

Familial spontaneous pneumothorax

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Purpose of review

Over 10% of patients with primary spontaneous pneumothorax report a positive family history of the disease. While some cases can be attributed to rare inherited connective tissue diseases, several families with familial spontaneous pneumothorax have been described that do not show clinical evidence of these monogenic disorders. Until recently the molecular underpinning of this disease was unknown.

Recent findings

In the last 18 months, mutations in the gene encoding folliculin (*FLCN*) have been identified in individuals with familial spontaneous pneumothorax. Mutations in this gene were known previously to cause a rare skin disease, Birt–Hogg–Dubé syndrome, an autosomal dominantly inherited disease characterized by benign skin tumors, diverse types of renal cancer, pulmonary cysts, and spontaneous pneumothorax. Two animal models and studies of renal cancers support a tumor-suppressor function for folliculin. The presence of thin-walled cysts in basilar and subpleural locations of the lung is a feature of this disease. Most families display reduced penetrance of the pneumothorax phenotype. Several individuals with a family history of spontaneous pneumothorax have a mutation in the folliculin gene.

Summary

A significant fraction of families with familial spontaneous pneumothorax have mutations in the folliculin gene and should be considered a *forme fruste* of Birt–Hogg–Dubé syndrome.

Keywords

Birt–Hogg–Dubé syndrome, familial spontaneous pneumothorax, folliculin

Introduction

A primary spontaneous pneumothorax occurs when air collects in the pleural space without preceding trauma in a healthy individual, and without obvious underlying lung disease. It typically occurs in patients between 18 and 40 years of age, whereas a secondary pneumothorax usually occurs in older patients with lung diseases such as chronic obstructive pulmonary disease, cystic fibrosis, pyogenic infections, pulmonary fibrosis and cancer. The incidence of primary spontaneous pneumothorax is estimated to be approximately 7.4–18 per 100 000 per year for men and approximately 1.2–6 per 100 000 per year for women [1,2]. It has been noted that the typical person who presents with a spontaneous pneumothorax has an asthenic body habitus, being taller and thinner than the average person [3].

Radiographic and thoroscopic examinations of patients with primary spontaneous pneumothoraces often reveal underlying subtle lung abnormalities in the form of blebs, bullae, and cysts. Blebs and bullae were discovered on the affected side 76% of the time when a video-assisted thoroscopic surgery (VATS) procedure was performed, and 100% of the time when thoracotomy or sternotomy was performed [4]. Given this association, primary spontaneous pneumothorax has been considered a form of distal acinar emphysema. In this subtype of emphysema, the airspace enlargement is confined to subpleural or paraseptal locations, so that most of the lung parenchyma is spared. The disease is clinically silent, unless one of the blebs ruptures and causes a pneumothorax. The pathogenesis of the blebs is not well understood but has been attributed to congenital abnormalities [5], increased mechanical stresses at the apex in the upright lung [6], and bronchiolar inflammation and fibrosis [7]. As is the case for the more common form of emphysema, the expression of primary spontaneous pneumothorax is related to the amount and duration of smoking. The relative risk of pneumothorax is 7 times higher in light smokers (defined as smoking 1–12 cigarettes per day), 21 times higher in moderate smokers (13–22 cigarettes per day), and over 80 times higher in heavy smokers (> 22 cigarettes per day) [8].

Monogenic disorders associated with spontaneous pneumothorax

Overall, a positive family history is found in 11.5% of individuals who present with a spontaneous pneumothorax [9]. The clustering of familial spontaneous pneumothorax was first reported by Faber in 1921

Curr Opin Pulm Med 12:268–272. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Pulmonary Medicine 2006, 12:268–272

Abbreviation

CT computed tomography

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1070-5287

Table 1 Monogenic diseases associated with spontaneous pneumothorax

Disease	Gene(s)	Chromosomal location
Marfan syndrome	Fibrillin 1	15q21.1
Homocystinuria	Cystathionine β -synthase	21q22.3
Ehlers–Danlos syndrome	Multiple	Multiple
α_1 -Antitrypsin deficiency	α_1 -Antitrypsin	14q32.1
Birt–Hogg–Dubé syndrome	Folliculin	17p11.2

[10]. It has long been recognized that a primary spontaneous pneumothorax may occur in patients with any of several different inherited monogenic disorders. While the appearance of a pneumothorax is not the primary finding in patients with these disorders, they must be considered when evaluating a case of familial spontaneous pneumothorax. The disorders are listed in Table 1, and include Marfan syndrome, homocystinuria, Ehlers–Danlos syndrome, α_1 -antitrypsin deficiency and Birt–Hogg–Dubé syndrome.

Marfan syndrome is an autosomal dominant disease caused by mutations in the gene encoding fibrillin 1. Patients display great clinical variability. The major manifestations include increased height, disproportionately long limbs and digits, subluxation of the lens of the eye, and dilation of the aortic root, whereas apical blebs and spontaneous pneumothorax have been described as minor criteria [11]. The frequency of spontaneous pneumothorax in patients with Marfan syndrome is estimated to be 4.4–11%, while other pulmonary conditions such as bullae, bronchiectasis, and upper lobe fibrosis are relatively less common [12,13].

Homocystinuria is a metabolic disorder caused by cystathionine β -synthase deficiency which shares skeletal and ocular features with Marfan syndrome, in addition to mental retardation and vascular thrombosis. Spontaneous pneumothorax is a minor feature [14,15].

Ehlers–Danlos syndrome is a genetically heterogeneous collection of disorders characterized by hyperextensible skin, dystrophic scarring, easy bruising, and joint hypermobility [16]. Pulmonary complications have been most commonly reported for patients with the vascular subtype (type IV), which is characterized by facial appearance, thin, translucent skin, extensive bruising, and often catastrophic arterial, intestinal or uterine rupture. Features of cystic lung disease, including subpleural blebs, apical bullae, pneumothorax and hemopneumothorax, have all been reported [17].

α_1 -Antitrypsin is a major plasma serine protease inhibitor which plays an important role in the lung, antagonizing the effect of leukocyte elastase. Deficiency of this protein leads to a high risk of developing panacinar emphyse-

ma in the third to fifth decades of life [18]. Patients homozygous for the PiZ variant of α_1 -antitrypsin demonstrate predominantly lower-lobe, basilar emphysema [19]. Rare case reports have noted an association between spontaneous pneumothorax, apical bullae, and α_1 -antitrypsin deficiency [20,21].

Birt–Hogg–Dubé syndrome was originally described in 1977 [22] as an autosomal dominant skin disorder characterized by multiple fibrofolliculomas, trichodiscomas, and acrochordons. In the subsequent years, the disease was associated with spontaneous pneumothorax and renal cancer with multiple histologic subtypes [23]. The disease is caused by mutations in the folliculin (*FLCN*) gene [24]. A mutational hotspot involving a tract of eight cytosines in exon 11 has been identified by multiple investigators [24,25,26*]. The function of the folliculin protein is currently unknown, although the gene is highly conserved across species [24]. Study of folliculin mRNA has revealed its widespread expression in various tissues, including skin and skin appendages, type 1 pneumocytes and stromal cells of the lung, distal nephrons of the kidneys, as well as selected cell types in the brain and lymph nodes, and various cells with secretory functions. Two animal models, canine hereditary renal cystadenocarcinoma and nodular dermatofibrosis in the German shepherd [27] and the Nihon rat model of renal cancer [28,29*], support a tumor-suppressor function for folliculin. Its role as a tumor suppressor is further supported by the loss of the wild-type *FLCN* allele or a somatic second-hit mutation in renal cancers from patients with Birt–Hogg–Dubé syndrome [25,30*] or from those with sporadic renal cancers [31,32].

Families with familial spontaneous pneumothorax have been reported in which the affected individuals have none of the characteristic features of the above monogenic disorders. It had been thought previously that familial spontaneous pneumothorax is a disorder distinct from known monogenic diseases at both the clinical and molecular levels. As discussed below, however, research done in the last 18 months has demonstrated mutations in the Birt–Hogg–Dubé syndrome gene, encoding folliculin (*FLCN*) in multiple cases of familial spontaneous pneumothorax. These cases can now be considered part of the phenotypic spectrum for Birt–Hogg–Dubé syndrome.

Genetics of familial spontaneous pneumothorax

In 1991, Abolnik *et al.* [9] postulated two modes of inheritance for familial spontaneous pneumothorax: autosomal dominant with reduced penetrance in some families, and X-linked recessive in others. It was noted in their study that affected individuals in the families with presumed X-linked recessive inheritance were

usually younger and had fewer episodes of spontaneous pneumothorax than those in the autosomal dominant group. For the pedigrees consistent with an autosomal dominant pattern of inheritance with variable penetrance, the penetrance rate was estimated to be 50% for males and 35% for females.

Case reports of other families have been rare. Some have reported cases of affected fraternal twins or siblings within a family, but these have included small numbers of affected individuals [33–37]. The largest families for whom case reports have been published have suggested an autosomal dominant mode of inheritance with variable penetrance [38–44]. The genetic underpinning for this disorder was not known prior to 2005.

Mutations in the folliculin gene cause familial spontaneous pneumothorax

Painter *et al.* [45^{••}] studied one large Finnish family with dominant familial spontaneous pneumothorax. All individuals in this kindred were evaluated with high-resolution computed tomography (CT) scans of the chest. Fourteen individuals (including five who had a spontaneous pneumothorax) were found to have between 1 and > 30 pulmonary cysts, 1–6 cm in diameter, distributed throughout the lungs. Whole-genome linkage analysis revealed that all the family members with the pulmonary cysts inherited a common haplotype identical by descent on chromosome 17 and were heterozygous carriers of a 4 bp deletion in the fourth exon of the gene encoding folliculin (*FLCN*), the same gene associated with Birt–Hogg–Dubé syndrome. The mutation is predicted to cause a frameshift and premature termination of the folliculin protein. Of all the individuals who carried a mutation, there was 100% penetrance of the pulmonary cyst phenotype, but much lower penetrance (approx. 40%) of the pneumothorax phenotype.

In another study [46^{••}], families were collected solely on the basis of a familial spontaneous pneumothorax phenotype. A candidate gene approach revealed that the pneumothorax phenotype in two Caucasian families was linked to genetic markers that flanked the *FLCN* gene. Sequencing of genomic DNA from these individuals revealed two novel nonsense mutations that are predicted to prematurely truncate the folliculin protein. These two studies [45^{••}, 46^{••}] used two different genetic approaches to study familial spontaneous pneumothorax, and both revealed novel mutations in the gene that previously had been associated with Birt–Hogg–Dubé syndrome.

Since the skin findings of Birt–Hogg–Dubé syndrome generally appear in the fourth decade and become progressively more noticeable with age, and since the renal cancer can be a late finding associated with this syndrome,

a spontaneous pneumothorax may be the first presenting manifestation of Birt–Hogg–Dubé syndrome. Spontaneous pneumothorax may also be the only manifestation of Birt–Hogg–Dubé syndrome. Zbar *et al.* [23] found several individuals who were disease gene carriers with only the pneumothorax phenotype, who were ‘skin negative’. Overall, individuals with Birt–Hogg–Dubé syndrome have a 50-fold higher risk of developing a spontaneous pneumothorax. Between 11.5% and 32% of patients develop this feature of the disease. In contrast, over 80% have pulmonary cysts, as detected by high-resolution CT scans of the chest [23, 26[•]].

The pulmonary cysts have been described as sharply margined air-containing lesions with walls 2 mm thick or less and measuring ≥ 1 cm in diameter [47[•]]. The majority are located in basilar and subpleural locations, but small intraparenchymal cysts have also been described [23]. They are generally not confined to the apices of the lung, as is generally found in patients with sporadic spontaneous pneumothorax [48]. In some individuals pneumothorax occurs repeatedly and affects both lungs. At the time of surgical repair, blebs are generally seen on the pleural surface [23, 46^{••}]. Given the high recurrence rate of pneumothorax in many patients and the multitude of pulmonary cysts, surgical intervention with resection and pleurodesis would be an acceptable treatment option, even for a first-episode pneumothorax.

Resected lung tissue from non-smokers has revealed subpleural cysts and underlying emphysematous changes [46^{••}]. At the present time, it is not known how mutations in folliculin give rise to the pulmonary cysts. The animal models of disease do not report a pulmonary phenotype. Folliculin is expressed in the macrophages within the alveolar space and in some cell types of the lung connective tissue, suggesting that it may have a role in the response to triggers such as tobacco smoke, or in tissue remodeling [49].

So, how many cases of familial spontaneous pneumothorax can be explained by mutations in the folliculin gene? This remains to be seen. We have continued to collect families on the basis of the familial spontaneous pneumothorax phenotype and have found four additional mutations in this gene in patients of Caucasian, African American and Asian Ancestry (in preparation).

Families with familial spontaneous pneumothorax with a mutation in folliculin (*FLCN*) can be considered a *forme fruste* of Birt–Hogg–Dubé syndrome. These individuals and other members of their families should be evaluated for the dermatologic manifestations of the disease. Given the association of renal cancer with Birt–Hogg–Dubé syndrome, patients with familial spontaneous pneumothorax and *FLCN* mutations should be screened and

followed for kidney masses. Surgery is recommended for patients when at least one tumor becomes greater than 3 cm in diameter, and surgery or close observation is recommended for smaller tumors [50^{*}]. First-degree relatives should be counseled about their risk for developing the disease.

The molecular basis for familial spontaneous pneumothorax not explained by mutations in the follliculin gene is currently unknown. Collection and study of these families with this rare disorder may lead to the identification of additional genes which will provide insights into the molecular basis of this rare type of emphysema.

Conclusion

It is of particular interest to the pulmonologist that multiple different mutations in the gene encoding follliculin have been found in several families with familial spontaneous pneumothorax. These families represent part of the phenotypic spectrum of Birt–Hogg–Dubé syndrome, with the pneumothorax being one of the first presenting manifestations of the syndrome. While all patients with familial spontaneous pneumothorax should be evaluated for Marfan syndrome, Ehlers–Danlos syndrome and α_1 -antitrypsin deficiency, one should also look carefully for skin folliculomas and ask about a personal or family history of renal cancer. High-resolution CT scans of the chest documenting the presence of pulmonary cysts and their distribution may provide important clues to this disorder.

Acknowledgements

The authors wish to thank all the families and individuals that participated in this research, and Melissa Nolasco for technical expertise. This work is supported by NIH grant IK23RR02063201. C.K.G. is a Parker B. Francis Fellow in Pulmonary Research and a Charles E. Culppeper Medical Scholar.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 278).

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