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Combining clinical, radiological and genetic approaches to pneumothorax management

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ABSTRACT

Familial spontaneous pneumothorax (FSP) accounts for 10% of primary spontaneous pneumothoraces. Appropriate investigation of FSP enables early diagnosis of serious monogenic diseases and the practice of precision medicine. Here, we show that a pneumothorax genetics multidisciplinary team (MDT) can efficiently diagnose a range of syndromic causes of FSP. A sizeable group (73.6%) of clinically unclassifiable FSPs remains. Using whole genome sequencing we demonstrate that most of these cases are not known monogenic disorders. Therefore, clinico-radiological assessment by an MDT has high sensitivity for currently known clinically important monogenic causes of FSP, which has relevance for the design of efficient pneumothorax services.

INTRODUCTION

Primary spontaneous pneumothorax (PSP) affects 1 in 10 000 people with 10% having affected relatives, so-called familial spontaneous pneumothorax (FSP).[1 2] FSPs comprise a diverse group of disorders with extrapulmonary manifestations ranging from renal cancer to arterial dissection.[1 2] We previously proposed FSPs be classified into those conditions with aberrant extracellular matrix or defective tumour-suppressor pathways.[1 2] A third group of unclassifiable FSPs currently defies diagnosis, but it is unclear if these represent *formes frustes* of known syndromes or are as yet undescribed disorders.[3] Our pneumothorax clinic provided a resource of well-phenotyped individuals who have been assessed by a respiratory-genetics multidisciplinary team (MDT) over a 12-year period. We set out to analyse this cohort, combined with additional whole genome sequencing (WGS) data from the 100 000 Genomes Project, to assess the efficiency of existing clinico-radiological pathways for the diagnosis of FSP.

METHODS

Between 2008 and 2020, 492 patients were recruited consecutively from our pneumothorax clinic. Familial cases were reviewed by a pneumothorax genetics MDT comprising respiratory physicians, clinical geneticists, and thoracic radiologists. Detailed methods are provided in online supplemental file 1.

RESULTS

Local demographics biased our cohort towards younger individuals with few cases of secondary spontaneous pneumothorax (SSP) (online supplemental

table S1; figure 1A). Overall, 5-year recurrence was 38.6%±2.5%, but this rose to 44.5%±3.4% by 10 years (figure 1B). Five-year recurrence for those 50 years or younger was 41.9%±2.8%, but only 20.7%±4.8% for those >50 years, perhaps owing to higher mortality (39.3%±5.6% at 5 years for >50 years vs 1.0%±0.6% for ≤50 years; figure 1C,D). The comparatively high overall recurrence rate seen in our series may, therefore, reflect the predominance of younger patients. The sex ratio was 3:1 male:female, with no mortality difference between sexes (online supplemental table S1; figure 1E and online supplemental figure S1A). However, 10-year recurrence was significantly higher for females (63.1%±9.4% vs 41.3%±3.5%, p=0.041; online supplemental figure S1B). This persisted when patients >50 years were excluded (p=0.017; figure 1F). Lymphangioleiomyomatosis (LAM) was diagnosed in two women (1.8% of 113 female cases), while thoracic endometriosis (catamenial pneumothorax) was diagnosed in 9 (7.9% of female cases). Both patients with LAM suffered recurrences, as did 7 (77.8%) of the women with catamenial pneumothorax. These conditions may, therefore, contribute to the increased risk of recurrence we observed in women.

A positive family history of pneumothorax was elicited in 14.6% of patients (14.0% of males, 16.8% of females) and was associated with a significantly increased chance of recurrence (figure 2A,B; online supplemental table S1). Overall, 5-year FSP recurrence was 49.6%±6.6% vs 36.7%±2.7% for sporadic pneumothoraces (p=0.034; figure 2A and online supplemental figure S1C). For patients 50 years or younger, 5-year FSP recurrence was 54.7%±7.1% vs 36.2%±2.9% of sporadic pneumothoraces (p=0.025; figure 2B).

Targeted genetic testing guided by a pneumothorax MDT yielded a genetic diagnosis in 26.4% (19/72) of FSP cases (figure 2C). Birt-Hogg-Dubé syndrome was the most common, accounting for 47% of genetic diagnoses (2% of all 492 patients), followed by Marfan (21%), vascular Ehlers-Danlos (11%) and Loeys-Dietz syndromes (11%). Alpha1-antitrypsin deficiency and tuberous sclerosis were more uncommon (5%). We did not observe significant changes in rates of diagnosis over time.

A majority of individuals with FSP (73.6%) failed to fulfil the diagnostic criteria for known genetic disorders. To examine this further, 33 individuals with unclassifiable FSP (27 probands, 6 affected relatives; 64% male) were recruited to the 100 000 Genomes Project[4 5] (online supplemental table S2).
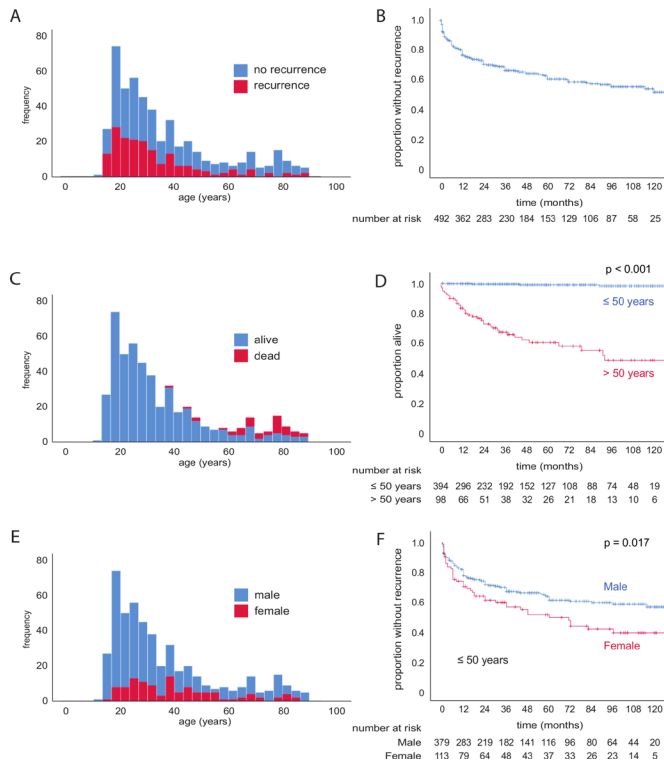
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Figure 1 Pneumothorax clinic patent characteristics, survival and pneumothorax recurrence. (A) Histogram of patients; no recurrence (blue), recurrence (red). (B) Kaplan-Meier curve and number at risk table of pneumothorax recurrence. (C) Histogram of patients, alive (blue), died (red). (D) Kaplan-Meier curve and number at risk table of survival; patients 50 years of age or younger (blue), over 50 years old (red). P value calculated by log-rank test. (E) Histogram of patients; male (blue), female (red). (F) Kaplan-Meier curve and number at risk table of pneumothorax recurrence in patients 50 years of age or younger; male (blue), female (red). P value calculated by log-rank test.

Figure 2 Familial spontaneous pneumothorax patient characteristics. (A) Histogram of patients; no family history of pneumothorax (blue), familial pneumothorax (red). (B) Kaplan-Meier curve of pneumothorax recurrence in patients 50 years of age or younger; no family history of pneumothorax 'sporadic' (blue), familial pneumothorax (red). P value calculated by log-rank test. (C) Relative proportion of monogenic disorder diagnoses made. (D) Thoracic CT scan of patient identified to have Birt-Hogg-Dubé by whole genome sequencing. noted small cyst, one of two that were present. TSC, tuberous sclerosis complex.

The crowdsourcing tool PanelApp was used to generate a pneumothorax gene panel. Candidate genes were scored by members of the Genomics England online community and ten genes received sufficient endorsement to be declared 'green genes' and included in the pneumothorax panel (table 1). WGS data from the 33 unclassifiable FSP patients were annotated for pathogenicity based on variant segregation within families, frequency in control populations, effect on protein coding, and mode of inheritance. 'Tier 1' variants were defined as high-impact variants (eg, likely loss of function) and de novo moderate-impact variants (eg, missense) in this panel. A single tier 1 variant was identified in the genome of one patient: a previously reported pathological variant of *FLCN* (c.1062+2T>G) indicating a diagnosis of Birt-Hogg-Dubé syndrome. The proband had no cutaneous features of Birt-Hogg-Dubé syndrome and no family history of renal malignancy. The thoracic CT was rereviewed and, in hindsight, noted to show two small cystic lesions (figure 2D). No other tier 1 pathogenic variants were identified indicating that clinico-radiological assessment had been highly successful in excluding known genetic causes of FSP (sensitivity 96%, 26/27 probands).

DISCUSSION

In our cohort of 492 patients with pneumothorax, 14.6% had FSP. Of these, 26.4% were diagnosed clinically with a monogenic disorder, most commo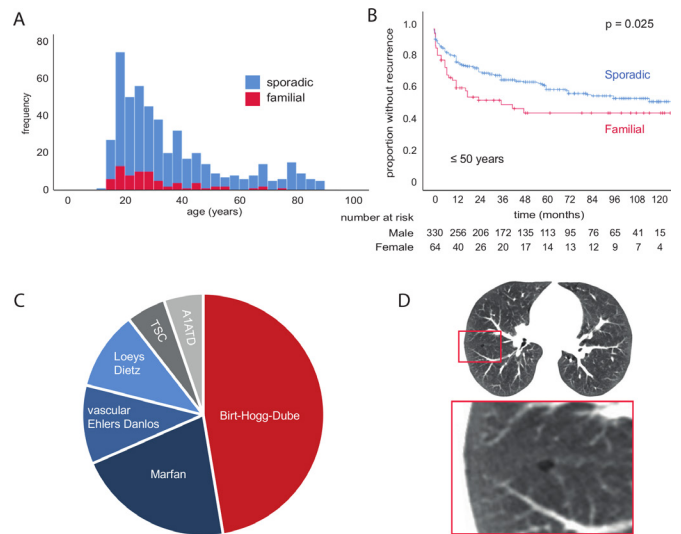nly Birt-Hogg-Dubé syndrome. Previous studies in Chinese and European populations suggested that up to 10% of pneumothoraces are due to *FLCN* mutations.[6 7] In our cohort, the overall proportion was much less at 9 of 492 (2%). To our knowledge, this is the first report of an association between FSP and increased chance of recurrence compared with sporadic pneumothorax. Female sex was also associated with an increased risk of recurrence.

WGS of 33 individuals with unclassifiable FSP revealed a single tier 1 variant indicating that clinico-radiological assessment has high sensitivity for known FSP syndromes, consequently the

Table 1 PanelApp familial pneumothorax gene panel

Gene	Mode of inheritance	Details	OMIM
COL3A1	Monoalleilic, autosomal	Ehlers-Danlos syndrome, vascular type	130 050
FBN1	Monoalleilic, autosomal	Marfan syndrome	154 700
FLCN	Monoalleilic, autosomal	Primary Spontaneous Pneumothorax	173 600
		Birt-Hogg-Dubé Syndrome	135 150
SERPINA1	Biallelic, autosomal	Alpha-1-antrypsin deficiency	613 490
TGFBR1	Monoalleilic, autosomal	Loeys-Dietz syndrome type 1	609 192
TGFBR2	Monoalleilic, autosomal	Loeys-Dietz syndrome type 2	610 168
TGFB2	Monoalleilic, autosomal	Loeys-Dietz syndrome type 4	614 816
TGFB3	Monoalleilic, autosomal	Loeys-Dietz syndrome type 5	615 582
TSC1	Monoalleilic, autosomal	Tuberous sclerosis 1	191 100
TSC2	Monoalleilic, autosomal	Tuberous sclerosis 2	613 254

Familial primary spontaneous pneumothorax 'green gene' list generated using NHS Genomic England PanelApp crowdsourcing tool: panel V.2.20 https://panelapp.genomicsengland.co.uk/panels/105/. https://omim.org/.
COL3A1, collagen, type III, alpha-1; FBN1, fibrillin 1; FLCN, folliculin; NHS, National Health Service; OMIM, Online Mendelian Inheritance in Man; SERPINA1, alpha-1-antitrypsin; TGFBR1, transforming growth factor-beta receptor, type I; TSC1, tuberous sclerosis complex subunit 1.

majority of genetic risk in FSP remains unexplained. A previous genome-wide association study (GWAS) reported an association between PSP and the single nucleotide polymorphism (SNP) rs4733649 in the *SLC6A1* gene.[8] None of the 33 individuals nor 8854 sequenced non-pneumothorax controls had this SNP so we cannot confirm the association (not shown). COPD is a cause of SSP. Deficiency of α_1-antitrypsin is its most common monogenic cause but accounts for under 2% of prevalent cases.[9] GWASs have implicated other genes in COPD (*HHIP, CHRNA5, HTR4, FAM13A, RIN3, TGFB2, GSTCD-NPNT, CYP2A6* and *IL27-CCDC101*),[10] but no pathogenic variants were identified in these genes in our cases.

An important limitation of our study is its geographical restriction to one centre. National analysis of FSP will be necessary to determine its population prevalence.

In summary, assessment by a pneumothorax MDT has high sensitivity for diagnosis of monogenic causes of FSP by enabling targeted genetic testing. We find FSP increases the risk of recurrence compared with sporadic pneumothoraces. A substantial proportion of the genetic risk for FSP remains unaccounted for, but ongoing analysis of the 100 000 Genomes dataset will address this.

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