Family history of pulmonary fibrosis impacts prognosis in patients with sarcoidosis

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To the Editor:

Sarcoidosis is a multisystem granulomatous inflammatory disorder of unknown aetiology which preferentially affects the lungs and lymph nodes, and is one of the most common forms of interstitial lung disease (ILD). Disease course in sarcoidosis is heterogeneous, varying from benign and self-resolving to progressive and lethal, and the extent of pulmonary fibrosis (PF) has been identified as a predictor of mortality [1]. For patients with chronic ILD, a self-reported family history of ILD was shown to predict a shorter survival [2]. However, as sarcoidosis patients have never been included in such analyses, the impact of having a family member with PF in this condition remains undocumented. In this study, we determined the disease phenotype of sarcoidosis patients with a self-reported family history of PF. Furthermore, genetic factors associated with a risk for familial pulmonary fibrosis (FPF) [3] were evaluated.

Sarcoidosis patients reporting one or more relatives with PF in a family health questionnaire [4] or the patient's medical record were retrospectively identified in the St Antonius Hospital in Nieuwegein, the Netherlands, between January 1999 and March 2022 (figure 1a). Diagnosis of sarcoidosis was based on the World Association for Sarcoidosis and Other Granulomatous Disorders guidelines [5] and parenchymal usual interstitial pneumonia (UIP) classification was based on the latest American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociación Latinoamericana de Tórax idiopathic pulmonary fibrosis (IPF) guideline [6] after reviewal by an expert thoracic radiologist. Whole exome sequencing, quantitative PCR telomere length assays and *MUC5B* rs35705950 genotyping were performed as previously described [7, 8] with minor alterations. The study was approved by the institute's medical ethics committee (R05–08A) and all patients signed an informed consent. Data are expressed as median and interquartile range. A p-value <0.05 was considered significant.

We identified 18 sarcoidosis patients reporting one (n=13 first degree and n=3 second degree) or more (n=2, all first degree) family members with PF (further details can be found in figure 1b). Disease duration prior to presentation at the St Antonius Hospital was 1.8 (0.3–6.7) years. Pulmonary involvement (n=15) and thoracic adenopathies (n=17) were the most frequently reported locations, followed by neurological (n=4), dermatological (n=2), ophthalmological (n=2) and cardiac (n=1) localisations. At presentation, 11 out of 18 (61%) had fibrosis on high-resolution computed tomography, in the form of reticulations (n=9), (traction) bronchiectasis (n=10), or honeycombing (n=4). Ground glass opacities were observed in three, consolidations in six and pulmonary nodules in eight patients. On follow-up thoracic imaging (n=15 patients, among which 10 showed fibrosis on computed tomography upon presentation), fibrosis increased in eight patients and remained stable in two. Overall, initial UIP (n=3) or probable UIP (n=1) patterns remained preserved over time, while two patients with a pattern suggesting an alternative diagnosis evolved towards an indeterminate for UIP pattern.

Lung function tests were available for 16 patients (figure 1c and d) and showed that 43% had a decreased forced vital capacity (FVC) (figure 1c). After a median lung function test follow-up of 3.7 (1.0–10.4) years, six patients experienced an FVC decline of ⩾5% and two a decrease of diffusion capacity of the lung for carbon monoxide (D_{LCO}) of ⩾10% over a one-year period (figure 1c and d).

Shareable abstract (@ERSpublications)
Having a family member with pulmonary fibrosis (PF) impacts the prognosis of sarcoidosis patients, as the majority of patients reporting at least one relative with PF present fibrotic characteristics and one-third develop a progressive phenotype https://bit.ly/40KC7Cr

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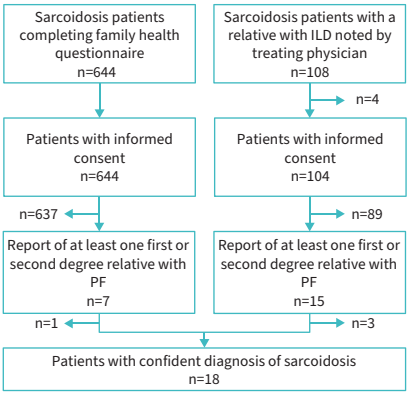
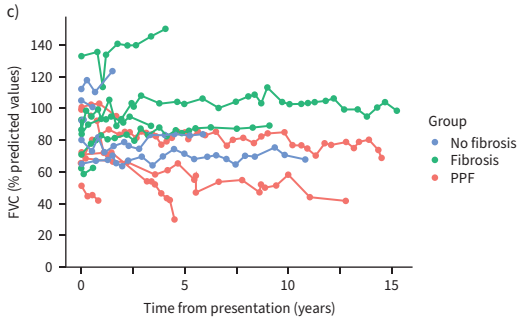
a)



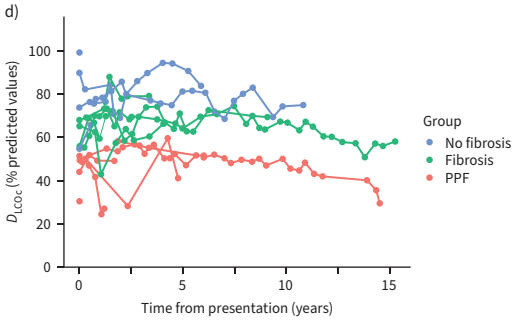
b)

	Sarcoidosis patients with ≥1 relative with PF
Patients (n)	18
Age at diagnosis, years (median (IQR))	51 (39–60)
Age at presentation St Antonius Hospital, years (median (IQR))	57 (43–65)
Sex, male (n(%))	9 (50)
Smoking status, ever/never (n(%))[#]	9 (53)/8 (47)
Sarcoidosis diagnosis with histology (n(%))	15 (83)
Median FVC at presentation, % predicted (median (IQR))	82 (67–100)
Median D_{LCOc} at presentation, % predicted (median (IQR))[¶]	56 (49–69)
Presence of fibrosis on HRCT at presentation (n(%))	11 (61)
HRCT pattern in fibrotic patients, UIP/pUIP/indUIP/alt (n(%))	3 (27)/1 (9)/1 (9)/6 (55)
Extent of fibrosis, % of total parenchyma (median (IQR))	10 (5–20)
Patients fulfilling PPF criteria (n(%))[+,§,f]	6 (35)

c)



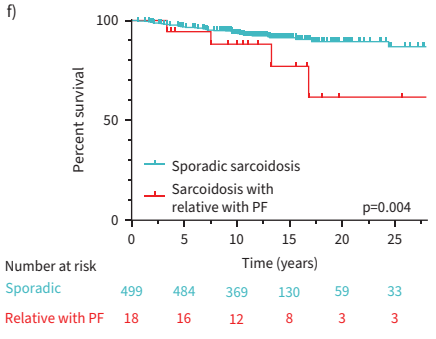
d)



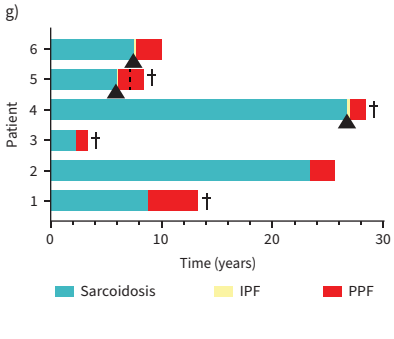
e)

	whole cohort, n=18				
	progressive, n=6	not progressive, n=12		p-value between all groups	p-value PPF vs not progressive
	PPF	Fibrosis	No fibrosis		
Patients (n)	6	5	7		
Age at diagnosis (median (IQR))	54 (40–61)	53 (31–61)	48 (39–59)	ns	ns
Sex, male/female (n)	2/4	3/2	4/3	ns	ns
Smoking status, ever/never (%)	40/60[#]	80/20	43/57	ns	ns
Live status, died/lung transplantation/alive (n)	4/1/2	1/0/4	0/0/7	0.06[##]	0.02
HRCT pattern in fibrotic patients, UIP/pUIP/indUIP/alt (n)	3/1/0/2	0/0/1/4	NA		
Median FVC at presentation (% predicted value (IQR))	72 (62–100)	84 (66–113)	92 (72–109)	ns	ns
Median D_{LCOc} at presentation (% predicted value (IQR))[¶]	49 (40–53)	60 (56–67)	82 (59–97)	0.03[##]	0.01
MUC5B T-allele frequency	0.50	0.10	0.21	ns	0.05
TL percentile for age, >10th/<10th (n)	3/3	2/3	6/1	ns	ns
Rare TRG variant, patient/relative (n)	2/1	0/2	0/1	NA	NA

f)



g)



CT	TL	*MUC5B*	TRG
pUIP	<p10	TT	No
Alt	>p10	GT	*RTEL1*
UIP	<p10	GG	*TERT*
UIP	>p10	GT	No
Alt	<p10	GT	No
UIP	>p10	GT	No

FIGURE 1 Characteristics of sarcoidosis patients reporting at least one relative with PF. a) Flowchart of patients selection. b) Clinical characteristics of patients. c and d) Evolution of FVC (c) and D_{LCO}c (d) over time in the cohort after presentation at the St Antonius Hospital according to fibrotic status and progressiveness. e) Characteristics of patients stratified by clinical subtype: progressive patients fulfilling PPF criteria, non-progressive patients with fibrosis and without fibrosis. Patients were compared based on group attribution and progressive status. Live status (alive/dead) was lower in the PPF group compared to the non-fibrotic group in the separate group analysis (p=0.06) and compared to the pooled non-progressive

group. D_{LCO}c at presentation at the St Antonius Hospital differed significantly between groups and was lower in the PPF group compared to the non-fibrotic group in the separate group analysis and compared to the pooled non-progressive group. *MUC5B* rs35705950 minor T allele frequency was increased in PPF patients when compared to pooled non-progressive patients (p=0.05). f) Kaplan–Meier curve of transplant-free survival from time of sarcoidosis diagnosis in sarcoidosis patients with a relative with PF compared with a cohort of sporadic sarcoidosis patients. The latter patients (n=499) where identified from a cohort of sarcoidosis patients who completed a family health questionnaire, did not report any ILD in their relatives and had available survival data [4]. Log rank test shows an worse survival in sarcoidosis patients with a relative with PF (p= 0.004). g) Radiological and genetic characteristics as well as clinical course of PPF patients from the date of diagnosis regarding the presence of sarcoidosis (blue), idiopathic pulmonary fibrosis diagnosis and presence (arrowhead and cream) and PPF (red) until censoring or death (represented by cross signs). The dotted line represents lung transplantation in one patient. ILD: interstitial lung disease; PF: pulmonary fibrosis; IQR: interquartile range; FVC: forced volume capacity; D_{LCO}c: corrected diffusion capacity of the lung for carbon monoxide; HRCT: high resolution computed tomography; UIP: usual interstitial pneumonia; pUIP: probable UIP; indUIP: indeterminate for UIP; alt: alternative diagnosis; PPF: progressive pulmonary fibrosis; TL: telomere length; TRG: telomere-related gene variant; CT: CT pattern; p10: percentile 10. MUC5B allele pertains to *MUC5B* rs35705950. [#]: missing smoking data n=1; [¶]: missing D_{LCO}c values n=2; [+]: missing follow-up n=1; [§]: missing D_{LCO}c follow-up values n=3; [f]: less than one year lung function follow-up n=4; [##]: Between PPF and No Fibrosis patients. Data are presented as median and IQR. χ^2 or when appropriate Fisher exact test were used for intergroup comparison of categorical variables. When more than two groups were analysed, a pairwise Fisher test was used, applying a Bonferroni correction. Mann–Whitney U-test and Kruskal–Wallis' test with Dunn's *post hoc* test were used for comparison of continuous variables in two or more than two groups respectively. Transplant-free survival analysis was performed using a Kaplan–Meier approach with log-rank test.

During follow-up, five patients died, all with fibrosis, and one patient underwent lung transplantation for terminal PF. For the total group, median time from the date of diagnosis to death, transplantation or censoring was 11.6 (7.5–17.1) years (figure 1f, survival data censored 31 August 2023). We subsequently identified a group of sarcoidosis patients who did not report relatives with sarcoidosis or other ILDs in their family health questionnaire (n=499) [4]. The former group was older (sporadic sarcoidosis age at diagnosis 43 (36–51) years *versus* sarcoidosis patients reporting a family member with PF age at diagnosis 51 (39–60) years; p=0.02) while sex did not differ significantly between the groups (male/female n=277/222 *versus* 9/9; p=0.64). Patients with a family history of PF had a worse survival than patients with sporadic sarcoidosis as assessed by log rank test(p=0.004) (figure 1f).

Based on clinical, lung functional and radiological evolution, three subtypes of patients could be distinguished. Firstly, six patients fulfilled criteria for progressive pulmonary fibrosis (PPF) [6]. These patients had a lower diffusion capacity at presentation (figure 1e). A diagnosis of IPF was finally made in three of these patients a median of 7.5 years after the initial diagnosis of sarcoidosis, and IPF was suggested in one other (figure 1e). This was based on clinical disease behaviour at the time of IPF diagnosis, which was deemed unlikely to be due to their previously diagnosed sarcoidosis (of note, all patients in the PPF group had a histology contributing to the initial sarcoidosis diagnosis). Furthermore, four out of the five total deaths and the one lung transplantation occurred in this PPF group (figure 1e–g). Secondly, five patients displayed PF on their high-resolution computed tomography without clinical evidence for disease progression over the years. Four with available follow-up images showed iconographic stability or minimal progression. Finally, seven patients had no signs of fibrosis and showed a relatively preserved lung function and benign disease evolution (figure 1c–e). Importantly, there was no difference in follow-up time between the subtypes (p=0.25).

Genetic analysis (figure 1e) performed in all 18 subjects showed that the *MUC5B* rs35705950 minor T-allele frequency (MAF) was 0.27 which was significantly higher than in our published control (MAF=0.09; p=0.002) [9] and advanced pulmonary sarcoidosis (MAF=0.11; p=0.01) [10] populations. PPF patients displayed a higher MAF than non-PPF patients (MAF=0.50 *versus* 0.17; p=0.05). Furthermore, telomere length percentile for age was below the 10th percentile in 39% of the cohort, which was more frequent than the 19% in our published unsorted sarcoidosis population (p=0.11) [11]. Whole exome sequencing revealed a rare variant in two subjects (11%) who developed PPF. The *RTEL1* c.3791G>A (p.Arg1264His) variant was classified as likely pathogenic and the *TERT* c.3256C>T p.(Arg1086Cys) was considered a variant of unknown significance (VUS). For eight patients, genetic data from family members with PF was available, including the patient with the *TERT* (c.3256C>T) variant, confirming its presence in three relatives. However, three sarcoidosis patients in whom no variant of interest was detected had an affected relative with a telomere-related gene (TRG) variant: one *RTEL1* (c.3392C>A; p.(Thr1131Lys), classified as VUS), one *TERT* (c.1272dup; p.(Val425fs), classified as pathogenic) and one *TINF2* (c.*75C>G; likely disruptive, classified as VUS). Of note, all patients in the PPF group carried either the *MUC5B* T-allele or a TRG variant.

Recently, FPF was defined as any fibrotic ILD in at least two blood related first- or second-degree family members [3]. Available evidence showed these patients to have progressive disease and reduced survival comparable to IPF. The current study is the first to describe a group of sarcoidosis patients with a positive familial history for PF and reveals that disease course is highly variable with development of PPF between 2.2 and 27 years after diagnosis and 5 out of 11 fibrotic patients not progressing. This suggests a more benign course than previously published FPF cohorts [2, 3]. Nonetheless, only 20% of overall sarcoidosis patients will develop fibrosis [12], and only a subset will show a progressive phenotype [6]. This is in stark contrast with our findings, where 60% showed signs of fibrosis and ultimately one-third of our cohort showed a progressive phenotype. Overall, this group of patients thus shows an intermediate clinical course, in-between FPF and sporadic (fibrotic) sarcoidosis. Furthermore, progressive patients displayed atypical radiological findings for sarcoidosis with the presence of a (probable) UIP pattern, potentially reflecting a concomitant sarcoidosis and IPF entity which has recently been described in two small cohorts [13, 14].

Given the clinical variability, identification of at-risk individuals seems paramount. Interestingly, we detected a TRG variant or the *MUC5B* T-allele in all six PPF sarcoidosis patients. A previous report in an unselected sarcoidosis cohort showed that the T-allele did not associate with fibrotic sarcoidosis or disease progression over 4 years [15]. However, only 1% of sarcoidosis patients have a relative with PF [4], potentially resulting in the dilution of this signal, and suggesting that this is a specific subgroup of sarcoidosis. Known sarcoidosis associated genetic variants tend to be implicated in immunological pathways. The high frequency of genetic risk factors for IPF in sarcoidosis patients with a family member with PF suggests that fibrogenesis and progression of fibrosis is driven by the same genetic background as in IPF. Our data indicates that genetic screening may inform the long-term disease course of this high-risk subgroup of sarcoidosis patients and as such concurs with the European Respiratory Society statement [3]. Limitations of this study are nonetheless the small number of observations and its retrospective nature, and further confirmatory studies in prospective cohorts are needed.

In summary, this is the first study showing that sarcoidosis patients reporting PF in a relative are part of the spectrum of FPF and are at high-risk for progressive fibrotic disease, although rate of disease progression is highly variable.

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