiscomas are different forms of the same lesion.

Case Description

We present the case of a 54-year-old woman who was seen for the appearance, 20 years earlier, of multiple whitish papules on the cheeks, nose (Figure 1), and neck (Figure 2).

She underwent surgery for a uterine myoma and a melanoma on the right wrist 20 and 18 years earlier, respectively. In the last year she had undergone excision of 18 acrochordons from the axillas at another center.

Of note in her family history was that her mother and 2 of her children had similar lesions. An aunt and 2 of her maternal cousins had had spontaneous pneumothoraces in their youth, and a maternal uncle and 1 of his daughters had undergone operations for renal tumors (Figure 3).

Biopsies were taken of 1 of the lesions on the neck and another on the left cheek. Pathology study of both lesions was compatible with a diagnosis of fibrofolliculoma (Figures 4 and 5).

With the data from the medical and family history and the histopathology result we made a diagnosis of BHD syndrome.

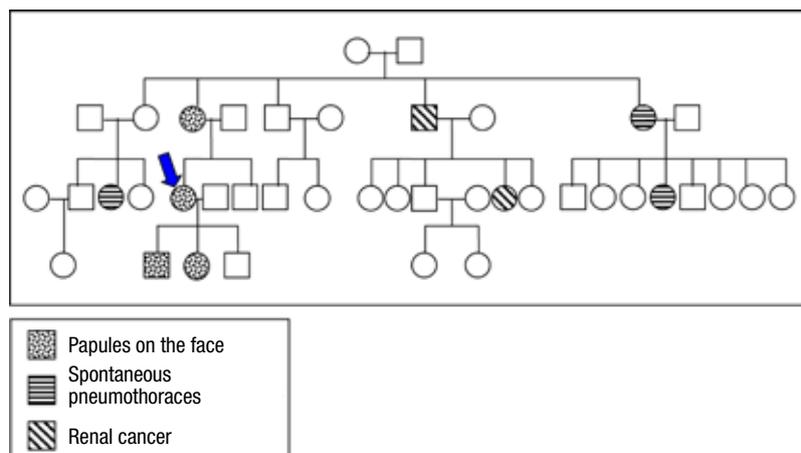


Figure 3 Genealogy of our patient (blue arrow).

Chest radiograph and abdominal ultrasound were performed, excluding lung cysts and renal masses.

Molecular genetic study performed using multiplex ligation-dependent probe amplification (MLPA) revealed

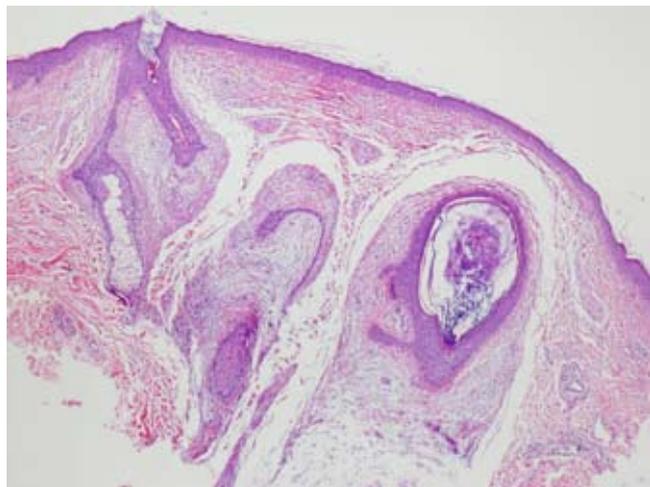


Figure 4 In the center are distorted hair follicles surrounded by a loose basophilic mucoid stroma. Thin cords of follicular epithelial cells run out from the wall of the distorted follicle and anastomose together and with the wall. Hematoxylin-eosin, original magnification $\times 10$.

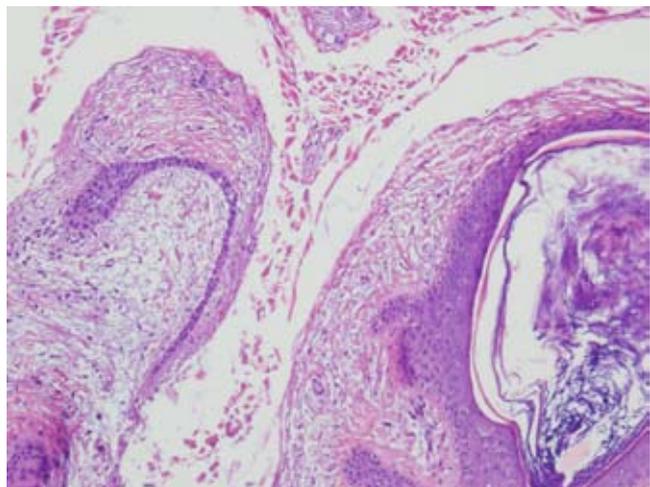


Figure 5 Detail of the cords of follicular epithelial cells. Hematoxylin-eosin, original magnification $\times 40$.

deletion of exon 14 of the *FLCN* gene in the sample from the patient (Figure 6). This mutation has not previously been reported in the literature, but due to the loss of the Poly(A) signal, it can be expected to be responsible for the syndrome.

Discussion

The existence of BHD syndrome has been questioned by some authors, who suggested that the fibrofolliculomas and trichodiscomas probably formed part of a single disorder and that the acrochordons were a casual association as they are so common in the general population.³ In 1999, however, Toro et al⁴ drew attention to the association between this syndrome and the appearance of familial renal tumors and recommended performing computed tomography or abdominal ultrasound on patients and their relatives.

In 2002, Zbar et al⁵ described the association between BHD and a familial increase in the incidence of spontaneous pneumothorax in adolescence, an association already hinted at by Binet et al.⁶

Further associations with BHD syndrome have been reported, such as polyposis coli and colon carcinoma, and there has been a report that suggests that BHD syndrome and Hornstein-Knickenberg syndrome are one and the same.⁷ However, a large, later study found no significant increase in the risk of polyps and cancer of the colon in BHD.⁵

The locus responsible for the syndrome was detected on chromosome 17p11.2 using genetic segregation, which identified the mutated germline in a new gene called *FLCN*.^{1,8}

Messenger RNA expression of the BHD gene has been detected in a wide variety of tissues, including the skin and adnexa, the distal nephron, and the lung.⁹

Subsequent studies in families with this syndrome enabled different insertions, deletions, and nonsense mutations to be detected in that gene; these mutations gave rise to the production of a defective form of the folliculin protein.²

Folliculin is a protein formed of 579 amino acids. Its function has not been fully elucidated, although it is thought to have tumor suppressor properties. The protein with which it interacts, folliculin interacting protein 1 (FNIP1), has been identified. FNIP1, in turn, interacts with the 5'-adenosine monophosphate-activated protein kinase, an important sensor of cell energy status that downregulates

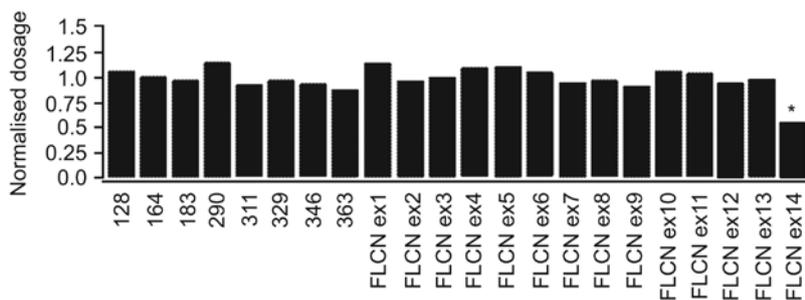


Figure 6 Analysis of the number of copies by multiplex ligation-dependent probe amplification (MLPA). The normalized dosages of the probe are shown for the patient. *FLCN* MLPA kit (MRC-Holland).

Table 1 Diagnostic Criteria of the European BHD Consortium.**Major:**

- At least 5 fibrofolliculomas or trichodiscomas with onset in adult life and with at least 1 confirmed histopathologically.
- A pathogenic *FLCN* germline mutation.

Minor:

- Multiple lung cysts: bilateral basal cysts with no other apparent cause, with or without spontaneous pneumothorax.
- Multifocal or bilateral renal cancer of early onset (<50 years), or renal cancer of mixed chromophobe and oncocytic histology.
- A first-degree relative with Birt-Hogg-Dubé syndrome.

Diagnosis of Birt Hogg Dubé syndrome requires the presence of 1 major or 2 minor criteria.

the mammalian target of rapamycin (mTOR), which is the key regulator of cell growth and proliferation.¹⁰

The *FLCN* gene is formed of 14 exons. The latest review by Toro et al¹¹ described the 73 published germline mutations and showed that exon 11 is the most common site of mutation, specifically at nucleotide 1733. Mutations have also been reported in all the other exons except exons 8 and 10. To date, the only mutation found in exon 14 affected nucleotide 2034. The new mutation described in our patient, the complete deletion of exon 14, has not previously been reported in the literature.

Recently, the European BHD Consortium¹² proposed a list of diagnostic criteria for BHD syndrome (table 1).

We would also like to highlight the association of BHD syndrome with a cutaneous melanoma in our patient. There are 4 other cases reported in the literature in which BHD is associated with melanoma.^{1,4,13,14} We believe this association is interesting; the defective production of folliculin-a protein thought to have tumor suppressor properties-in this syndrome could imply that it may also be involved in protecting the body against other tumors such as melanoma.

Conclusions

Apart from describing a new mutation in the *BHD* gene, we consider it interesting to recall that this syndrome, characterized by skin lesions of benign appearance on the face and neck, is associated with lung disease and renal tumors that can be diagnosed early through monitoring of these patients using periodic ultrasound and computed tomography.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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