Supplementary text

Patient ascertainment - The Cambridge Pneumothorax Clinic is a specialist service established in 2008 for the assessment of pneumothorax in a large teaching hospital in the south east of England. The practice in our hospital is that all patients presenting with pneumothorax, whether admitted or treated conservatively as outpatients, are referred to the Pneumothorax Clinic to be seen at 2-weeks (or 6-weeks if referred for surgery during their admission). Patients with traumatic pneumothorax are also referred to the Pneumothorax Clinic, but were excluded from this study. Each patient underwent standardised clinical assessment to identify syndromic causes of pneumothorax including detailed family history and physical examination such as dermatological and skeletal assessment, as we have described elsewhere (1-3). In most cases a positive family history related to the presence of pneumothorax in first- or second-degree family members (49 first-degree relatives: 68.1% of 72, 7 children, 27 parents, 15 siblings; 19 second-degree relatives: 26.3% of 72, 14 uncles/aunts, 5 grandparents), but a well-documented case in more distant relatives would also be considered significant (4 third-degree relatives: 5.6%, 2 cousins, 2 great-uncles). Low dose high-resolution thoracic computed tomographic (CT) imaging and transthoracic echocardiography were performed in certain circumstances: following pneumothorax recurrence; or all female patients; or patients whose history or clinical examination suggested a specific syndromic cause. All cases where a syndromic cause was considered possible were reviewed at a pneumothorax genetics MDT comprising respiratory physicians, clinical geneticists, and thoracic radiologists.

Data analysis - Data are presented as absolute values, percentages, mean ± standard error or median (interquartile rage). Survival data were used to generate Kaplan-Meier curves using SPSS 26 (SPSS, Chicago, IL, USA) to compare between groups including, but not restricted to: sex, age, family history, and treatment received, using the log-rank test. Survival tables provide cumulative survival and standard error; life tables provide number exposed to risk at each timepoint. P values <0.05 is considered statistically significant.

100,000 Genomes Project – Whole genome sequencing (WGS) was performed on eligible participants within the 100,000 Genomes Project (4, 5). Briefly, inclusion required a proband to have suffered a spontaneous pneumothorax and have at least one affected relative. Clinical assessment was performed and prospective participants excluded if found to suffer from a known syndromic cause. WGS data were screened for likely pathological variants; those variants with >0.005 frequency in the Genome Aggregation Consortium database (gnomAD (6)) were disregarded. Next, variants predicted to be benign by either SIFT or PolyPhen bioinformatics were excluded. Of the remaining variants, only those in protein coding-sequences were analysed further. Those found to occur in three or more individuals were identified and assessed for appropriate inheritance. Comparison was made with public databases, including gnomAD (6), and with a cohort of 8854 “control” individuals recruited to the 100,000 Genomes Project for non-syndromic cases of cancer. Phenotypic information from recruitment questionnaires, past medical history, from NHS Hospital Episode Statistics, were scrutinised.

Clinical assessment and standard operating procedures:

All new patients are assessed using a standard clinic *pro forma*:

History

Presentation

Past medical history
Pneumothorax
Hernias
Dislocation
Orthodontics
Eyes
Vascular

Family history
Pneumothorax
Hernias
Dislocation
Orthodontics
Eyes
Vascular
Renal malignancy

Social history
Tobacco/Cannabis

Examination
Height, weight, BMI
Arm span (arm / height ratio)
Uvula (e.g., bifid)
Dentition (e.g., crowding, micrognathia)
Palate (e.g., high arched)
Face (e.g., hypertelorism.)
Skin (e.g., striae, lesions)
Murdoch Walker (wrist) sign
Steinberg's (thumb) sign
Beighton score
Hind foot abnormalities
Heart sounds

Investigations

Low dose thoracic CT scan and transthoracic echocardiogram requested for:

- All patients with recurrent pneumothoraces or slow-to-resolve cases
- All patients with a family history of pneumothorax
- All female patients (may need to be delayed if pregnant)
- When clinical features are identified raising suspicion of a syndromic cause, e.g., skin lesions of Birt-Hogg-Dubé syndrome or Tuberous Sclerosis, arachnodactyly

Pneumothorax Genetics MDT format

To be quorate the following must be present:

- Respiratory consultant physician
- Clinical genetics consultant
- Thoracic radiology consultant

MDT outcomes include

- Syndromic cause unlikely – no further action
- Syndromic cause likely – targeted genetic testing arranged
- Syndromic cause possible – further investigation and/or review in Clinical Genetics clinic arranged

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Supplementary Legend:

Supplementary Figure S1. (A) Kaplan Meier curve of survival among all male (blue) and female (red) patients. (B) Kaplan Meier curve of pneumothorax recurrence in all male (blue) and female (red) patients. P value calculated by log-rank test. (C) Kaplan Meier curve of pneumothorax recurrence in all patients; no family history of pneumothorax “sporadic” (blue), familial pneumothorax (red). P value calculated by log-rank test.

Table S1. Clinic patient characteristics

Patients		N = 492	5-year recurrence (SEM)
Male sex – N (%)		379 (77.0% of 492)	
Median age (range) -- year		29.2 (12-89)	38.6% (2.5%)
	Males	27.6 (12-89)	36.6% (2.9%)
	Female	38.7 (16-84)	45.1% (5.3%)
Family history – N (%)		72 (14.6% of 492)	49.6% (6.6%)
	Males	53 (14.0% of 379 males)	43.7% (7.5%)
	Female	19 (16.8% of 113 females)	63.5% (12.4%)
Height – mean (SD) – cm			
	Males	180 (8) N = 205	
	Females	169 (7) N = 54	
Weight – mean (SD) – kg			
	Males	67.2 (11.8) N = 125	
	Females	58.7 (16.2) N = 31	
BMI – mean (SD)			
	Males	20.9 (3.5) N = 125	
	Females	21.5 (3.9) N = 31	
Arm span – mean (SD) - cm			
	Males	184 (8) N = 191	
	Females	173 (9) N = 50	
Arm span: height ratio			
	Males	1.03 (0.03) N = 188	
	Females	1.02 (0.03) N = 50	
Smoking – N (%)			
	Never	213 (47.0%)	43.8% (3.8%)
	Tobacco	Ever 151 (30.7%); current 79 (16.0%)	34.2% (4.3%)
	Cannabis	Ever 104 (21.1); current 85 (17.2%)	35.5% (5.5%)
	Missing data	6 (1.2%)	
Recurrences		N = 170	
Male – N (%)		130 (76.5% of 170)	
Ipsilateral – N (%)		120 (70.5% of 170)	

Table S2. Demographics of familial pneumothorax patients recruited to 100,000 Genomes Project

Patients		N = 33
Male sex – N (%)		21 (63.6% of 33)
Median age (range) -- year		29.0 (4-76)
	Males	24.5 (4-76)
	Female	48 (23-57)
Median age at first pneumothorax (range)		21.0 (4-76)
	Males	24.5 (4-76)
	Female	48.0 (23-57)
Ethnicity – N (%)		
	White	28 (85%)
	Black	2 (6%)
	Not stated	3 (9%)

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