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There should be a procedure for certification of sleep centres and physicians http://ow.ly/HLGm3

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Prevalence of Birt–Hogg–Dubé syndrome in patients with apparently primary spontaneous pneumothorax

To the Editor:

Pneumothorax is classified "spontaneous pneumothorax" if there is no external force causing it and is classified as "primary spontaneous pneumothorax" (PSP) if there is no underlying lung disease. According to the guidelines of the British Thoracic Society (BTS), "no underlying lung disease" is based on history, physical examination and chest radiography [1].

Several years ago we evaluated the site of cystic lesions by thoracic computed tomography (CT) (slice thickness 10 mm) in a group of 101 PSP patients. These lesions were described as blebs and bullae, and defined as air-containing thin-walled spaces in the pulmonary parenchyma [2]. The most common area found was subpleural in the upper lobes; however, in a minority (5%), only small cystic lesions were found below the level of the main carina.

To confirm this finding in a more recent cohort, we reviewed the cohorts of PSP patients from a general and a university hospital. In 69 patients, CT had been performed within 1 year before or after the PSP and all CTs were scored on the presence of cyst(s) below the level of the carina. The mean age of the whole group was 37.6 years, the recurrence rate was 28.2% and a positive family history of spontaneous pneumothorax was noted in 16.2% of cases. In seven (10%) patients, >50% of the cysts were located below the level of the carina (table 1).

TABLE 1 Characteristics of the spontaneous pneumothorax (SP) patients

Patient with >50% of cysts under the carina	Sex (age at first PSP years)	Recurrence of PSP	Recurrences of PSP n	Lung cysts under carina n (%)	Renal-cell cancer (age at diagnosis years)	FF	Family history of SP	*FLCN* mutation[#]
1	M (24)	Yes	3	6 (81)	Yes (44)	No	No	c.510C>G; p.Tyr170X
2	F (20)	Yes	8	13 (84)	No	No	No	c.610_611delGCinsTA p.Ala240X
3	M (62)	No		10 (100)	NA	NA	NA	Not tested
4	M (75)	No		3 (100)	Yes (74)	NA	NA	Not tested
5	M (20)	Yes	2	3 (67)	NA	NA	NA	Not tested
6	M (29)	No		4 (75)	NA	NA	NA	Not tested
7	F (52)	No		35 (52)	NA	NA	No	Not tested

Patient with BHD syndrome (family)	Sex (age at first PSP years)	Delay between first symptom of PSP and final diagnosis of BHD (months)	Recurrence of PSP	Recurrences of PSP n	Lung cysts n	Renal tumour	FF	Smoking history	*FLCN* mutation
1 (84)	F (20)	243	Yes	8	13	No	Minimal[¶]	No	c.610_611delGCinsTA (p.Ala240X)
2 (85)	M (26)	153	Yes	6	140	No	Minimal[¶]	No	c.1408_1418del (p.Gly470fs)
3 (94)	M (40)	81	Yes	3	74	No	No	No	c.1539-2A>G

PSP: primary spontaneous pneumothorax; FF: fibrofolliculoma; *FLCN*: *folliculin*; M: male; F: female; NA: not applicable; BHD: Birt–Hogg–Dubé. [#]: tested 216 months (patient 1) and 243 months (patient 2) after first episode of PSP. [¶]: very subtle minimal facial skin lesions, probably FF; clinical diagnoses and skin biopsy for histopathology not performed.

These results confirm our earlier findings and might be important because this location of lung cysts is found in a disease with a high frequency of (recurrent) pneumothorax, the Birt–Hogg–Dubé (BHD) syndrome [3].

BHD syndrome is an autosomal dominant condition caused by germline mutations in the *folliculin* (*FLCN*) gene, and further characterised by skin fibrofolliculomas and a high risk of renal-cell cancer. Clinical manifestations of BHD syndrome are variable, and spontaneous pneumothorax may be the first and only manifestation of BHD syndrome in isolated and familial cases [4–8]. As most BHD patients have normal lungs on chest radiography and neither impairment of pulmonary function nor pulmonary complaints prior to the pneumothorax, based on history, physical examination and chest radiography, a pneumothorax will most likely be classified as PSP [1].

We performed a pilot study to test whether the CT-detected rate of cysts below the main carina in 5–10% of PSP patients might be caused by undiagnosed BHD syndrome in PSP patients. A questionnaire was sent out to patients previously (between 2000 and 2013) diagnosed with PSP, based on BTS criteria [1]. We invited them to participate voluntarily in a pilot study in which CT of the thorax and *FLCN* mutation analysis were performed. The number of participants was restricted to 40. This study was approved by the ethics committee of the VU University Medical Center, Amsterdam, the Netherlands (NL31417.029.10). All patients provided written informed consent.

Cysts were found below the level of the main carina in three patients and all three had a pathogenic *FLCN* mutation (7.5%, 95% CI 1.5–20.3%). The *FLCN* mutations detected in these patients were a nonsense mutation (c.610_611delGCinsTA (p.Ala240X)), a frameshift mutation (c.1408_1418del (p.Gly470fs)) and a splice site mutation (c.1539-2A>G) (table 1). After being diagnosed in this study, one of these patients was presented as a case report illustrating the characteristic findings in a BHD syndrome patient [8].

According to current guidelines for BHD syndrome [9], family members were invited for mutation analysis and four additional *FLCN* mutation carriers (one each in families A and B, and two in family C) were found. Subsequently magnetic resonance imaging (MRI) of the kidneys was performed. One of them had an asymptomatic, 15-mm solid mass on renal MRI. Further analysis revealed a clear-cell renal-cell carcinoma that was treated with nephron-sparing therapy. Among the 37 cases with PSP without the pathogenic *FLCN* mutation, no cysts were found in the basal parts of the lungs.

Our findings are in line with a previously reported prospective study in a Chinese population with PSP. Ren *et al.* [10] found 10 (9.8%) patients with a pathogenic *FLCN* mutation among an unselected cohort of 102 PSP patients. Unfortunately, extensive details on radiological findings were not reported.

Our retrospective evaluation of CTs of PSP patients shows that cysts in the basal parts of the lung are relatively rare (frequency up to 10%) but could be an important finding as these patients may have BHD syndrome. In our pilot study, we confirmed earlier findings in a Chinese population that BHD syndrome might be responsible for pneumothorax in up to 10% of the PSP patients.

With current guidelines, this diagnosis will most probably be missed among PSP patients. This raises the question of whether CT should become a part of the diagnostic investigations in patients presenting with PSP. Arguments to support this are not only the high recurrence rate in BHD, which makes it attractive to treat these patients at the first pneumothorax much more aggressively than according to guidelines for PSP [11], but also the possibility to detect, through an affected pneumothorax patient, more family members with the pathogenic mutation and initiate life-long yearly screening of the kidneys in all carriers as the risk of developing renal-cell cancer is high [12]. Based on our database and the literature, it is likely that detecting a BHD syndrome family through a pneumothorax case will result in early diagnosis of renal-cell cancer in a large number of affected cases [13].

In summary, current guidelines for PSP result in underdiagnosis of BHD syndrome. BHD syndrome is probably the cause of the pneumothorax in 5–10% of PSP cases. Diagnosis of BHD syndrome will improve early detection of renal-cell cancer in these patients as well as in affected relatives.

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Birt–Hogg–Dubé syndrome is probably the cause of pneumothorax in 5–10% of primary spontaneous pneumothorax patients http://ow.ly/FiIGS

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Inherent weaknesses of the current ICD coding system regarding idiopathic pulmonary fibrosis

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is the most prevalent of the idiopathic interstitial pneumonias (IIPs). It carries an ominous prognosis with a median survival of 3 years. Its epidemiology is poorly described because of its rarity and lack of unanimity in diagnostic and coding practices [1]. However, during the last few years, significant improvement has been achieved in our understanding of the pathogenesis, diagnosis