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# Phenotypic characterization of interstitial lung disease associated with mutations in *SFTPC* and *ABCA3* in adults

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## Introduction & Methods

Interstitial lung disease is associated with pathogenic variants in surfactant-related genes *SFTPC* and *ABCA3*.

Despite numerous paediatric studies, data is lacking in adults.

We conducted a multicenter retrospective study of all consecutive adult patients diagnosed with ILD associated with variants in *SFTPC* or *ABCA3* in the French rare pulmonary diseases network, OrphaLung.

Chest computed tomography features were centrally reviewed by 2 radiologists, genetic data were reviewed by 2 molecular geneticists and lung biopsies were reviewed by local expert pathologists.

## Results

### Population

N = 36 patients (22 in the *SFTPC* group / 14 in the *ABCA3* group)

- 55% carriers of the Ile73Thr variant in the *SFTPC* group
- 33% carriers of the Glu292Val variant in the *ABCA3* group

Demographics	Overall population (n=36)	<i>SFTPC</i> (n=22)	<i>ABCA3</i> (n=14)	p-value
Age at diagnosis of ILD (years), median (IQR)	34 (19.3 – 44.2)	38.9 (23.2 - 47.6)	31.5 (19.1 – 40.6)	0.24
Male sex (%)	20 (55.6)	17 (77)	3 (21.4)	0.002
Respiratory symptoms during childhood (%)	11 (30.6)	6 (27.3)	5 (35.7)	0.72
History of neonatal respiratory distress (%)	5 (22.7)	2 (9.1)	3 (21.4)	0.36
Familial history of ILD (%)	22 (61.1)	18 (81.8)	4 (28.6)	0.004
Ever smoker (%)	10 (27.8)	7 (31.8)	3 (21.4)	0.71

## Lung function

Pulmonary function tests, median (IQR)	Overall population (n=36)	<i>SFTPC</i> (n=22)	<i>ABCA3</i> (n=14)	p-value
Time from diagnosis of ILD to baseline PFT (years)	0.8 (0.2 - 8.7)	0.8 (0.3 - 7.9)	0.8 (0.2 - 7.6)	0.84
FVC %predicted (n = 35)	59 (52 - 72)	66 (45 - 80)	55.5 (52 - 62.5)	0.17
FEV1 %predicted (n = 30)	63.2 (48.3 - 73.3)	71 (54.8 - 86.8)	55 (43.3 - 60.3)	0.01
FEV1/FVC (n = 30)	0.9 (0.78 - 0.92)	0.9 (0.81 - 0.92)	0.8 (0.74 - 0.88)	0.093
TLC %predicted (n = 29)	65 (59 - 76)	65 (55.3 - 78.3)	64 (60.5 - 73.5)	0.89
DLco %predicted (n = 28)	44 (35.4 - 50)	46 (39.5 - 53.5)	36.1 (26 - 38)	0.01
Kco %predicted (n = 23)	67.8 (52.4 - 82.5)	76 (63.3 - 91.5)	52.8 (36 - 68)	0.11

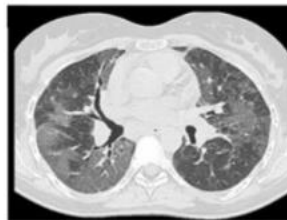
## Radiographic findings

Unclassifiable fibrosing ILD (85%):

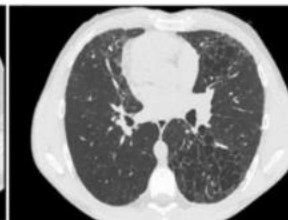
- With predominant GGO (44%)
- With predominant cysts (9%)
- Mixed GGO and cysts (32%)

Other findings:

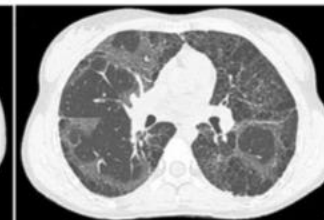
- > 90% with fibrosis features
- Emphysema (38%)
- Apical caps (88%)



GGO



Cysts



Mixed

## Histopathology

N = 16 patients with available data

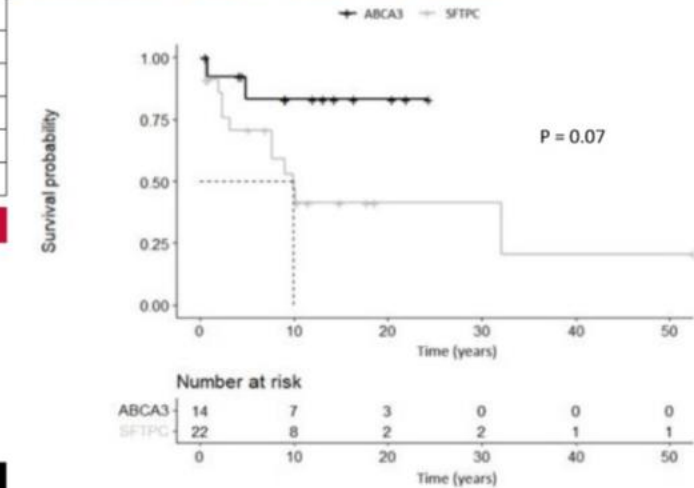
- *SFTPC* (n = 9): 33% UIP, 22% end-stage fibrosis, 11% NSIP
- *ABCA3* (n = 7): 71% NSIP
- Other findings: emphysema, bronchiolitis, cysts, fibroelastosis foci

## Prognosis

N = 5 patients died (4 *SFTPC* / 1 *ABCA3*)

N = 9 underwent lung transplantation (8 *SFTPC* / 1 *ABCA3*)

Exacerbation of ILD in 42 % of the patients



## Conclusion

- Variants in the surfactant-related genes *SFTPC* and *ABCA3* are a very rare cause of ILD in adults.
- They are associated with a non-UIP phenotype of fibrotic ILD, with severe prognosis.
- A radiological pattern of fibrosing ILD with GGO and/or cysts may help identify these rare conditions.

ABCA3, ATP-binding cassette type A3; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; GGO, ground-glass opacities; IQR, interquartile range; ILD, interstitial lung disease; KCO, carbon monoxide transfer coefficient; NSIP, nonspecific interstitial pneumonia; PFT, pulmonary function tests; SD, standard deviation; SFTPC, surfactant protein C; TLC, total lung capacity; UIP, usual interstitial pneumonia.

