



# The Importance of Genetic Factors in the Management of Spontaneous Pneumothorax

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## Abstract

**Purpose of Review** Spontaneous pneumothoraces can be the presenting phenotype in a variety of different syndromic genetic conditions. Respiratory physicians therefore have the opportunity to diagnose and manage these patients early to prevent serious complications associated with these syndromes.

**Recent Findings** The genetic syndromes that present with pneumothoraces can be split broadly between those resulting from defective extracellular matrix formation and those caused by defective tumour-suppressor pathways. When connective tissues are weakened, lifelong surveillance for arterial dilatation can be life-saving as surgical intervention is effective. Long-term aggressive treatment of blood pressure can also commence, although some controversy surrounds which drugs are most effective and precisely how these drugs modify disease progression. Rational treatments of syndromes in which tumour suppressor function is lost are being developed and, in some instances, can already be offered.

**Summary** Careful clinical assessment of spontaneous pneumothorax may identify an underlying causal condition and facilitate life-saving intervention. Respiratory physicians must therefore be aware of these diseases and their diagnostic criteria.

**Keywords** Pneumothorax · Marfan syndrome · Vascular Ehlers Danlos syndrome, vEDS · Loeys-Dietz · Tuberosus sclerosis complex · TSC · Lymphangi leiomyomatosis · Birt-Hogg-Dubé syndrome · Genetics

## Introduction

Pneumothorax, the presence of air within the pleural space, has been a medical diagnosis since Jean Itard coined the term early in the nineteenth century. When pneumothorax occurs without obvious lung pathology or trauma, it is termed primary spontaneous pneumothorax and happens to approximately 1 in 10,000 of the population [1]. A typical patient will be tall and slender, the so-called asthenic phenotype. Males, who

outnumber females with pneumothorax 3:1, tend to present in their late teens to late twenties, while the ages of affected women are more evenly spread from late teens onward [2].

Despite the relative rarity of primary spontaneous pneumothorax, 10% of patients report having an affected family member indicating a strong genetic component to this condition [3]. Such families are said to have ‘familial pneumothorax’, and unlike sporadic cases, there appears to be a more equal distribution between males and females [4]. We previously suggested that familial pneumothoraces be categorised into those syndromes resulting from a weakened extracellular matrix and those that affect tumour suppressor genes, the former typically causing emphysematous changes, the latter cause pulmonary cysts [4].

Familial pneumothorax frequently represents only one part of a broader syndrome. Given the essential role of connective tissues in providing structural integrity to organs, it is unsurprising that mutations of the extracellular matrix have diverse effects, in particular, in the cardiovascular system. By contrast, mutations that impair tumour suppressor pathways permit excessive cellular proliferation leading to the development of both benign and malignant neoplasms.

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Targeted preemptive management of individuals with specific genetic defects can reduce morbidity and mortality, so-called precision medicine. By helping to identify individuals with genetic defects, pneumothorax can enable precision medicine to be practiced and lead to patient benefit. It is therefore important that respiratory physicians are able to identify individuals with a syndromic cause for their pneumothoraces and ensure onward referral to appropriate specialist healthcare providers. In this review, we describe the diagnosis and management of the most frequently encountered genetic syndromes linked with the development of pneumothorax.

## Connective Tissue Disorders

### Marfan Syndrome

#### Genetics

Marfan syndrome is perhaps one of the best known causes of familial pneumothorax and has an incidence of 1:5000 to 1:10,000 [5]. It was first described by Antoine Marfan at the end of the nineteenth century when he treated a young girl with unusually long thin limbs [6]. Five decades later, a case of pneumothorax in the context of Marfan syndrome was reported, subsequently followed by many others [7]. Marfan syndrome is an autosomal dominant disorder and in 1991 three groups simultaneously reported causative mutations in the *FBNI* gene, which encodes the glycoprotein fibrillin-1 [8–10]. In addition to a role in extracellular matrix structure, fibrillin-1 helps to regulate *TGF $\beta$*  signalling and both of these functions account for the complex thoracic and extrathoracic manifestations of the disorder.

#### Clinical features

*FBNI* is a large and highly polymorphic gene, and so sequencing is a complex and often confusing process [11]. For this reason, a diagnosis of Marfan syndrome depends on identification of its clinical features as laid out by the revised Ghent nosology (Table 1). The abnormal bone growth first noted by Marfan over a century ago leads to tall stature, chest wall abnormalities (pectus carinatum or excavatum), scoliosis and arachnodactyly. The excessive length of long bones relative to others, e.g. vertebrae, can make the arm span disproportionately long compared with the height. In the respiratory clinic, it is straightforward to measure arm span relative to height as a screening tool. An arm span that is more than 1.05-fold that of the height raises the possibility of aberrant bone growth (Table 1, systemic features). Arachnodactyly is similarly easy to check using two clinical signs: the Walker-Murdoch sign is positive if the thumb and small finger of one hand can completely encircle the opposite wrist; Steinberg's

**Table 1** Revised Ghent criteria for the diagnosis of Marfan syndrome. Adapted from [11]

Marfan syndrome:
Diagnosis requires one of:
(1) Aortic diameter at the sinuses of Valsalva ( $Z$ score $\geq 2$ ) AND ectopia lentis
(2) Aortic diameter at the sinuses of Valsalva ( $Z$ score $\geq 2$ ) AND known disease-associate <i>FBNI</i> mutation
(3) Aortic diameter at the sinuses of Valsalva ( $Z$ score $\geq 2$ ) AND systemic score* ( $\geq 7$ pts)
(4) Ectopia lentis AND aortic disease-associate <i>FBNI</i> mutation
(5) Ectopia lentis AND family history of Marfan syndrome
(6) Systemic score ( $\geq 7$ points) AND family history of Marfan syndrome
(7) Aortic diameter at the sinuses of Valsalva ( $Z \geq 2$ above 20 years old, $\geq 3$ below 20 years) AND family history of Marfan syndrome
*Scoring of systemic features:
• Wrist AND thumb sign—3 (wrist OR thumb sign—1)
• Pectus carinatum deformity—2 (pectus excavatum or chest asymmetry—1)
• Hindfoot deformity—2 (plain pes planus—1)
• Pneumothorax—2
• Dural ectasia—2
• Protrusio acetabuli—2
• Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis—1
• Scoliosis or thoracolumbar kyphosis—1
• Reduced elbow extension—1
• Facial features (3/5)—1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
• Skin striae—1
• Myopia $> 3$ diopters—1
• Mitral valve prolapse (all types)—1
Maximum total: 20 points; score $\geq 7$ indicates systemic involvement

sign is positive when the patient can adduct the thumb across the palm sufficiently far that the distal phalanx of the thumb protrudes when the fingers are closed over it. Ocular manifestations include lens subluxation and retinal detachment, which can be appreciated by slit-lamp examination. However, the most clinically significant manifestations of Marfan syndrome are its cardiovascular features including cardiomyopathy, mitral or aortic valve degeneration and aortic root dilatation [11].

Pneumothoraces have been estimated to occur in up to 10% of patients with Marfan syndrome, although their aetiology is controversial. Although 5–9.6% of Marfan patients have evidence of blebs on CT [5], this is not significantly different to the general population [12]. It has been theorised that skeletal deformities may alter the lung parenchymal tension, predisposing individuals to pneumothorax [13].

#### Management

Prompt diagnosis and management are critical to decrease the risk of life-threatening complications associated with aortic aneurysms. Annual echocardiography allows monitoring of the aortic root, although more frequent imaging might be necessary when the aortic root is widening [14]. Therapy with

beta-blockade was initially shown to slow the rate of aortic dilatation and reduce complications associated with aortic aneurysms [15]; however, metaanalyses have concluded both in favour and against their use in Marfan syndrome [16, 17]. A recent Cochrane review determined that while there is evidence that beta-blockers reduce the rate of aortic diameter change, the quality of evidence is relatively poor [18]. On balance, until definitive trials can be performed, it is recommended that individuals with Marfan syndrome continue to be treated with beta-blockade.

Angiotensin receptor blockade has been proposed for the treatment of patients with Marfan syndrome since; in addition to beneficial effects on aortic haemodynamics, these drugs may also inhibit the overactive *TGF $\beta$*  pathway in Marfan syndrome. A small-scale study showed benefit of losartan in slowing aortic-root enlargement in young individuals resistant to beta-blockers [19]; however, subsequent studies failed to show a difference between losartan and beta-blockers therapy in progression of aortic disease [20, 21].

Surgery is indicated if pharmacological treatment fails and the aortic root dilates to 50 mm (or 45 mm if there is a family history of dissection or severe aortic regurgitation) [22]. Total root replacement or valve sparing root replacement can be performed, the latter having the advantage of sparing the individual from lifelong anticoagulation. Recent meta-analyses and systematic reviews showed comparable outcomes between the two procedures [23, 24], although surgeon experience and case-specific features mean valve-sparing surgery will not be appropriate for all patients [23, 25].

Annual ophthalmologic examination has been recommended for individuals with Marfan syndrome [26]. If clinically significant lens subluxation is noted, corrective lenses or surgical extraction followed by artificial lens replacement can be offered [26].

## Vascular Ehlers-Danlos Syndrome

### Genetics

Although “Ehlers-Danlos syndrome” has been recognised since the 1930s, it is in fact a group of weakly related conditions that share a propensity toward hypermobile joints. At present, only vascular Ehlers-Danlos syndrome (vEDS or EDS type 4) is known to be a risk factor for the development of pneumothorax. vEDS is rare (1 case per 100,000 population) but is potentially a more serious connective tissue disorder than Marfan syndrome. It is caused by autosomal dominant mutations in the *COL3A1* gene, which encodes collagen type III [27]. This protein is found in many connective tissues including the pulmonary vasculature and lung parenchyma [28]. In contrast to Marfan syndrome, molecular testing is often helpful in establishing a diagnosis of vEDS, but if genetic testing proves negative yet clinical suspicion remains

high, biochemical abnormalities of collagen type III can be sought using cultured fibroblasts [29].

### Clinical features

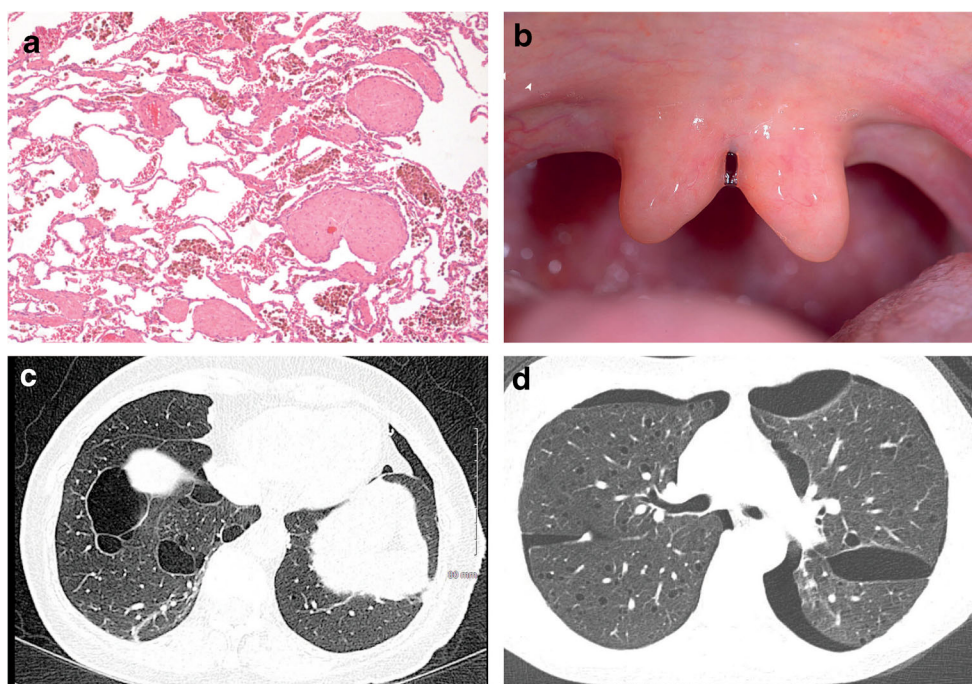
Diagnostic criteria developed in 2017 advise that vEDS should be suspected in patients with unexplained arterial aneurysms, dissection or rupture; intestinal rupture; uterine rupture during pregnancy; or a family history of vEDS [30]. However, pneumothorax is also a relatively frequent presenting feature of vEDS and offers a crucial opportunity to diagnose the condition before life-threatening complications occur [31, 32]. Other pulmonary features of vEDS reflect vascular fragility with spontaneous haemothorax and haemoptysis. Radiology may reveal pulmonary cavitation, which often leads clinicians to suspect pulmonary vasculitis. Consequently, a majority of vEDS diagnoses are made only after lung biopsy shows no vasculitis but evidence of recurrent haemorrhage, such as haemosiderin-laden macrophages and fibrous nodules with osseous metaplasia (Fig. 1a) [34].

A diagnosis of vEDS should be suspected clinically in patients who are hypermobile or have relatives with hypermobility. For this reason, we recommend that Beighton scores are recorded for all patients with spontaneous pneumothorax (Table 2). Other more rare skeletal features include clubfoot, congenital hip dislocation and facial dysmorphism with narrow nose, deep-set eyes, micrognathia and thin lips. A simple dermatological examination can reveal thin skin that bruises easily. A history (or family history) of spontaneous bowel or uterine rupture may also be elicited.

### Management

Owing in large part to its rarity, the management for vEDS is yet to be codified in definitive guidelines. Centres with experience of treating vEDS report that management is optimised through development of multidisciplinary teams comprising physicians, vascular surgeons and general surgeons [29]. In our own hospital, this team also includes respiratory, cardiology and genetics consultants, neurosurgeons and radiologists.

Surveillance for cardiovascular complications by echocardiography every 3 years has been recommended [36]. A randomised controlled trial and a subsequent observational study using celiprolol, a combined beta-1 antagonist and beta-2 partial agonist, showed a reduction in adverse arterial events, so this drug is often used [37, 38]. In the absence of clear guidelines, decisions on elective vascular procedures have to be made on a case-by-case basis. Owing to fragility of the blood vessels, open surgery can be challenging in vEDS, and so elective procedures are performed less frequently than in other diseases affecting connective tissues. The rise of endovascular approaches, however, may alter this balance in the future [39].



**Fig. 1** Syndromic causes of pneumothorax. **a** Vascular Ehlers Danlos syndrome. Lung parenchyma stained with haematoxylin and eosin. Magnification  $\times 16$  objective. Note hemosiderin-laden intraalveolar macrophages, suggesting prior pulmonary haemorrhage, and foci of intraalveolar organisation. **b** Loeys-Dietz syndrome. Bifid uvula. Reproduced with permission from [33•]. **c** Lymphangioliomyomatosis.

For patients that have suffered from gastrointestinal complications, a recent systematic review suggested that end ileostomies or ileorectal anastomoses are preferable over colostomies due to the risk of reperforation and anastomotic leaks with the latter [40].

## Loeys-Dietz Syndrome

### Genetics

Loeys-Dietz syndrome is a relative newcomer to the list of pneumothorax-associated disorders. It was first described in

**Table 2** The Beighton score of hypermobility. Adapted from [35]

#### Beighton score

1 point is given for each of the following tests. Tests 1–4 are performed on both right and left sides so can score a maximum of 2 points each. The maximum possible score is 9. The maximum normal score is considered to be 5.

- (1) Passive dorsiflexion of the little finger beyond  $90^\circ$  with the forearm flat on the table
- (2) Passive opposition of the thumb to the flexor aspect of the forearm
- (3) Hyperextension of the elbow beyond  $10^\circ$
- (4) Hyperextension of the knee beyond  $10^\circ$
- (5) Forward flexion of the trunk so the palms of the hands rest easily on the floor

2005 as a syndrome comprising craniofacial midline fusion defects, vascular tortuosity and neurodevelopmental defects [41••] but is now recognised to occur in more subtle forms. It is an autosomal dominant disorder caused by mutations in genes of the TGF $\beta$  signalling pathway: *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1* and *TGFBR2* [42].

### Clinical features

We reported pneumothorax as the presenting feature in an individual with normal neurodevelopment ultimately confirmed to have Loeys-Dietz syndrome (LDS) with a *TGFBR2* mutation [33•]. It is important to make an early diagnosis to permit preventive treatment of the cardiovascular risk. Arterial dissection may arise in a broader range of vessels in patients with LDS; this should therefore be considered even if the former arises below the diaphragm [43]. Other clinical features suggestive of LDS include midline fusion defects, with severely affected individuals having hypertelorism or cleft lip, while milder cases may have only a bifid uvula. The latter can easily be seen in the respiratory clinic by inspecting the oropharynx (Fig. 1b). Other features include skeletal abnormalities (pectus excavatum or carinatum, scoliosis, joint laxity or contracture) and skin changes (easy bruising, translucency and dystrophic scars) [41••]. A lack of ocular changes distinguishes LDS from Marfan syndrome.



It has been suggested that LDS requires evidence of aneurysm or dissection and a pathogenic mutation in any of the genes outlined above [43]. This guidance expands on previous reports suggesting that only mutations in *TGFBR1* and *TGFBR2* be considered [44]. Current guidance stresses that craniofacial features and cutaneous features may be very mild; however, the presence of severe craniofacial deformity predicts a poor prognosis [44].

### Management

As with other connective tissue disorders, cardiovascular surveillance is important in LDS. Echocardiography should be performed at least annually and more regularly in severely affected individuals. Since a wider range of vessels can be affected, we recommend periodic magnetic resonance angiography from the head to lower limbs in selected patients. Prophylactic antihypertensives are often used albeit with a smaller evidence base than exists for Marfan syndrome. Angiotensin receptor blockers have the theoretical added benefit of antagonising the TGF $\beta$  pathway offering a scientifically plausible advantage over beta-blockers; as yet, head to head trials are lacking. Unlike Marfan syndrome, dissections have frequently been reported with aneurysmal diameters of only 40 mm with prophylactic surgery advocated for aneurysms of this size [44, 45].

### $\alpha_1$ -Antitrypsin Deficiency

Alpha 1-antitrypsin deficiency is a recessive condition caused by mutations of the *SERPINA1* gene [46]. This encodes  $\alpha_1$ -antitrypsin, which is an abundant plasma protein that inhibits neutrophil elastase. Mutations in *SERPINA1* reduce the level of circulating  $\alpha_1$ -antitrypsin allowing uninhibited neutrophil elastase to degrade elastin fibres in the lungs. This can cause pulmonary emphysema even in nonsmokers and in some cases leads to pneumothorax [47]. The retention of polymerised  $\alpha_1$ -antitrypsin in the liver may cause cirrhosis or hepatocellular carcinoma; hence, surveillance imaging of the liver is recommended. In some countries, treatment with  $\alpha_1$ -antitrypsin augmentation therapy is available, but in all countries, lifestyle changes (smoking cessation, avoidance of excessive alcohol) can be suggested. If necessary, lung and/or liver transplantation can be considered.

### Homocystinuria

Homocystinuria is a rare metabolic disorder that affects only 1 in 200,000 people and is inherited in an autosomal recessive manner. Several genes can be mutated to cause the condition, but the most common is *CBS* encoding cystathionine  $\beta$ -synthase. This is responsible for the homocysteinylolation of various proteins, including fibrillin-1, which likely explains the

skeletal and ocular features homocystinuria shares with Marfan syndrome [4]. Patients also carry a markedly increased risk of thrombosis, which is responsible for much of the morbidity of the condition. Neurological complications including intellectual disability and seizures, and cutaneous abnormalities such as livedo reticularis or malar flush are frequently observed [4]. There are rare reported cases in the literature of pneumothorax due to homocystinuria [48].

### Cutis Laxa

Cutis laxa is characterised by hypoelastic, sagging skin particularly prominent around the neck, armpits and groin. Various mutant genes are reported including *ATP6V0A2*, *ATP7A*, *EFEMP2*, *ELN* and *FBLN5*; the modes of inheritance are variable, recessive forms typically being more severe [49]. The morbidity of the condition depends on the organs affected, which can include the intestines, joints, blood vessels and lungs. In the lungs, it can cause emphysema and rarely pneumothorax [50].

## Syndromes Related to Tumour Suppressor Mutations

### Tuberous Sclerosis and Pulmonary Lymphangiomyomatosis

#### Genetics

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder, which like Marfan syndrome dates back to the nineteenth century [51]. It is caused by loss-of-function mutations in either of two tumour suppressor genes, *TSC1* and *TSC2*, which encode the proteins hamartin and tuberlin respectively [52]. These proteins form a complex that inhibits mTORC1, a kinase involved in regulating cell proliferation, differentiation and adhesion [53]. Perhaps unsurprisingly, the dysfunction of these proteins leads to benign and malignant neoplasms affecting various tissues including the skin, central nervous system, bone, kidney, heart and lung [54].

#### Clinical features

TSC can be diagnosed either molecularly or clinically [55]. For the molecular route, a germline pathogenic mutation in *TSC1* or *TSC2* is required. Clinically, patients need two major features or one major feature with two or more minor features (Table 3) [55].

The most significant pulmonary manifestation of TSC is lymphangiomyomatosis (LAM). When individuals with TSC are subjected to thoracic CT imaging, up to 40% have pulmonary cysts consistent with a diagnosis of LAM, which

**Table 3** Clinical diagnostic criteria for tuberous sclerosis. Adapted from [55]

## Major features:

- (1) Angiofibromas ( $\geq 3$ ) or fibrous cephalic plaque
- (2) Cardiac rhabdomyoma
- (3) Cortical dysplasias, including tubers and cerebral white matter migration lines
- (4) Subependymal giant cell astrocytoma
- (5) Subependymal nodules
- (6) Hypomelanotic macules (3 to  $>5$  mm in diameter)
- (7) Shagreen patch
- (8) Multiple retinal nodular hamartomas
- (9) Renal angiomyolipoma
- (10) Ungual fibromas ( $\geq 2$ )
- (11) Lymphangiomyomatosis (LAM)

## Minor features:

- (1) Numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs (“Confetti skin lesions”)
- (2) Dental enamel pits ( $> 3$ )
- (3) Intraoral fibromas ( $\geq 2$ )
- (4) Multiple renal cysts
- (5) Non-renal hamartomas
- (6) Retinal achromic patch

in turn is the third commonest cause of morbidity in TSC [56]. Proliferation of abnormal smooth muscle cells, so-called ‘LAM cells’, causes the formation of cysts throughout the lungs (Fig. 1c). Around 60% of these patients experience pneumothorax, which is often the presenting feature of LAM [57].

Most patients with sporadic LAM (not associated with TSC) are women of childbearing age, which reflects the sensitivity of LAM cells to female sex hormones. LAM cells in sporadic disease are commonly found to have somatic mutations in *TSC2* or more rarely *TSC1* [58]. In patients with sporadic LAM, diagnosis is reached more easily if additional features are present such as angiomyolipomas, chylous effusions or lymphangiomyomas [59]. More recently, serum levels of vascular endothelial growth factor-D (VEGF-D) above 800 pg/ml have been shown to have diagnostic and prognostic value [59]. Although the literature has suggested that patients with sporadic LAM have more severe pulmonary manifestations compared with TSC-associated LAM, this may reflect lead-time bias since TSC patients will more often be diagnosed earlier because of preemptive screening [60].

## Management

Patients found to have LAM should be screened for evidence of TSC and vice versa [58]. An early diagnosis of LAM is particularly important because the pulmonary disease can progress rapidly during pregnancy, and so individuals should be provided with appropriate counselling and support [61]. We have cared for several women in whom pregnancy-associated pneumothorax was the presenting feature of LAM.

LAM can run a benign course, and the 10-year transplant-free survival is reported to be 86% [62]. However, it is important to monitor women with the condition by pulmonary function testing. These tests can be challenging for patients with severe neurological complications of TSC, and in these patients, serial measurements of VEGF-D or regular radiological examinations may be offered instead [63, 64].

In those women who suffer progressive loss of lung function, treatment with an inhibitor mTORC1, such as sirolimus, can be given [65]. Rarely, lung transplantation is required, although LAM can recur in the transplanted organ [66].

## Birt-Hogg Dubé Syndrome

### Genetics

Folliculin is encoded by the *FLCN* gene, mutations of which cause the autosomal dominant disease Birt-Hogg-Dubé syndrome (BHDS) [67]. Like tuberin and hamartin in TSC, folliculin regulates mTORC1 although the precise mechanism is still incompletely understood. The large *FLCN* gene contains 14 exons and approximately 150 different pathogenic *FLCN* mutations have been identified [67]. These span the entire coding region, although several mutational ‘hot spots’ exist. Of these, a polycytosine tract in exon 11 is the most important and accounts for nearly 50% of all *FLCN* mutations, either as inserted (c.1285dupC) or deleted (c.1285delC) residues [68].

### Clinical features

In contrast to tuberous sclerosis, Birt-Hogg-Dubé syndrome predominantly affects only a handful of tissues: the kidney, skin and lungs. In the kidney, it can manifest as renal cancers presenting typically in the fifth decade [67]. Only around a quarter of patients develop renal cancers because further random somatic mutations are required for oncogenesis, the so-called two-hit hypothesis [69]. Most of the renal tumours in Birt-Hogg-Dubé syndrome are atypical hybrid oncocytoma-chromophobe or chromophobe types. This is in contradistinction to other familial renal cancer syndromes, such as von-Hippel-Lindau syndrome in which more typical clear cell cancers are frequently seen [70]. An important consequence of this is that the atypical tumours of Birt-Hogg-Dubé syndrome are less easily detected by renal ultrasound scanning and can be missed unless renal MRI scanning is performed.

Individuals with Birt-Hogg-Dubé syndrome can also have skin changes including fibrofolliculomas, trichodiscomas, perifollicular fibromas and acrochordons. The most common are fibrofolliculomas, which are a useful marker of the condition when detected in the clinic. Respiratory physicians should be familiar with these lesions and when in doubt seek dermatological assistance. Fibrofolliculomas are benign tumours of the

follicular epithelium that present as smooth, 2–4 mm, white or flesh-coloured papules found on the face, ears and upper torso.

The lung manifestations are the most commonly observed features of Birt-Hogg-Dubé syndrome, pulmonary cysts being almost universal [67]. Irregular, sometimes septated cysts occur characteristically toward the bases or at least below the level of the carina and tend to be medially sited. This distinguishes Birt-Hogg-Dubé syndrome from LAM which has round cysts that are more evenly spread throughout the lung fields (Fig. 1d) [67]. Although the pathogenesis of these cysts is uncertain, the ‘stretch theory’ arose because folliculin plays a role in regulating cell-cell adhesion through the formation of the folliculin-plakophilin-4 complex, perhaps independent of its role in mTORC1 regulation [71]. It is hypothesised that a lack of folliculin increases cell-cell adhesion and that, over time, the stress induced by respiratory movement causes the alveolar space to rupture and form cysts [71, 72]. Interestingly, this predicts that cyst numbers or size will increase over time, but evidence for this is currently lacking. Pneumothoraces can occur because the cysts are frequently subpleural. Indeed, Birt-Hogg-Dubé syndrome is by far the most common genetic cause of familial pneumothorax, accounting for around 50% of cases in which a diagnosis is made, ahead of Marfan syndrome and vEDS. The age at which Birt-Hogg-Dubé syndrome patients present with pneumothoraces is around a decade earlier than the age they develop renal carcinomas.

## Management

If a diagnosis of Birt-Hogg-Dubé syndrome is made at the time of the pneumothorax, patients can be offered renal surveillance imaging (ideally with annual MRI) and thereby have early renal cancers diagnosed. This is especially appealing because these renal tumours tend to be curable if excised before reaching 3 cm. If the tumour is 3 cm or less then a partial nephrectomy can be performed, but for larger tumours, a full nephrectomy may be indicated [73]. At present, it is recommended that patients are screened annually from the age of 20 years [73], but recently, a 14-year old with Birt-Hogg-Dubé syndrome was reported as having developed a renal cancer, and so this guidance might change [74].

Fibrofolliculomas are benign, and so treatment is only undertaken for cosmetic reasons. Topical anti-mTORC1 has thus far proved unsuccessful in treating the lesions [75] and fibrofolliculomas often recur following laser therapy [76]. Electrocoagulation followed by curettage is therefore the treatment of choice [77].

## Conclusion

Pneumothorax is an important presenting feature in several genetic disorders that carry high risks of morbidity and

mortality later in life. By far, the most common syndromic cause of pneumothorax is Birt-Hogg-Dubé syndrome. Careful clinical assessment of spontaneous pneumothorax can identify this and many other conditions to enable life-saving interventions to be commenced. Because many of these conditions have autosomal inheritance, the diagnosis of one proband frequently leads to the diagnosis of many affected but subclinical family members, thus widening the potential clinical benefit. Respiratory physicians must therefore be alert to these diseases and their diagnostic implications.

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## Compliance with Ethical Standards

**Conflict of Interest** Kenki Matsumoto and Stefan J. Marciniak declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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