Secondary spontaneous pneumothorax as the presenting manifestation of filamin A-associated lung disease

To the Editor:

Spontaneous pneumothorax occurs in 14.1 individuals per 100 000 [1]. Patients with pneumothoraces secondary to chronic lung disease tend to be >50 years old, with males more commonly affected (12.0 *versus* 4.5 per 100 000 population) [1]. Primary spontaneous pneumothorax has a significant genetic predisposition with ∼10% of patients having an affected relative. We previously showed that in 26% of such families, a molecular diagnosis can be made by sequencing directed by clinical and radiological assessment [2]. The most common monogenic cause that accounts for half of all familial pneumothoraces is Birt–Hogg–Dubé syndrome, with tuberous sclerosis, Marfan syndrome, vascular Ehlers–Danlos syndrome and Loeys–Dietz syndrome accounting for a majority of the remaining cases [2–4]. However, in 74% of people with familial pneumothorax, the cause remains unknown suggesting the existence of unidentified risk genes [2].

The study of rare syndromes can shed light on extreme phenotypes including familial pneumothorax, which prompted the creation of the National Health Service (NHS) Rare Disease Collaborative Network in Familial Pneumothorax. Here, we report the case of an adult female who presented with a spontaneous pneumothorax secondary to emphysema on a background of epilepsy and congenital cardiac defects associated with a heterozygous mutation in filamin A (*FLNA*).

In 2020, a 34-year-old woman presented to her local hospital with breathlessness following a viral illness and was found to have a right pneumothorax (figure 1a). Being early in the coronavirus disease 2019 (COVID-19) pandemic, community testing for COVID-19 was not yet available and several days later, her inpatient PCR testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative. A chest drain was placed on admission but a persistent air leak necessitated a semielective video-assisted thoracic surgical bullectomy and pleurectomy. Unenhanced computed tomography (CT) of the thorax demonstrated bilateral apical-predominant emphysema and air trapping (figure 1b). A comparison of CT images from 2012 and 2020 revealed that the lung parenchyma was abnormal almost a decade earlier, although some progression had occurred (figure 1c and d). She had never smoked and had no relevant occupational exposures. Analysis of the surgical sample revealed emphysematous changes, fibrosis, a chronic inflammatory infiltrate, haemorrhage and dystrophic calcification (figure 1e and f). During her admission, her eosinophil count rose to 2.7×10^9 per L, but returned to normal following discharge without corticosteroid treatment. Physiological testing once she had recovered from surgery showed forced expiratory volume in 1 s (FEV_1) 1.37 L (47% predicted), forced vital capacity (FVC) 2.39 L (69% predicted), total lung capacity 3.91 L (85% predicted), residual volume 1.46 L (104% predicted), transfer factor of the lung for carbon monoxide (T_{LCO}) 48.5% predicted; her FEV_1 improved by 14.7% following nebulised salbutamol. During a 6-min walk of 560 m, she desaturated from 99% to 87%. An echocardiogram revealed no evidence of pulmonary hypertension. 2 years later, she suffered a contralateral recurrent pneumothorax requiring further surgery. When reviewed in the clinic on recovery, circulating α_1-antitrypsin levels were low–normal at 1.0 g·L^{-1} with a Pi*MS phenotype, a level and phenotype not normally associated with lung disease [5]. 4 years after presentation, she remained active and in full employment. Her primary symptom was of breathlessness on climbing stairs. Her spirometry showed FEV_1 1.33 L (47% predicted), FVC 2.08 L (60% predicted) and T_{LCO} 44.3% predicted.

Her past medical history was complex. She had been diagnosed with a patent foramen ovale and required surgical ligation of a persistent ductus arteriosus aged 4 years (figure 1g). Available imaging between the
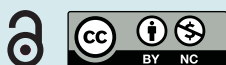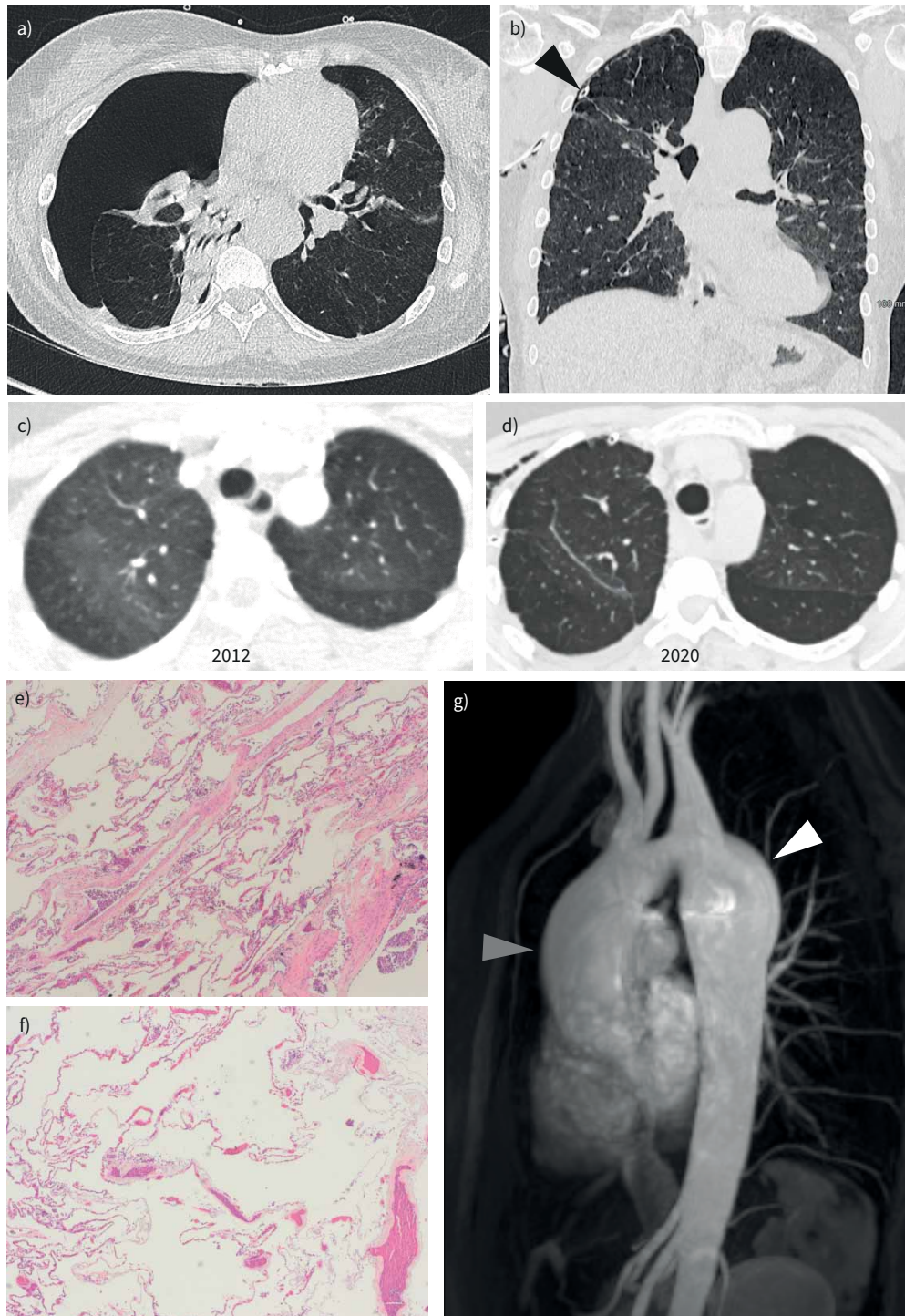
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Secondary pneumothorax due to early-onset emphysema can be a presenting feature of filamin A mutation. https://bit.ly/3ycAeCs

FIGURE 1 Filamin A (*FLNA*) loss-of-function. a) Single axial computed tomography (CT) slice of the lower chest shows large right pneumothorax with shift of the mediastinal structures to the left and collapse of the right lower lobe. b) Coronal reformat of unenhanced CT chest after drain insertion (arrowhead) with near complete reinflation of the right lung. CT shows bilateral apical predominant emphysema and lobular areas of reduced attenuation and hypovascularity, with overinflation of secondary pulmonary lobules most in keeping with small airways obstruction. c) CT from 2012 performed for assessment of the aorta and d) 2020 showing a reduction in density of the lung parenchyma with progressive overinflation and emphysema in the lung apices. e) Emphysematous lung parenchyma. Mesothelial proliferation near the surface in proximity of bulla. Magnification: 100×. f) Congested vessels. Magnification: 100×. g) Maximum intensity project magnetic resonance image of the thoracic aorta demonstrates mild dilatation of the ascending aorta up to 36 mm diameter (grey arrowhead) and of the distal arch/proximal descending thoracic aorta up to 42 mm diameter (white arrowhead). Normal aortic diameter would be 20–30 mm. Incidental anomalous retro-oesophageal course of the right subclavian and common origin of the brachiocephalic artery and left common carotid arteries.

ages of 27 and 34 years showed aortic dilation without progression. She developed complex focal and secondary generalised seizures aged 7 years and magnetic resonance imaging of her brain revealed periventricular nodular heterotopia (PVNH). There was no family history of neurodevelopmental delay, or cardiac or lung disease. Genetic testing in adulthood confirmed that she was heterozygous for a novel pathogenic *FLNA* frameshift variant (c.6913delT, p.Tyr2305fs). She had borderline von Willebrand disease, thrombocytopenia, menorrhagia and borderline anaemia. There was no family history of pneumothorax or epilepsy. Owing to her complex phenotype, she was referred to our Pneumothorax Genetics service. Subsequent family follow up showed that her healthy sister had a normal genotype. Parental testing was not possible.

FLNA is an X-linked gene implicated in a wide spectrum of connective tissue, skeletal, cardiovascular and gastrointestinal disorders [6]. Pulmonary manifestations of *FLNA* loss-of-function variants are thought to manifest during early childhood and include congenital emphysema, bronchopulmonary dysplasia, pulmonary hypertension and interstitial lung disease [7, 8]. Recently, a small number of female patients have been diagnosed with *FLNA*-associated emphysema in adulthood [9]. Our case is the first in which *FLNA*-associated emphysematous lung changes have presented with spontaneous pneumothorax.

Filamin A is an actin-crosslinking protein with roles in cell division, motility, adhesion and polarisation that account for its importance in vessel wall integrity and platelet function. *FLNA* gain-of-function variants cause X-linked otopalatodigital syndrome spectrum disorders, which are primarily skeletal dysplasias that affect males more severely [6]. In contrast, loss-of-function mutations often manifest as seizures and are associated with PVNH, a congenital brain anomaly characterised by ectopic accumulations of neurons that fail to migrate to the cerebral cortex during development [10]. Most affected males die *in utero* or the perinatal period, while many carrier females have normal or only mildly impaired psychomotor development. Due to the variable phenotype and rarity of *FLNA* loss-of-function mutations, diagnosis is frequently delayed, with the causative *FLNA* variant being identified many years after the onset of seizures [10]. Other complications associated with *FLNA* loss-of-function mutations include atrial and ventricular septal cardiac defects, persistence of the ductus arteriosus, dilatation and rupture of the thoracic aorta, coagulopathy and gastric motility problems including chronic intestinal pseudo-obstruction. Clinical signs that may be present on examination include joint hypermobility and shortening of the distal phalanges.

Severe congenital lung disease comprising pulmonary emphysema, septal thickening and pruning of the pulmonary vasculature were described in 26 cases of heterozygous children [7] (and references therein). Pulmonary hypertension has been reported in affected individuals and several children have required lung transplantation [8]. In 2019, the first adult to be diagnosed as a result of *FLNA*-associated lung disease was reported [11]. The 22-year-old female never-smoker had been investigated as a child for repeated respiratory illnesses, and found to have congenital lobar emphysema, mild pulmonary hypertension and a small patent ductus arteriosus. At 6 years of age, she had suffered a spontaneous pneumothorax. In adulthood, when investigated for progressive dyspnoea, a CT showed severe confluent emphysema and multiple apical bullae. In 2021, two further cases, a mother and daughter, were reported with *FLNA* loss-of-function-associated emphysema diagnosed in adulthood [12]. The 32-year-old proband had diffuse centrilobular emphysema despite a trivial smoking history, while her 71-year-old never-smoker mother had developed "idiopathic emphysema" in her forties. Both mother and daughter had PVNH and recurrent seizures.

Our case is the first report of an adult female with asymptomatic *FLNA*-associated lung disease diagnosed as a result of a spontaneous pneumothorax. *FLNA*-associated lung disease should therefore be considered as a rare cause of pneumothorax in women who present with a background of emphysema with or without a history of epilepsy and congenital heart disease. In addition to being at risk of progressive lung disease, these women are at risk of valvular heart disease and progressive aortic dilatation [13]. We therefore recommend that all women and children found to have loss-of function *FLNA* mutations are screened for the associated respiratory and aortic manifestations. Genetic counselling should be offered to carrier women, whose daughters will each have a one in two chance of being heterozygous carriers and whose liveborn sons are expected to be unaffected due to early loss of affected male pregnancies. Importantly, because women and girls with *FLNA* loss-of-function mutations can be asymptomatic even with PVNH or *FLNA*-associated lung disease, we recommend that carrier testing should be offered to all at-risk female relatives. A prolonged diagnostic odyssey prior to genetic testing is a recurring theme in the lived experiences of patients with rare genetic disorders [14]. In this light, easy access to specialistic diagnostic support, such as that offered by the NHS Rare Disease Collaborative Network in Familial Pneumothorax, and a readiness of generalists to make use of this can help to speed diagnosis.

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