



CASE STUDY

Familial spontaneous pneumothorax and lung cysts due to a *Folliculin* exon 10 mutation

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ABSTRACT: Approximately 10% of patients who have a spontaneous pneumothorax have a positive family history. In 1977, Birt, Hogg and Dube (BHD) described a genodermatosis characterised by benign tumours of the hair follicle that has been associated with renal neoplasms and spontaneous pneumothorax. The BHD locus is located on chromosome 17p11.2 and is now known to be due to heterozygous germline mutations in the *Folliculin* gene.

We report three generations of an English family who suffered spontaneous pneumothoraces in the absence of other features of the BHD syndrome and were found to have lung cysts. In addition, we report an antenatal diagnosis (34 weeks gestation) of lung cysts in one affected family member. Genetic analysis in the family has revealed a unique deletion mutation (c. 1537 del-C) involving exon 10.

To our knowledge, this mutation has not been previously described and there is no previous report of antenatal detection of the pulmonary abnormality in BHD syndrome.

KEYWORDS: Birt–Hogg–Dube syndrome, *Folliculin* gene, pneumothorax

Spontaneous pneumothorax is a condition often affecting tall individuals. Most cases are isolated. Familial spontaneous pneumothorax is much rarer and was first reported by FABER [1] in 1921. Spontaneous pneumothoraces have also been described in inherited disorders such as α_1 -antitrypsin deficiency, Marfans syndrome, Ehlers–Danlos syndrome, tuberous sclerosis, cystic fibrosis and Birt–Hogg–Dube (BHD) syndrome.

A.R. Birt, G.R. Hogg and W.J. Dube originally described a syndrome of multiple hamartomas of the hair follicle (fibrofolliculomas, trichodiscomas and acrochordons) inherited in an autosomal dominant pattern [2]. These individuals were found to have a higher than average incidence of renal and colonic neoplasia and spontaneous pneumothorax [3]. While all reported families with BHD syndrome mutations involve the *Folliculin* (FLCN) gene, the clinical phenotype in terms of dermatosis, neoplasia and pneumothorax is highly variable.

Mutations in the FLCN locus on chromosome 17p11.2 can predispose to lung cysts and spontaneous pneumothorax. A diagnosis of BHD

syndrome confers a seven-fold increased risk of developing renal neoplasia and a 50-fold increased risk of spontaneous pneumothorax.

Here we report a family harbouring a novel mutation in FLCN that presented as isolated familial spontaneous pneumothorax. The affected family members had neither the typical skin lesions nor the renal neoplasia characteristic of BHD syndrome. In one member of the affected family this defect was identified antenatally.

CASE HISTORY

A 69-yr-old female nonsmoker presented with sudden onset of dyspnoea. Clinical examination and a chest radiograph confirmed a right-sided pneumothorax. An intercostal drain was inserted with complete resolution. However, a detailed history suggested that many other members of our patient's family had also suffered spontaneous pneumothorax.

Figure 1 shows the family pedigree of the index case (I2). Her older brother (I1) had previously been diagnosed with a pneumothorax. This required an intercostal drain and took 3 weeks to resolve. Her younger brother (I3) has never

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Received:

April 24 2008

Accepted after revision:

March 11 2009

STATEMENT OF INTEREST

None declared.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

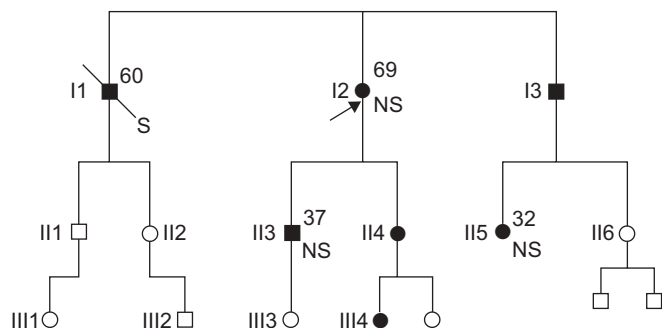


FIGURE 1. Pedigree chart for the family. Generation identifier numbers (I-III) are located to the left of each generation and identifier numbers are listed below each family member. Circles indicate females and squares refer to males. Solid symbols indicate those affected by lung cysts, while open symbols refer to subjects unaffected by lung cysts. A diagonal line drawn through the symbol indicates a deceased subject. Arrow denotes proband. The age of onset of pneumothorax and the smoking history are indicated. S: smoker; NS: nonsmoker.

presented clinically with a pneumothorax. Both children of I1 are healthy and have never suffered pneumothoraces. The index patient's son (II3) presented with a left-sided pneumothorax at age 37 yrs. A persistent air leak required surgical intervention with a left bullectomy and pleurectomy. His sister (II4) has never suffered a pneumothorax. II5 had repeated pneumothoraces on the left side, and one on the right. She underwent both left and right pleurectomy and bullectomy at different times. There is no history of consanguinity.

Antenatal evidence

II4 underwent an abdominal ultrasound for suspected intra-uterine growth retardation 34 weeks into her first pregnancy, which revealed an abnormality in the fetal lung. The left lower lobe was replaced by a solid mass containing numerous cystic spaces displacing the pericardial sac. The baby was delivered by caesarean section at 36 weeks, continued to thrive and today is a healthy teenager with no respiratory problems.

Pulmonary function tests

The pulmonary function of patient I2 and her daughter II4 are listed in table 1.

TABLE 1 Pulmonary function parameters for patient I2 and her daughter II4		
	I2	II4
FEV ₁ L	1.77 (95.7)	2.59 (103)
FVC L	2.3 (102.6)	3.12 (106.5)
FEV ₁ % VC _{max}	76.8	82.9
RV L	1.91 (97.1)	1.97 (131.6)
TLC L	4.14 (90.5)	4.87 (108.1)
T _{L,CO} mmol·min ⁻¹ ·kPa ⁻¹	4.23 (63.4)	7.31 (91.8)
K _{CO} mmol·min ⁻¹ ·kPa ⁻¹ ·L ⁻¹	1.34 (91.9)	1.81 (102.6)

Percentage of predicted normal values are given in parentheses. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; VC: vital capacity; RV: residual volume; TLC: total lung capacity; T_{L,CO}: transfer factor of the lung for carbon monoxide; K_{CO}: transfer coefficient.

Radiology

Radiological screening by high-resolution computed tomography (CT) scan of the chest was offered to the patient and her family. Multiple pulmonary cysts were found in five out of the six family members who were screened (figs 2 and 3). The number of cysts varied from three in II4 to 17 in I2. Cysts were distributed throughout all lobes. Subpleural cysts were more numerous than intraparenchymal ones. The cysts were mostly thin walled, with a few having a thickness of up to 2 mm, or no discernable wall. The largest cyst in our series was 5 cm in diameter. The lung parenchyma in between these cysts was normal.

III4 was the granddaughter of the index case, and was found to have an abnormality antenatally. A CT scan of the chest after birth revealed an oval soft tissue mass in the left lower lobe containing cysts, which appeared to regress on follow-up scan. There were no distinguishing features to this lesion. It gradually transformed into a persistent soft tissue opacity in the left lower lobe.

Sonographic examination of the kidneys in the index patient revealed no additional lesions.

Genetics

Direct sequencing of the coding exons of the FLCN gene from genomic DNA of the index case (I2) found her to be heterozygous for a novel exon 10 c.1537 del-C mutation. The same mutation was identified in her daughter, II4.

DISCUSSION

We report a family with lung cysts and spontaneous pneumothorax in three generations, in whom a deletion mutation was identified in exon 10 of the FLCN gene. There was no evidence of skin lesions in the family. There was no history of renal or other neoplasia that might be expected as part of the BHD syndrome.

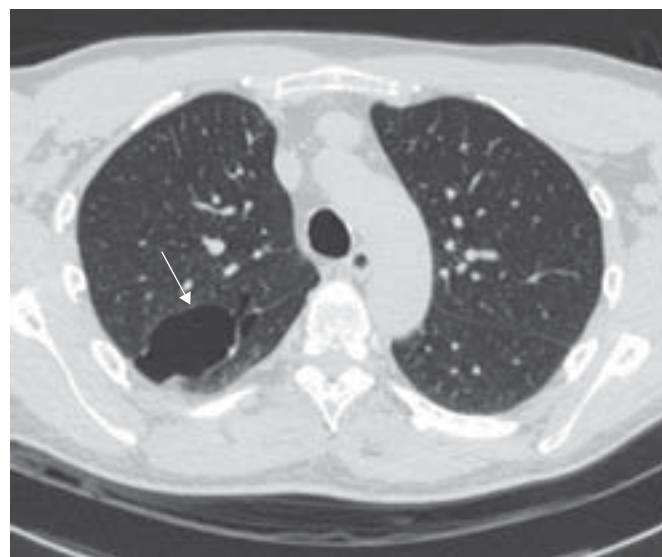


FIGURE 2. Contrast-enhanced computed tomography of patient I2 showing thin-walled subpleural cysts (arrow).



FIGURE 3. Non-enhanced computed tomography of patient II2 showing a small right pneumothorax and thin-walled cysts in both lungs (arrows).

Mutations in *FLCN* cause the BHD syndrome and mutations have been identified along the entire length of the gene (exons 4, 5, 6, 7, 9, 11, 12, 13 and 14) [4]. The isolated pneumothorax phenotype has previously been reported in association with mutations on exon 4 [5] and exons 9 and 12 [6]. It is possible that these regions (and exon 10) encode functional domains particularly relevant to lung development. It is interesting to note that, among patients with mutations in the exon 11 hotspot, significantly fewer renal tumours were observed in patients with c-deletion than those with c-insertion mutations [4]. An alternative explanation may be that the BHD tumour phenotype requires the presence of additional modifier genes absent in the isolated pneumothorax families [5].

The *FLCN* gene codes for folliculin, the function of which is incompletely characterised. Mutations in the gene result in formation of a truncated protein. The *FLCN* mRNA is expressed within stromal cells of connective tissue and epithelial cells lining alveolar spaces of the lung. One proposal is that *FLCN* mutation may cause abnormal release of inflammatory mediators from these cells which could result in altered matrix degradation and remodelling [5].

Developmentally, at 28 weeks of gestation, the respiratory bronchioles subdivide to produce terminal sacs (primitive alveoli). The alveoli start to mature at about 36 weeks of gestation [7]. The finding of a lung cyst at 34 weeks gestation

in this family suggests that cysts can begin to form around the time of lung maturation. Postnatal peripheral alveolarisation may account for the predominant subpleural distribution of the pulmonary cysts [6].

In practical terms, it is essential that a family history be elicited in all patients who present with a spontaneous pneumothorax. A positive family history is likely to indicate a rare underlying disorder. If diagnosed with BHD, there is a seven-fold risk of developing renal neoplasia and a 50-fold increased risk of pneumothorax [3, 4]. In some affected individuals it may be appropriate to consider prophylactic pleurodesis. Pregnant mothers should be warned that a fetal ultrasound may detect lung abnormalities after 30 weeks of gestation. Conversely, the finding of lung abnormality antenatally should alert the clinician to the possible diagnosis of BHD syndrome.

In conclusion, identifying families with spontaneous pneumothorax is clinically important, as these individuals and their relatives are at increased risk. Identifying and reporting the genotype will contribute towards understanding the genotype–phenotype associations and, in the future, may help explain the molecular basis of cystic lung diseases.

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