Identification if a New *FLCN* Variant in a Patient with Suspected Birt-Hogg-Dubé Syndrome Presented with Cutaneous Late-Onset Angiofibroma

Thanyasak Bespinyowong MD, Tanattrin Bunnag MSc, Chavalit Supsrisunjai MD PhD.
Institute of Dermatology, Bangkok, Thailand.

ABSTRACT:
A 63-year-old female presented with a 40-year history of multiple skin-colored facial papules with previous medical history of two episodes of spontaneous pneumothorax at the age of 28 and 62 years. Multiple cysts in both lungs were detected by high-resolution computed tomography chest. Physical examination revealed multiple skin-colored facial papules on her nose and malar area. Sanger sequencing of *FLCN* showed a new heterozygous mutation, c.1448T>C, p.Leu483Pro, potentially resulting in abnormally functioning protein. Even in the absence of characteristic skin histology, the diagnosis was made using one major criterion (*FLCN* germline mutation) and one minor criterion (many lung cysts) in accordance with the European Birt-Hogg-Dubé Syndrome Consortium diagnostic criteria[6].
Key words: Birt-Hogg-Dubé Syndrome, Missense Mutation, Angiofibroma, *FLCN* gene

Case report

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant genodermatosis caused by heterozygous loss-of-function mutations in the *FLCN* gene, which is expressed in the skin, kidney, and lung. Fibrofolliculomas, trichodiscomas, and acrochordons with an increased incidence of spontaneous pneumothorax, and kidney tumors are the hallmarks of BHDS[1]. Patients with BHDS have been found to have a variety of germline *FLCN* mutations, such as nonsense, minor insertions/deletions, splice-site, and occasionally missense mutations[2,3].

Here we describe a 63-year-old female presented to our institute with a 40-year history of multiple skin-colored facial papules with previous medical history of two episodes of spontaneous pneumothorax at the age of 28 and 62 years. Multiple cysts in both lungs with varying size and shape and multiple subpleural bullae at both lungs, predominantly on lower lobes were detected by high-resolution computed tomography chest (Figure 1A). She underwent left intercostal chest drainage and endoscopic bronchial occlusion. Physical examination revealed multiple skin-colored facial papules on her nose and malar area (Figure 1B) and punch biopsy on her facial papules was performed. Histopathological examination showed dermal fibroblast proliferation, dilated blood vessels, and concentric collagen arrangement (Figure 1C, D). One of the patient's sisters exhibited similar symptoms, including facial papules and spontaneous pneumothorax. However, she declined further examinations and genetic testing due to travel inconvenience (Figure 2A).

Correspondence Author: Dr Chavalit Supsrisunjai MD., Email: chervilius@hotmail.com

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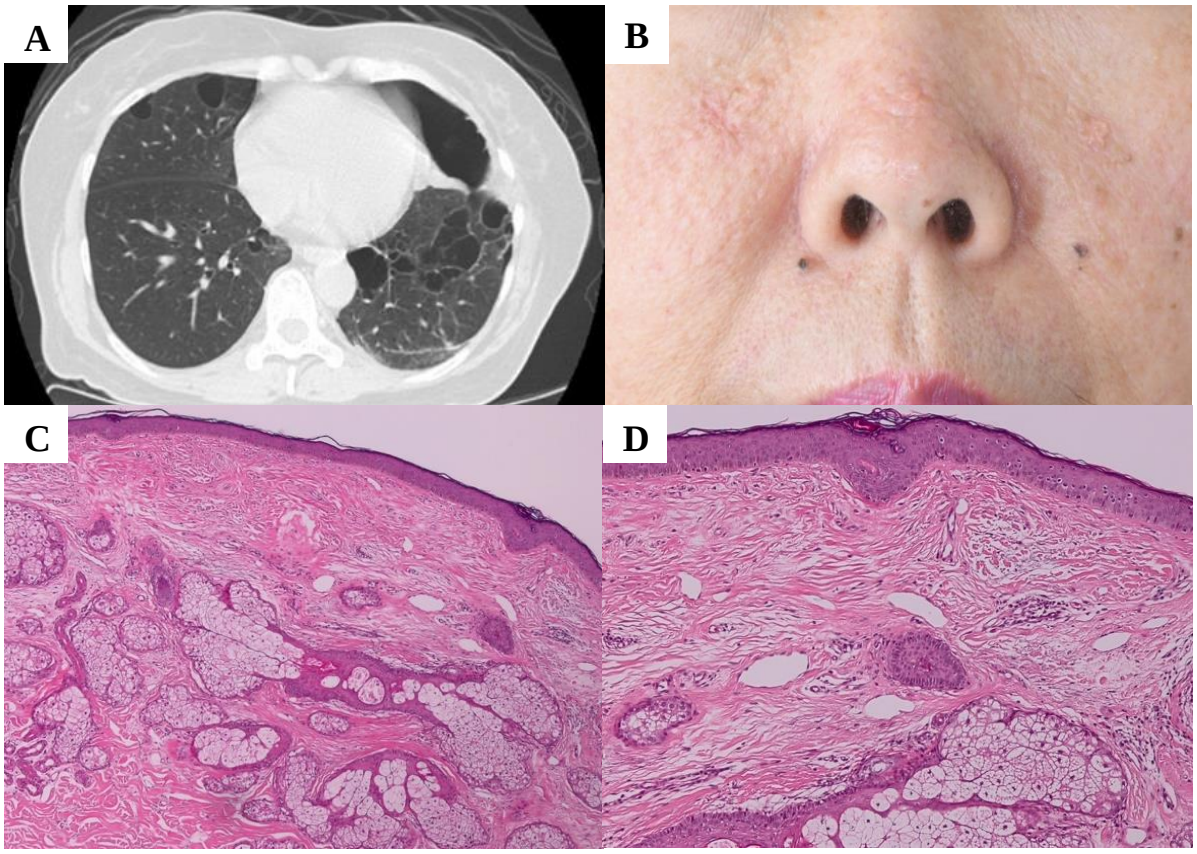

Figure 1 A HRCT chest: Multiple lung cysts and subpleural bullae, **B** Skin colored papules on the centrofacial area, **C, D** Histopathological examination showing dermal fibroblast proliferation, dilated blood vessels, and concentric collagen arrangement.

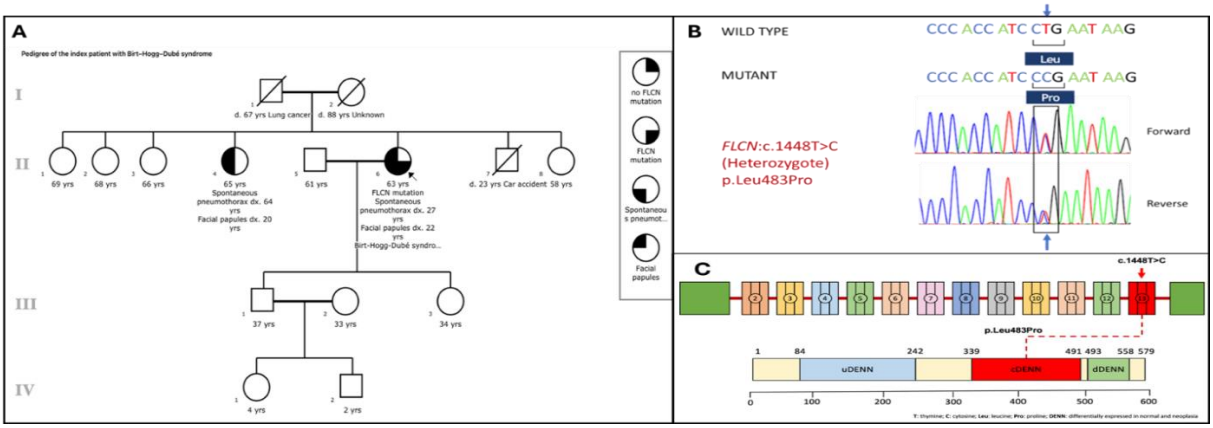

Figure 2 A Family pedigree of suspected BHDS patient, **B** Genetic testing (Sanger sequencing): *FLCN*:c.1448T>C (Heterozygote), p.Leu483Pro. **C**. Schematic diagram of missense mutation in *FLCN*'s 13th exon causing abnormal cDENN in folliculin protein

Sanger sequencing of all *FLCN* coding exons and flanking introns was done after obtaining informed consent[4,5]. Analysis of genomic DNA from the affected individuals showed a new heterozygous mutation, c.1448T>C, p.Leu483Pro, potentially resulting in abnormally functioning protein (Figure 2B, C). Nevertheless, additional functional research will be necessary to validate experimentally. Notably, genomic databases e.g. gnomAD browser (https://gnomad.broadinstitute.org/) do not contain this mutation. Based on ACMG criteria, it was a likely pathogenic variant.

Even in the absence of characteristic skin histology, the diagnosis was made using one major criterion (*FLCN* germline mutation) and one minor criterion (many lung cysts) in accordance with the European Birt-Hogg-Dubé Syndrome Consortium diagnostic criteria[6].

Cutaneous manifestation of BHDS usually appears after the age of 20 years[6]. Most common cutaneous manifestation of BHDS are fibrofolliculomas and trichodiscomas and present in more than 80% of patient with Birt-Hogg-Dube´ syndrome. Other cutaneous manifestations are achrocordons, collagenomas, angiofibroma and oral lesions[7]. However, our case showed characteristic features of angiofibroma and did not show other fibrous tumors, e.g., fibrofolliculomas, trichodiscomas, or acrochordons. Multiple facial angiofibromas are uncommon in BHDS, but more usually appear in tuberous sclerosis complex. Typically, multiple facial angiofibromas appear between 2 and 5 years of age and are present in 75% to 90% of patients with tuberous sclerosis complex[8]. However, facial angiofibromas appearance with later onset in adolescence or early adulthood may suggest BHDS or multiple endocrine neoplasia type 1[9]. These shared symptoms between tuberous sclerosis complex and BHDS may be due to a shared effect of the mutated proteins on signaling through the mTOR complex 1[10].

In BHDS, 80% of patients exhibit lung cysts, primarily in the basal lung zone, subpleural, and intrapulmonary areas without affecting lung parenchyma[7]. Spontaneous pneumothorax is the predominant chest symptom, with a prevalence of 22.5% to 38%[7]. Additionally, renal tumors occur in 19% to 35% of cases, with the most common being hybrid oncocytoma/chromophobe tumors, along with clear cell carcinoma and oncocytoma[7].

The patient opted for total facial angiofibroma removal with a CO_2 laser for cosmetic reasons. Evaluation of her pneumothorax and lung cyst involved high-resolution chest computed tomography, followed by left intercostal chest drainage and endoscopic bronchial occlusion. A renal ultrasound revealed no suspicious lesions associated with BHDS. Further investigations, including colonoscopy and thyroid ultrasound, are scheduled. Due to a possible connection between BHDS and malignant melanoma, full-body skin examinations should be performed every 6 to 12 months in order to identify suspect pigmented lesions[6].

Genetic counseling has been offered to the patient and close relatives who are 20 years of age or older[6]. Asymptomatic family members should undergo molecular genetic testing to ascertain whether continuous, lifetime clinical monitoring is required.

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