The Genetics of Pneumothorax

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Abstract

A genetic influence on spontaneous pneumothoraces – those occurring without a traumatic or iatrogenic cause – is supported by several lines of evidence: 1) Pneumothorax can cluster in families (i.e. familial spontaneous pneumothorax); 2) Mutations in the *FLCN* gene have been found in both familial and sporadic cases; and 3) Pneumothorax is a known complication of several genetic syndromes. Herein we review known genetic contributions to both sporadic and familial pneumothorax. We summarize the pneumothorax-associated genetic syndromes, including Birt-Hogg-Dubé syndrome, Marfan syndrome, vascular (type IV) Ehlers-Danlos syndrome, alpha-1-antitrypsin deficiency, tuberous sclerosis complex/lymphangioleiomyomatosis (LAM), Loeys-Dietz syndrome, cystic fibrosis, homocystinuria, and cutis laxa, among others. At times, pneumothorax is their herald manifestation. These syndromes have serious potential extrapulmonary complications (e.g. malignant renal tumors in Birt-Hogg-Dubé syndrome), and surveillance and/or treatment is available for most disorders; thus, establishing a diagnosis is critical. To facilitate this, we provide an algorithm to guide the clinician in discerning which cases of spontaneous pneumothorax may have a genetic or familial contribution, which cases warrant genetic testing, and which cases should prompt an evaluation by a geneticist.

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Introduction

Spontaneous pneumothoraces are defined by air in the pleural space arising from neither trauma nor an iatrogenic cause. An anatomic or mechanical cause is identifiable in all cases of secondary spontaneous pneumothorax, which by definition arise from clinically recognizable underlying lung disease (e.g. tuberculosis). Even in primary spontaneous pneumothorax, defined by a lack of overt lung disease, emphysema-like anomalies (blebs, cysts, or bullae) are observed at surgery or on CT in most cases (1). Additional anatomic associations include being taller and thinner than average (2). Smoking is the primary environmental risk factor for primary spontaneous pneumothorax (3).

Several lines of evidence support genetic contributions to pneumothorax. Foremost are familial clustering, observed in 10-12% of cases, and the finding of gene mutations in both familial and sporadic cases. Additionally, pneumothorax is a feature of several Mendelian disorders, for example Birt-Hogg-Dubé and Marfan syndromes.

In this review, we discuss known genetic contributions to both sporadic and familial pneumothorax and summarize the pneumothorax-associated genetic syndromes, all of which have serious potential complications and of which pneumothorax is occasionally the presenting feature. We provide an algorithm to guide the clinician in discerning which cases of spontaneous pneumothorax may have a genetic or familial contribution, and which of these cases should prompt genetic testing and/or evaluation by a geneticist.

Sporadic pneumothorax

Primary spontaneous pneumothoraces occur without a family history in the majority (88-90%) of cases (4, 5). We refer to these non-familial cases as sporadic pneumothorax.

Genetic studies of sporadic pneumothorax cohorts have focused on *FLCN*, the gene for Birt-Hogg-Dubé syndrome (BHDS). The BHDS phenotype includes lung cysts and pneumothorax in addition to renal cancer and skin findings, so investigators hypothesized that some variants in this gene might lead to a lung-only phenotype. No mutations were identified among ten sporadic cases screened by *FLCN* sequencing (6). However, among 92 sporadic pneumothorax patients screened for sequence errors and deletions, five (5%) had *FLCN* mutations (5). *FLCN* promoter methylation changes do not explain *FLCN*-negative sporadic pneumothorax (7).

Several additional studies of spontaneous pneumothorax have been reported that did not adequately enumerate family background. Nonetheless, if one were to assume that the majority of these cases are sporadic (supported by the higher prevalence of sporadic over familial pneumothorax), then these studies of all comers can provide insights regarding the role of genetics in sporadic pneumothorax:

To investigate whether mutations in the genes for additional pneumothorax-associated syndromes explain isolated pneumothorax, Zhang et al. screened for point mutations and deletions in *FBN1*, *COL3A1*, *CBS* , *SERPINA1* , *TSC1* and *TSC2* , and *FLCN* (8). Three of 21 subjects had predicted-pathogenic mutations: two (10%) in *FLCN* and one (5%) in *FBN1*. Three variants of uncertain significance (one in *FBN1*, *TSC1*, and *FLCN*) were also found. While blebs and emphysema-like changes in spontaneous pneumothorax are typically apical (1), BHDS features predominately lower-lobe cysts (9, 10). To investigate whether non-apical lung cysts might herald *FLCN* mutations among patients with spontaneous pneumothorax, Johannesma et al. screened 40 non-familial and familial SP patients with chest CT (11); indeed, all three subjects with cysts below the carina had *FLCN* mutations. To determine whether common genetic variants play a role in

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pneumothorax risk, Sousa et al. performed a genome-wide association study of spontaneous pneumothorax (12). No SNPs met the Bonferroni correction threshold in the replication dataset.

Familial pneumothorax

10-12% of patients with spontaneous pneumothorax have a family history, termed familial spontaneous pneumothorax (FSP) (4, 5). The male:female ratio in FSP is 1.7:1 (4), less skewed than for all spontaneous pneumothoraces (2.1-6.2:1) (13-16). The risk of recurrent pneumothorax may be higher in FSP (68-72%) (6, 17) than in sporadic pneumothorax (13-54%) (11-13, 18), although the studies arriving at these recurrence rates differ in methodology, making the comparison imperfect. A higher recurrence rate when a family history is known could argue for surgical intervention after the first pneumothorax (19, 20).

While some FSP families are identifiably autosomal dominant (AD) (Fig. 1a), in others the inheritance pattern is ambiguous (21). Indeed, among 29 FSP pedigrees, all were consistent with AD inheritance with a penetrance of 21% in females and 50% in males, but many of the pedigrees could also follow an X-linked recessive model (Fig. 1b) (4).

Several attempts have been made to map the genetic cause(s) of FSP. In three FSP families, pneumothorax did not segregate with *FBN1*, the disease gene for Marfan syndrome (22). Linkage to the HLA-A2B40 haplotype exists in some families (23, 24) but not others (17, 25). In a large FSP family, CT scans revealed multiple asymptomatic family members with bullae randomly distributed throughout the lungs, transmitted in an AD pattern (Fig. 1c) (26). A heterozygous, predicted-truncating mutation was found in *FLCN*, the disease gene for Birt-Hogg-Dubé syndrome (BHDS). The penetrance of bullae in mutation carriers was 100%; for pneumothorax it was ~40%. The prevalence of *FLCN* mutations in FSP is 17-50% (5, 6).

Thus, a considerable proportion of FSP is attributable to mutations in *FLCN*. The remainder of FSP is likely caused by mutations in one or more yet-undescribed disease genes. By definition, FSP families do not manifest renal or dermatological findings of BHDS. It is unknown what contributes to the full BHDS vs restricted FSP phenotype.

Genetic syndromes predisposing to pneumothorax

Pneumothorax is at times a feature of a multisystem genetic syndrome (Table 1, Figure 2). These can be divided into three mechanistic classes (27): 1) those arising from mutations in tumor suppressor genes; 2) connective tissue disorders; and 3) those in which normal lung architecture is effaced. Given that these syndromes have serious, often-preventable complications, it is essential to make the correct diagnosis when pneumothorax is the presenting manifestation.

Syndromes related to tumor suppressor genes

Birt-Hogg-Dubé syndrome

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant condition caused by heterozygous mutations in *FLCN*, encoding folliculin (28). The full BHDS phenotype includes skin lesions, kidney cancer, lung cysts, and pneumothorax (Fig. 2a-c) (29). Incomplete and age-dependent penetrance of features is characteristic (30). Skin findings include fibrofolliculomas (hamartomas of hair follicles) and trichodiscomas (tumors of the hair disk) (Fig. 2a) (29). These lesions are clinically identical, appearing as small, dome-shaped papules typically on the face, neck, chest, back, and arms. Skin tags are also observed frequently. Renal cancer subtypes include hybrid oncocytic/chromophobe tumors, chromophobe carcinomas, clear cell carcinomas, oncocytomas, and papillary renal cell carcinomas (31); their combined prevalence was estimated

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at 6.5% in a review of the literature (29), while a higher rate (~20%) was found in a selected set of NIH cases (30). Screening for renal tumors via imaging is the key intervention for BHDS; however, there is to date no concensus regarding the optimal modality (e.g. MRI, contrast CT, ultrasound) or the timing of imaging (i.e. earliest age, interval between tests), although algorithms have been suggested (29, 32). Although some authors have suggested colorectal cancer as a feature of BHDS (33), it is not an accepted part of the phenotype (29, 32, 34).

The lung cysts of BHDS tend to be basal (below the carina) and subpleural (Fig. 2b-c) (9, 34). They vary in number and size, and most are non-spherical (9). Pulmonary cysts in BHDS have a penetrance of 83-100% (30, 34-37), while they are detected in 10% of unaffected control family members (34). BHDS cysts are usually asymptomatic, and spirometry is typically normal.

The prevalence of pneumothorax in BHDS is 22-41% (30, 34-38). Pneumothoraces in BHDS tend to arise in early- to mid-adulthood (37) but can affect children (39). They can be the presenting sign of BHDS (40). They are often recurrent (40-75%; (35, 37)). Resection or pleurodesis have been suggested after first-time pneumothorax in BHDS (41, 42).

Among BHDS patients, risk factors for pneumothorax include family history of pneumothorax (36), larger cyst size and number (37), extent of lower lung disease (35), flying (42, 43), and scuba diving (43). Curiously, smoking is not a risk factor (32, 37). There is no genotype-phenotype correlation nor modifier gene known to affect pneumothorax risk in BHDS (36).

How *FLCN* mutations lead to cyst formation is unknown. One proposal is based on the observation that folliculin is involved in cell:cell adhesion via the desmosomal protein PKP4/p0071 (44, 45); this suggests that poor stretch tolerance to lung pressure may allow cyst formation (46).

Tuberous sclerosis and pulmonary lymphangioleiomyomatosis (LAM)

Pulmonary lymphangioleiomyomatosis (LAM) is a progressive lung disease involving infiltration of the alveolar septa with smooth muscle-like LAM cells and the development of cysts that compromise normal lung parenchyma (47). LAM is typically diagnosed in young adulthood (48) and affects almost exclusively females – a presumed effect of estrogen (49-52). LAM occurs both sporadically and in association with tuberous sclerosis complex (TSC), an autosomal dominant genetic syndrome caused by germline loss-of-function mutations in *TSC1* (encoding hamartin) or *TSC2* (encoding tuberin) (53, 54). Multitudinous clinical findings are possible in TSC (Table 1; Fig. 2q-y), affecting the brain, skin, abdominal viscera, heart, eyes, mouth, and lung. The lung phenotypes include LAM and micronodular pneumocyte hyperplasia. Among LAM patients, TSC patients (TSC-LAM) make up 15%, while the remaining 85% are sporadic (48). A very small number of men have LAM, all of whom have TSC-LAM (55).

TSC is a syndrome of hamartomas, explained by hamartin's and tuberin's role in regulating cell growth and division via the mTORC1 and other pathways (56). Although women with sporadic LAM lack germline mutations in *TSC1/2*, mosaic inactivating mutations in these genes are found in the pulmonary LAM cells of most patients (57-60). Nearly 30% of sporadic LAM patients have renal angiomyolipomas (48), a feature of TSC, which contain *TSC2* mutations (57). The same *TSC2* mutation is found in the angiomyolipoma and the LAM cells (57). In addition, LAM can recur after lung transplantation, and the recurrent LAM cells carry the original *TSC2* mutation (61). These findings suggest that LAM is a low-grade, metastatic neoplasm (62).

Pneumothorax is the most common presenting sign of LAM (~1/3 of cases) (48). Other presenting features include shortness of breath, wheezing, and abnormal imaging including diffuse reticular pattern on X-ray and diffuse interstitial changes with infiltrates and cysts on CT (48).

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Cysts are generally <2 cm, round, and diffuse with no relationship to pleura or vessels, (41). CT reveals cystic changes consistent with LAM in 34-81% of women and 0-10% of men with TSC (63-65). With progression, LAM can cause chest pain, cough, hemoptysis, pleural effusions including chylous effusions, airway obstruction demonstrated via spirometry, and respiratory failure (48). Beyond imaging, the diagnosis of LAM is aided by lung biopsy, lymph node biopsy, and the serum biomarker VEGF-D (66-70).

The lifetime incidence of pneumothorax in LAM is 56-66% (48, 71, 72). Pneumothoraces are recurrent in 73-77% of patients (72, 73), with a mean number of 4.4 +/-0.5 (48). Risk factors for pneumothorax in LAM are prior pneumothorax (72), faster rate of FEV_1 decline (71), and larger cyst size (71). Individuals with a prior pneumothorax had lower VEGF-D levels (74). Chronic loculated pneumothoraces are not worsened by flight, leading to the recommendation to avoid flight only in LAM patients with recent pneumothorax or current symptoms of pneumothorax (75). Pregnancy exacerbates respiratory symptoms in some women with LAM (48) and appears to be a risk factor for pneumothorax (76), however a lack of prospective studies makes the risk difficult to quantify. Polymorphisms in extracellular matrix proteins (collagen, elastin, matrix metalloproteinase-1) were not associated with pneumothorax in one study (71).

The mTORC1 inhibitor sirolimus (Rapamycin) lowers the rate of decline of FEV_1 in women with LAM (77). This intervention is based on the discovery that *TSC2* mutations result in mTORC1 hyperactivation. Treatment with sirolimus is usually continued indefinitely since lung function was proven to decline after discontinuation. The impact of sirolimus on pneumothorax risk is unknown. Other treatments for LAM include oxygen, lung transplantation, and avoiding both smoking and estrogen supplementation (49, 66). Progesterone derivatives have been used

therapeutically (78) but without definitive benefit (48, 79). Pleurodesis is recommended after the first pneumothorax (67, 72) because of the likelihood of recurrence.

Syndromes of disordered connective tissue

Marfan Syndrome

Marfan syndrome is an autosomal dominant condition caused by heterozygous mutations in *FBN1*, encoding fibrillin 1. Marfan syndrome features include tall stature, thin body habitus, long limbs resulting in decreased upper segment to lower segment ratio, arachnodactyly, chest wall deformity, scoliosis, lens dislocation, and dilation/dissection/aneurysm/rupture of the aorta (Fig. 2d-i) (80). Screening and treatment for cardiovascular complications is the primary intervention in the disorder. Pulmonary features of Marfan syndrome can include congenital malformations (e.g. rudimentary middle lobe), cysts, emphysema, and pneumothorax (81). Large total and residual lung volumes may be present (82).

Apical blebs/bullae were found in Marfan syndrome patients at a rate of 8.9% with X-ray and 10% by CT (83). As 0-15% of healthy individuals have emphysema-like lesions including bullae by CT scan (1, 84) and 6% have blebs at surgery (85), it is unclear if these lung lesions are enriched in Marfan syndrome.

Pneumothorax is enriched among Marfan syndrome patients, estimated at 4-11% (83, 86, 87). Pneumothorax is one of the criteria of the Marfan systemic score (80). Among 8 patients, the median number of pneumothoraces was 1 (range 1-3) (83). Blebs or bullae are a risk factor for pneumothorax; pectus excavatum and smoking are not (83). Despite some familial clustering (88, 89), no genotype-phenotype correlation for pneumothorax is known (83).

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At times, pneumothorax is the presenting feature of Marfan syndrome (90). Among 10 sporadic pneumothorax patients screened for the syndrome via hand x-rays (for arachnodactyly) and clinical exam, four had "possible" Marfan syndrome and one had "full-fledged" disease (91). One of 21 (5%) sporadic pneumothorax patients had a stop-gain mutation in *FBN1* (8).

In the lung, fibrillin-containing microfibrils associate with elastin to help form elastic fibers. In a Marfan syndrome mouse model, age-dependent alveolar destruction occurs and appears to involve aberrant TGF-β signaling (92, 93). It is unclear in patients whether skeletal shape, lack of fibrillin, altered elastin, altered TGF-β signaling, or a combination leads to blebs/bullae and/or pneumothorax.

Vascular Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is a family of connective disorders mostly resulting from mutant collagens or related proteins (94). Of these subtypes, pneumothorax is a feature only of vascular EDS (type IV; vEDS).

vEDS is autosomal dominant, caused by heterozygous mutations in *COL3A1*, encoding the sole subunit of the homotrimeric type III collagen (95). vEDS can have fatal complications including rupture of arteries, the uterus, and intestines (96). Arterial rupture may be preceded by aneurysms or dissection (96). Other features include thin, translucent skin (Fig. 2j), characteristic facial features, easy bruising, clubfoot, congenital hip dislocation, lax small joints, carotid-cavernous sinus fistula, and pulmonary features (96). Screening and prevention incudes periodic imaging of the heart and vessels, blood pressure control, counseling regarding the risks of uterine rupture in pregnancy, and avoidance of colonoscopy and elective invasive arteriography (97).

Pulmonary complications of vEDS include cavitary lesions, cysts, bullae, fibrous nodules, pneumothorax, hemo-pneumothorax, and pulmonary hemorrhage (98, 99). Type III collagen in the lung is expressed in vessels and parenchymal fibroblasts (100). Thus, pulmonary complications of vEDS are proposed to result from poor tissue integrity (101, 102). The fibrous nodules, or fibrous pseudotumors, feature osseous metaplasia and may result from inefficient repair after injury to the pulmonary vessels or interstitium, with type I collagen favored over the absent type III collagen (99, 103-105).

Pneumothorax (99, 106, 107) or hemopneumothorax (108) can be the presenting symptom of vEDS. The penetrance of either pneumothorax or hemothorax in vEDS was 16% in a series diagnosed clinically (97); of individuals diagnosed molecularly, pneumothorax prevalence was 80% (109). There is no known genotype-phenotype correlation for vEDS. Standard treatment of pneumothorax has worked (98).

Loeys-Dietz syndrome

Loeys-Dietz syndrome is an autosomal dominant genetic disorder caused by mutations in *TGFBR2*, *TGFBR1*, *SMAD3*, *TGFB2*, and *TGFB3*. *SMAD2* is a provisional gene. These genes encode components of the TFG-β signaling pathway. Pneumothorax is an occasional feature of Loeys-Dietz syndrome (110). It has been described once as the presenting feature (111). Other features are vascular (arterial aneurysms, dissections, and tortuosity), skeletal (pectus excavatum or carinatum, joint laxity or contractures, cervical spine instability, scoliosis, arachnodactyly, club foot), craniofacial (bifid uvula [Fig. 2k] or cleft palate, hypertelorism, craniosynostosis), cutaneous (translucent skin, dystrophic scars, easy bruising), and uterine (rupture during pregnancy) (112). Vascular features lead to premature death (112).

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Homocystinuria

Homocystinuria is an autosomal recessive metabolic disorder caused by biallelic mutations in *CBS*, which encodes cystathionine β-synthase (113). Features are skeletal (tall stature with long limbs, scoliosis, pectus excavatum), ocular (lens dislocation, myopia), vascular (blood clots), CNS (intellectual disability, seizures), and cutaneous (hypopigmentation, livedo reticularis, malar flush) (Fig. 2o-p) (113). Plasma homocysteine and methionine are markedly elevated, and the condition can be diagnosed via elevated methionine on the newborn screen. (113) Therapy exists in the form of a methionine-restricted diet, supplementation with folate, B_{12}, B_6 (if responsive), betaine, and in certain circumstances anti-coagulation (113). Pneumothorax has been reported (114); the incidence is unknown. It has once been the presenting feature (115).

Cutis laxa

Cutis laxa describes loose, redundant, hypoelastic skin particularly over the neck, hands, groin, face, and trunk (Fig. 2n). It is a feature of at least 10 genetic syndromes (116). Several of the cutis laxa syndromes display early-onset emphysema, including autosomal dominant cutis laxa (*ELN* gene), autosomal recessive cutis laxa Ia/Ib (*FBLN4*/*FBLN5* genes), and Urban-Rifkin-Davis syndrome (*LTBP4* gene). Pneumothorax has been reported occasionally in patients with cutis laxa syndromes (117), more frequently among the subtypes that feature emphysema (118, 119). The incidence of pneumothorax is unknown, and pneumothorax has never been reported as the presenting symptom of a cutis laxa syndrome.

<u>Syndromes that efface normal lung architecture</u>

Alpha-1-antitrypsin deficiency

Alpha-1-antitrypsin deficiency (A1AT deficiency) is an autosomal recessive disease caused by mutations in *SERPINA1* (120). Its protein product, alpha-1 antitrypsin, inhibits the protease neutrophil elastase in the lungs. Individuals with bi-allelic mutations that in combination reduce the circulating levels or activity of A1AT to below ~35% of normal can have early-onset chronic obstructive pulmonary disease (Fig. 2l) (120). The typical pathology is a progressive, panacinar, predominantly lower-lobe emphysema presenting in early to mid-adulthood (121). Other lung findings can include chronic bronchitis and bronchiectasis (122), apical bullae (123), and pneumothorax.

Extrapulmonary complications include neonatal cholestatic jaundice, cirrhosis, and risk of hepatocellular carcinoma, resulting from polymerization of certain mutant forms of A1AT in the endoplasmic reticulum of hepatocytes (124). Panniculitis – painful inflammatory skin nodules/weeping lesions (Fig. 2m) – and vasculitis have also been reported (120).

The incidence of pneumothorax in A1AT deficiency is unknown (125, 126), however of patients homozygous for the most common mutant allele, Pi*Z, 2-3% die of pneumothorax (126, 127). Because pneumothorax can occasionally be the presenting symptom of A1AT deficiency (128, 129), several authors have screened for A1AT deficiency among patients with spontaneous pneumothorax: Estimates of A1AT range from 0 to 8% (1, 130-133). Although smoking is an important risk factor for lung disease progression (134) and death (127) in A1AT deficiency, its effect on pneumothorax risk is unknown. Also unknown is whether genotype or augmentation therapy (infusions of A1AT) can impact pneumothorax incidence or recurrence.

Cystic fibrosis

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Cystic fibrosis (CF) is caused by biallelic mutations in *CFTR*. Complications are gastrointestinal (meconium ileus, malabsorption, failure to thrive, pancreatic insufficiency and pancreatitis), reproductive (male infertility), and respiratory. Lung findings derive from thickened mucus affecting the mucociliary elevator and include recurrent infections, inflammation, bronchiectasis, cysts/cavitations, air trapping, hemoptysis, and pneumothorax (135). Pneumothorax as a herald sign of CF is probably rare because: 1) it is a late feature of the disease (136); and 2) CF is screened for in newborns in countries where it is prevalent, so the diagnosis is often made at birth.

Incidence of pneumothorax among CF patients was 2% in children over a 15-year interval (137) and 3% in all ages over a 10-year period (136). Lifetime prevalence was estimated at 8% during the 1950s-80s (138). Specific risk factors for pneumothorax in CF include: older age; FEV_1 <30% predicted; infection with *P. aeruginosa*, *B. cepacia*, or *Aspergillus*; allergic bronchopulmonary aspergillosis; massive hemoptysis; enteral feeding; and pancreatic insufficiency (136). Recurrence is 50-90% ipsilaterally and 46% contralaterally (136, 139). A pneumothorax carries an attributable mortality of 6-14% (140).

Mechanically, pneumothorax risk in CF may derive from effacement of normal lung structures, altered airflow dynamics, air trapping, use of inhaled medications, or noninvasive positive pressure ventilation (135). Risk does not correlate well with blebs or cysts (141). Among 21 CF *carriers*, one had pneumothorax and others had respiratory symptoms including nasal polyps causing obstruction (142), however a larger study showed no difference in pneumothorax, sinusitis, or other respiratory conditions (143).

Management of pneumothorax in CF is debated. Some suggest early surgical intervention (144, 145); others urge caution given potential future lung transplantation (146, 147).

Others

There are reports of pneumothorax in other genetic syndromes. These include: Sotos syndrome (148), spinocerebellar ataxia type 1 (149), telomerase reverse transcriptase (*TERT* gene) mutations (emphysema and pneumothorax in smokers) (150), hereditary mucoepithelial dysplasia (151), and diffuse dendriform pulmonary ossification (152).

A genetic approach to patients with spontaneous pneumothorax

Current clinical guidelines for the evaluation and management of pneumothorax do not address the familial, syndromic, or potentially syndromic cases (153, 154). We argue that establishing a genetic diagnosis is beneficial for patients and their relatives. For the index case, establishing a genetic etiology can guide pneumothorax management, including the need for pleurodesis after first pneumothorax. Moreover, given that the genetic forms of pneumothorax are associated with extra-pulmonary complications, a genetic diagnosis enables targeted surveillance and prophylaxis. Examples include blood pressure control and echocardiography in Marfan syndrome and surveillance for renal tumors in BHDS. The potential benefits to family – whether pneumothorax has occurred in other family members or not – are no less significant. Identification of a pathogenic genetic variant in the index case enables testing, counseling, and surveillance/prophylaxis in family members carrying the same variant. For these reasons, we recommend that an underlying genetic diagnosis be routinely entertained in patients with spontaneous pneumothorax.

Figure 3 provides a basic algorithm to evaluate this question, emphasizing the importance of a focused family history, targeted history taking and physical examination, and careful review

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of imaging. Figure 4 provides a graphical representation of which findings are associated with which syndromes.

In addition to pneumothorax, the family history should ascertain associated lung diseases (particularly emphysema, bronchiectasis, and CF), abnormal chest imaging (cysts/blebs/bullae), renal tumors (observed in BHDS and TSC), physical features consistent with pneumothorax-associated syndromes (see Table 1), and consanguinity (which could heighten suspicion for an autosomal recessive condition). While a positive family history can help flag patients, an absent family history should not dissuade pursuit of a genetic cause of pneumothorax; both FSP caused by *FLCN* mutations and dominant pneumothorax-associated syndromes can arise via *de novo* mutations (155) or display reduced penetrance, and autosomal recessive conditions frequently lack family history.

History taking and physical examination should include focused screening for features of pneumothorax-associated genetic syndromes (Table 1). A thorough examination of the skin is essential, as dermatologic manifestations of BHDS are often subtle. Skeletal anomalies, hyperextensibility, and distinct facial features could suggest a connective tissue disorder.

Current clinical guidelines do not recommend chest CT in first-time, unilateral spontaneous pneumothorax (153, 154). However, a recent study demonstrating the cost-effectiveness of CT to detect diffuse, cystic lung diseases in patients with first-time pneumothorax (156) is among the reasons some authors argue for the adoption of this practice (157). While acknowledging that the risk-benefit profile is unknown (11), we suggest considering chest CT in first-time pneumothorax if a family history is present or if the patient is female given that the mutational burden to cause pneumothorax in women appears to be higher (unpublished data) and because of the possibility of LAM. The presence of multiple (158) and/or non-apical cysts (11) may suggest BHDS or *FLCN*-

related FSP. Parenchymal lung disease might suggest A1AT deficiency or LAM, and airways disease CF. Aortic pathology might suggest Marfan syndrome or Loeys-Dietz syndrome.

We recommend genetic testing or evaluation in the following scenarios: An isolated family history of pneumothorax should prompt sequencing and deletion/duplication screening of *FLCN*. This will be positive in 17-50% of cases (5, 6). A family history of blebs/cysts/or bullae or a personal history of non-apical blebs/cysts/bullae should also prompt testing of *FLCN*. In the absence of positive family history and CT data, the merits of *FLCN* testing are not clear, although 10% of these patients will have pathogenic mutations as well. Should the personal or family medical history or the physical examination raise suspicion for a genetic syndrome, we recommend referral to a medical geneticist for a more detailed examination and consideration of genetic testing for pneumothorax-associated syndromes.

Summary

A genetic cause of pneumothorax can have high impact clinical implications. The generalist, emergency physician, radiologist, pulmonologist, surgeon, or other specialist, armed with the above recommendation, is enabled to raise the possibility of a genetic/familial diagnosis in pneumothorax patients. Additional studies – ideally prospective – that test the value of chest CT, genetic testing, and genetics referral to uncover genetic causes of pneumothorax, and the appropriateness of surgery after first-time pneumothorax, will enable the official "society" guidelines to be updated. Furthermore, yet-undiscovered genetic contributions to pneumothorax likely exist, which researchers will uncover in time via assembly and study of patient cohorts and by other methods.

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Supplemental Material

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Disclosure Declaration

The authors have no potential conflicts of interest to disclose.

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Table 1. Mendelian diseases associated with spontaneous pneumothorax.

AD, autosomal dominant. AR, autosomal recessive. P or PTX, pneumothorax. C, cysts.

Condition / Inheritance pattern	Pulmonary features (in addition to pneumothorax)	Extrapulmonary features	Penetrance (PTX/Cysts)	Gene(s)	Diagnostic criteria
Syndromes resulting from mutated tumor suppressor genes					
Birt-Hogg-Dubé syndrome AD	**Cysts:** Elliptical or lentiform, with predominantly basilar, medial, and subpleural distribution	**Skin lesions:** Fibrofolliculomas, trichodiscomas, acrochordons (skin tags) **Renal cancer:** Renal cell carcinomas, oncocytomas, and others	P: 22-41% C: 83-100%	*FLCN*	(29)
Tuberous sclerosis complex AD	**LAM:** Cysts, bullae, reticulonodular infiltrates, pleural effusions, obstructive physiology; female predominance Micronodular pneumocyte hyperplasia	**Brain:** Subependymal nodules, cortical dysplasia (tubers), cerebral white matter migration lines, subependymal giant cell astrocytomas, seizures or infantile spasms, developmental delay/ intellectual disability, autism, ADHD **Skin:** Hypopigmented macules (ash leaf spots), Shagreen patches, confetti lesions, facial angiofibromas, fibrous cephalic plaques, ungual fibromas **Kidney:** Angiomyolipomas (renal or extra-renal), renal cysts, renal cell carcinomas & oncocytomas **Heart:** Rhabdomyomas, arrhythmias **Eye:** Retinal nodular hamartomas, achromic retinal patches **Mouth:** Dental pits, intraoral fibromas	In LAM: P: 56-66% C: ~100%	*TSC2* *TSC1*	(159)
Syndromes of disordered connective tissue					
Marfan syndrome AD	Lungs usually normal; rare features include: Cysts Emphysema Congenital lung malformations Increased TLC and RV	**Skeletal:** Tall, thin habitus**,** ↓ upper:lower segment ratio**,** reduced elbow extension**,** arachnodactyly, hand/wrist signs, pectus excavatum/carinatum, scoliosis/kyphosis, hindfoot deformity, flat feet **Facial features:** Dolichocephaly, down-slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia **Eye:** Lens dislocation, severe myopia **Skin:** Striae **Cardiac:** Aortic dilation/dissection/aneurysm/ rupture**,** mitral valve prolapse	P: 4-11% C: 10% (bullae / blebs)	*FBN1*	(160)
Vascular (type IV) Ehlers Danlos syndrome AD	Cavitary lesions Cysts, bullae Fibrous nodules with osseous metaplasia	**Vascular:** Arterial aneurysm, dissection, rupture**,** carotid-cavernous sinus fistula **Organ rupture:** of colon or gravid uterus	P: 16-80%	*COL3A1*	(94)

	Hemo-pneumothorax or pulmonary hemorrhage	**Facial appearance:** Thin lips and nose, micrognathia, prominent eyes **Skin:** Translucent skin with visible veins, easy bruising **Orthopedic:** Clubfoot, congenital hip dislocation, lax small joints, muscle/tendon rupture			
Loeys-Dietz syndrome AD	N/A	**Vascular:** Arterial aneurysms, dissection, tortuosity **Skeletal:** Pectus excavatum or carinatum, joint laxity or contractures, cervical spine instability, scoliosis, arachnodactyly, club foot **Craniofacial:** Bifid uvula or cleft palate, hypertelorism, retrognathia **Cutaneous:** Translucent or dystrophic skin, easy bruising **Uterine rupture**	Unknown	*TGFBR1* *TGFBR2* *SMAD3* *TGFB2* *TGFB3* *SMAD2*	None
Homocystinuria AR	N/A	**Skeletal:** Marfanoid habitus **Eye:** Dislocated lens, myopia **Neurologic:** Intellectual disability, seizures **Vascular:** Thrombosis	Unknown	*CBS*	(161)
Cutis laxa* AD/AR *Note that features vary by subtype.	Bronchiectasis Emphysema	**Cutaneous:** Redundant, loose, hypoelastic skin **Facial:** Aged appearance **Vascular:** Aortic aneurysms, tortuosity **Musculoskeletal:** Joint laxity, scoliosis **Other:** Hernias	Unknown	*ELN* *FBLN4* *FBLN5* *LTBP4*	N/A
Syndromes that disrupt lung architecture					
Alpha-1-antitrypsin deficiency AR	Panacinar emphysema Bullae Bronchiectasis Obstruction	**Liver :** Cirrhosis, hepatocellular carcinoma, neonatal cholestatic jaundice **Skin:** Panniculitis **Inflammatory:** Vasculitis	Unknown	*SERPINA1*	(162)
Cystic fibrosis AR	Bronchiectasis Bacterial colonization/infection Cysts/cavitations Obstruction Respiratory failure	**GI:** Meconium ileus, pancreatic insufficiency, pancreatitis, malabsorption, failure to thrive **Male infertility** **ENT:** Nasal polyps, sinus disease	P: 8%	*CFTR*	(163)

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Figures

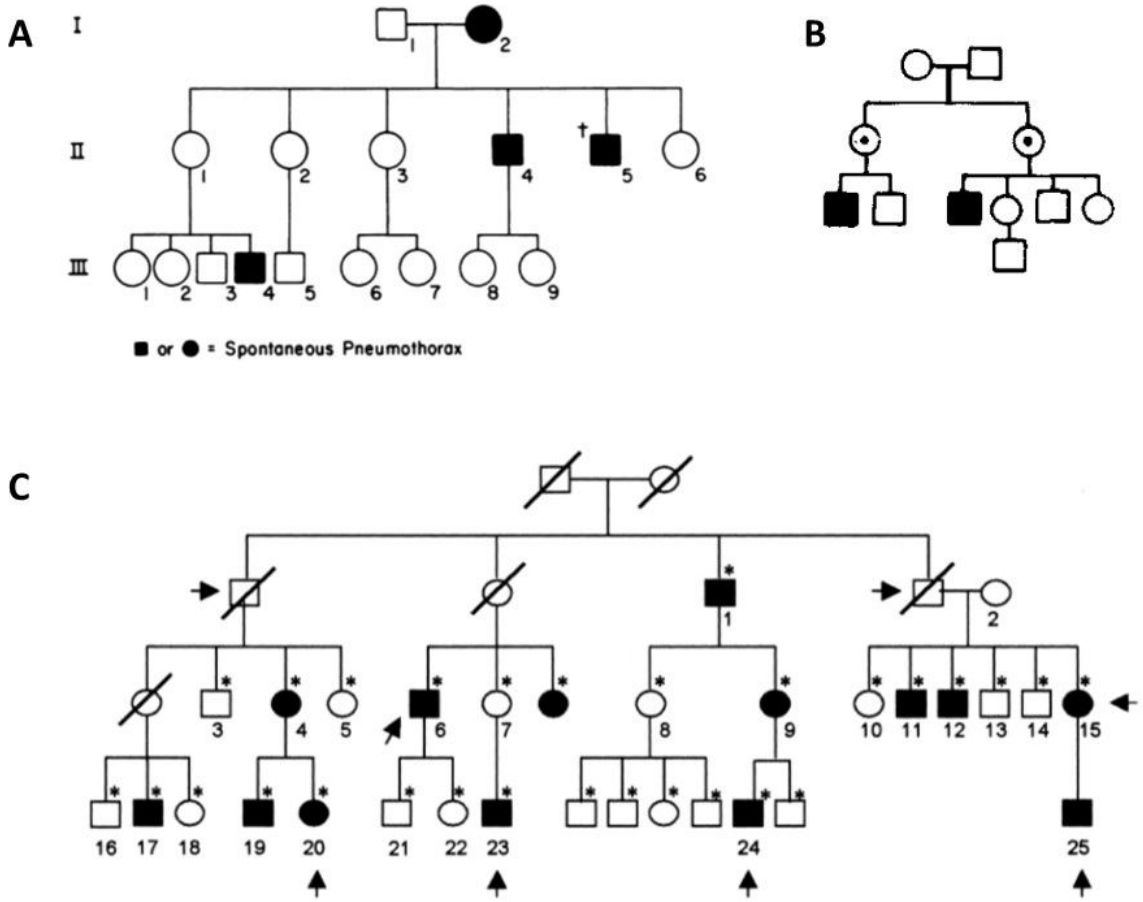

Figure 1. Pedigrees demonstrating familial spontaneous pneumothorax. a. Most pedigrees are consistent with autosomal dominant inheritance with incomplete penetrance. No causal gene reported for this family. Circles, females; squares, males; shaded, pneumothorax. Reproduced from (21). **b.** Some pedigrees are also consistent with X-linked recessive inheritance (versus AD with reduced penetrance in females). No causal gene reported for this family. Dot, obligate carrier. Reproduced from (4) **c.** Family with known *FLCN* mutation. CT lung findings (black shading) are more clearly autosomal dominant than pneumothorax (arrows). Individual 23 has a different bullae phenotype (apical instead of random distribution) and is mutation negative, likely explaining why

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his mother does not have bullae (different cause of pneumothorax in this branch of family). *, CT lung performed; diagonal line, deceased. Reproduced from (26).

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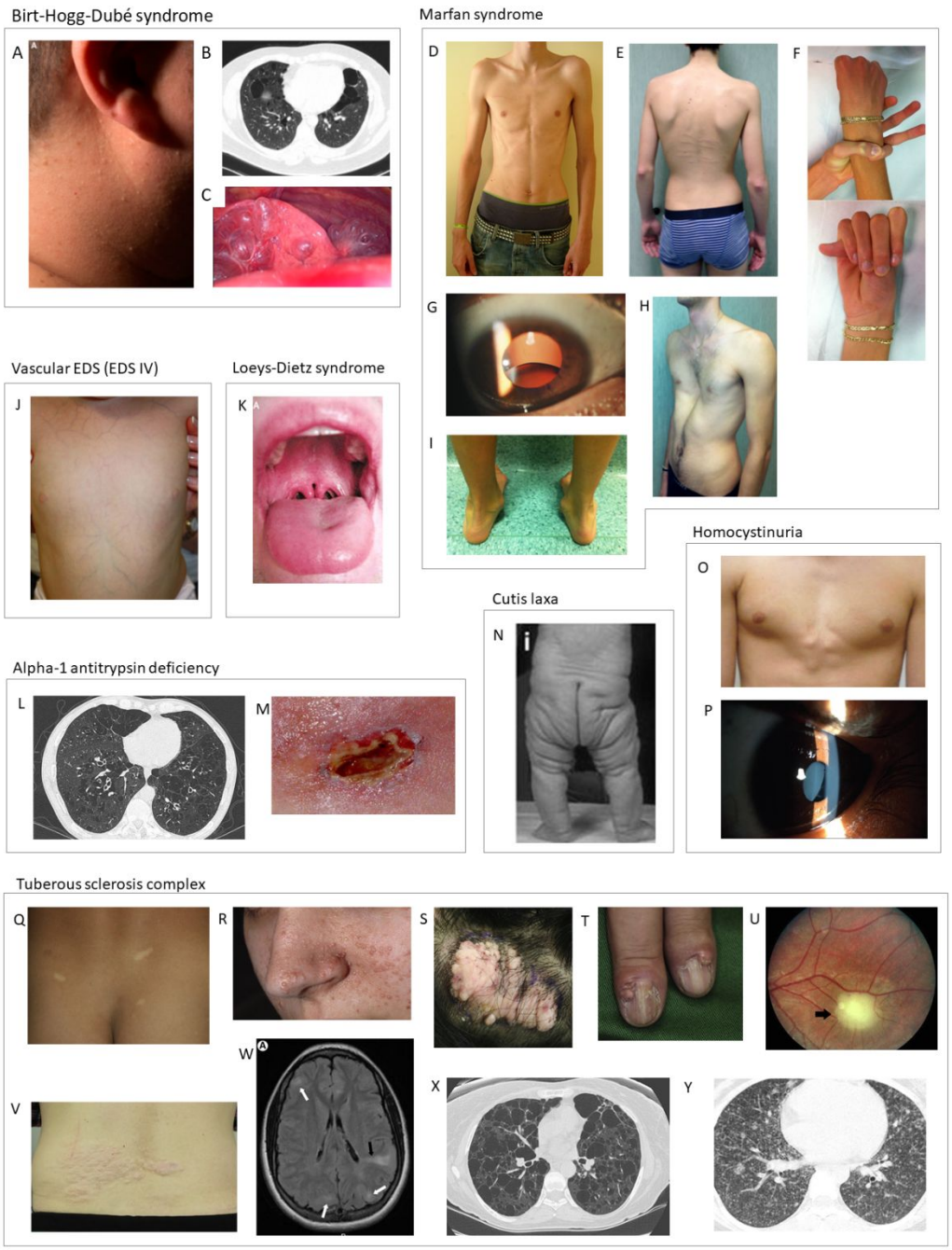

Figure 2. Physical exam findings of pneumothorax-associated syndromes. (a-c) Birt-Hogg-Dubé syndrome (BHDS). **a.** Fibrofolliculomas of the neck (164). **b.** Lung cysts and bullae; extra-apical location is characteristic (164). **c.** Pleural blebs on the surface of the left lower lobe; these can be missed on CT but seen during thoracoscopy/VATS (164). **(d-j)** Marfan syndrome. **d.**

Marfanoid body habitus (90). **e.** Scoliosis, striae, reduced elbow extension (165). **f.** Positive thumb and wrist signs indicating arachnodactyly (165). **g.** Lens dislocation (166). **h.** Pectus excavatum (165). **i.** Hindfoot deformity (165). (**j)** Vascular (type IV) EDS. **j.** Translucent skin on the torso of an infant (167). **(k)** Loeys-Dietz syndrome. **k.** Bifid uvula (168) **(l-m)** Alpha-1-antitrypsin deficiency. **l.** Panlobular emphysema (case courtesy of Dr. Jeremy Jones, Radiopaedia.org, rID:13441). **m.** Panniculitis (169). **(n)** Cutis laxa. **n.** Autosomal recessive cutis laxa IIa (170). **(o-p)** Homocystinuria. **o.** Chest wall deformity (171). **p.** Lens dislocation (172). **(q-y)** Tuberous sclerosis complex. **q.** hypopigmented macules (ash leaf spots) (159). **r.** angiofibromas (159). **s.** fibrous plaques (159). **t.** Ungual fibromas (159). **u.** Retinal hamartoma (159). **v.** Shagreen patch (159). **w.** Cortical dysplasia (tubers, white arrows; radial migration lines, black arrows) (159). **x.** Lymphangioleiomyomatosis (159). **y.** Multifocal micronodular pneumocyte hyperplasia (173). Images are reproduced from the sources cited above.

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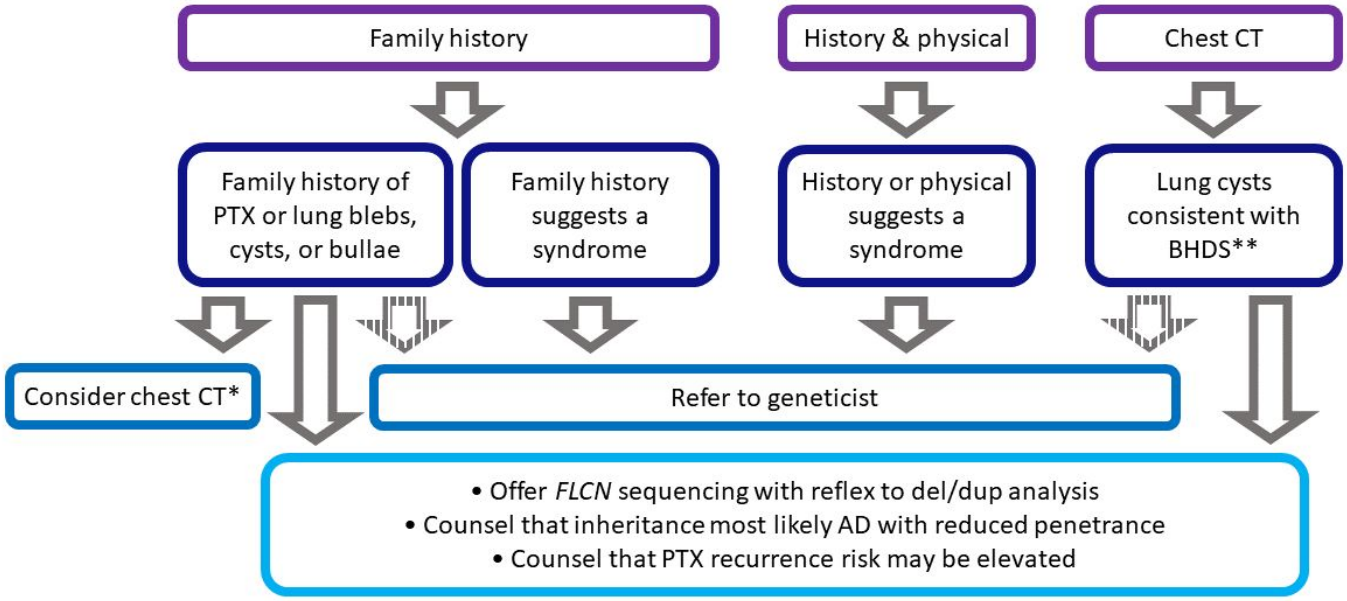

Figure 3. Proposed algorithm for identifying spontaneous pneumothoraces with a genetic basis. Algorithm should be applied to all patients with spontaneous pneumothorax. Dashed arrows are optional, based on the practitioner's comfort. **FLCN* testing in cases of absent family history is still reasonable, so long as a chest CT, if previously obtained, is not inconsistent with BHDS. **Chest CT findings in BHDS include bilateral, multifocal, predominately lower-lobe cysts.

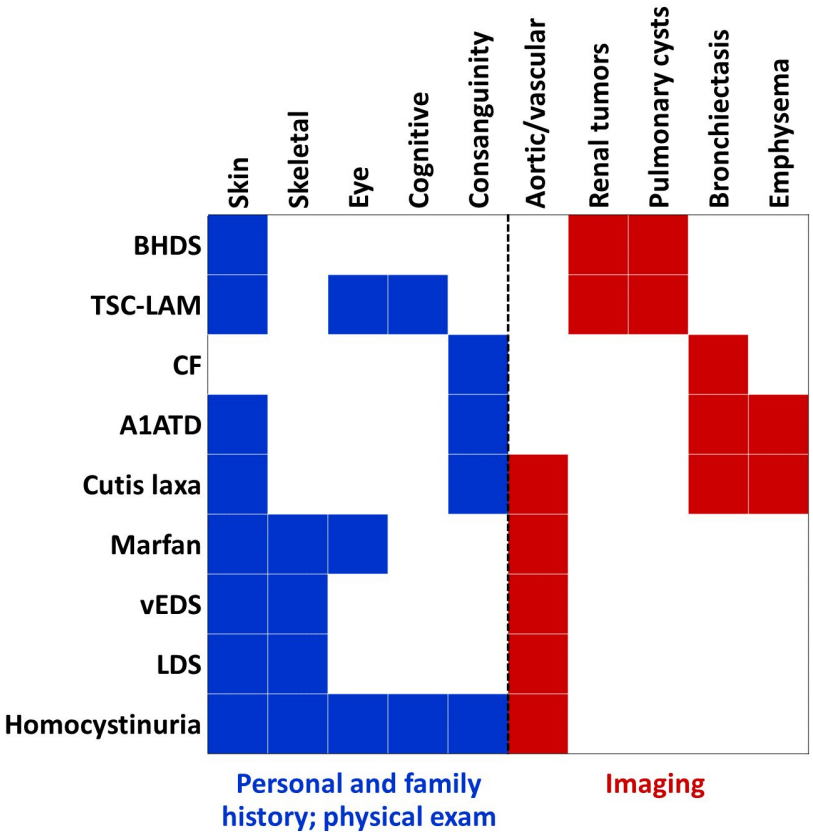

Figure 4. History, physical exam, and imaging findings that raise the possibility of a syndromic cause of pneumothorax. Syndromes predisposing to pneumothorax (X-axis) are intersected with their major features (Y-axis). Personal history/ family history/ physical exam findings are in blue. Imaging findings are in maroon. The skin findings of BHDS are age dependent; thus, skin exams of the parents or even grandparents may at times more informative than for the proband. BHDS, Birt-Hogg-Dubé syndrome; TSC-LAM, lymphangioleiomyomatosis in an individual with tuberous sclerosis; CF, cystic fibrosis; A1ATD, alpha-1-antitrypsin deficiency; vEDS, vascular Ehlers-Danlos syndrome; LDS, Loeys-Dietz syndrome.