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Introduction

- **Surfactant protein (SP)-B deficiency due to bi-allelic pathogenic variation** has been associated with **fatal forms** of interstitial lung diseases (**ILD**) in **newborns** and exceptional survival in young children.
- We herein report for the first time **two related adults** with **pulmonary fibrosis** due to a **homozygous *SFTPB* variation.**
- The aim of the study was to investigate **the pathogenicity effect** of the variation **c.582G>A p.(Gln194=)**

Methods

- ***In vitro* transcription analysis of the variation c.582G>A** : overexpression of *SFTPB* genomic constructs spanning exon 4 to 6 (NM_000542.5), WT or mutated in A549 cells. Analysis by electrophoresis and Sanger sequencing of the cDNA obtained by RT-PCR.
- ***Ex vivo* studies** : Haematoxylin & eosin **(HE)** stainings and i**mmunostaining** targeting **SP-B** and **SP-C** assessed on **biopsy of native lung explant of the proband.**

Results

Case presentation

- **The proband, homozygous for the variation (Fig.1A), presented a fibrosing ILD at 34 years. His thoracic CT-scan showed ground glass opacities and fibrosis. He received a bi-pulmonary transplantation at 51 years (Fig.1B).**
- **Proband's son, also homozygous for the variation (Fig.1A) presented alveolo-interstitial opacities and mild alveolar hemorrhage at 10 months. His thoracic CT-scan at 16 years showed mild ground glass opacities and mild ILD at 22 years (Fig.1B).**

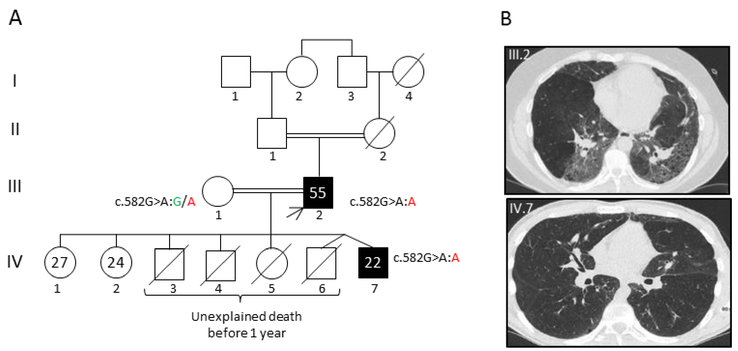

Figure 1: (A) Genealogical tree of the described family. The genotypes are provided with the reference nucleotide in green and the pathogenic variant in red. (B) The CT-scan of the proband at 51 years (left) and his son at 16 years (right)

Impact of the variation c.582G>A p.(Gln194=)

- *In vitro* transcription analysis of the variation revealed an **abnormal splicing with a persistence of correct spliced amplicons** as observed for the WT **(Fig.2).**
- HE staining of **lung proband showed fibroblastic foci with an usual interstitial pneumonia pattern.** Lung neonate presented thickened septa and normal healthy controls presented normal parenchyma **(Fig.3).**
- **Both SP-B and SP-C expression were altered for the proband.** SP-B staining showed an **almost complete loss of SP-B expression for the proband,** an absence of expression for the SP-B-deficient neonate and normal expression for controls. **SP-C/proSP-C was highly detected for the proband** and neonate as compared to the controls (**Fig.3).**

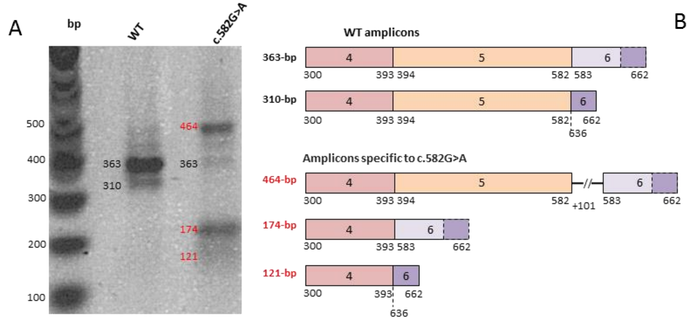

Figure 2 : (A) Agarose-BET gel of amplicons obtained by RT-PCR on RNAs from normal and mutant constructs expression. (B) Schematic representation of amplicons characterized by Sanger sequencing and corresponding to the fragments observed on agarose gel.

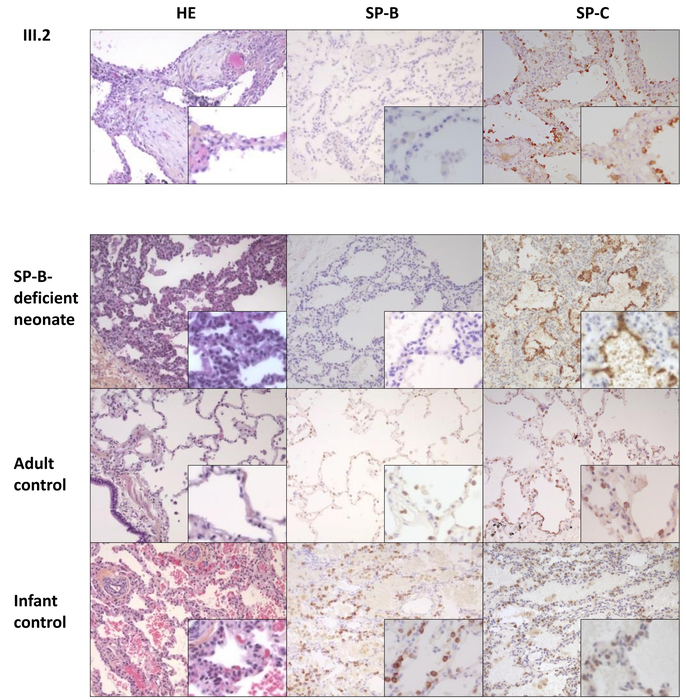

Figure 3 : The native lung explant examination of the proband (III.2) using Haematoxylin and eosin (HE) staining, SP-B and SP-C staining (magnification x20 and x40).

Conclusion and perspectives

- **The pathogenic variation c.582G>A p.(Gln194=) affected drastically splicing** as well as **SP-B and SP-C expression. However an hypomorphic effect , illustrated by the persistence of correct splicing and leading to a residual SP-B expression, could explain the long-term survival with fibrosing ILD in the two related adults.**
- **These findings lead to considered *SFTPB* variants in atypical presentations of ILD particularly in a familial context.**

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