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Hypomorphic mutation in *SFTPB* leads to adult pulmonary fibrosis

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Introduction

Surfactant protein (SP)-B deficiency caused by bi-allelic mutations of *SFTPB* has been associated with fatal forms of interstitial lung diseases (ILD) in newborns and exceptional survival in young children.

We report two related adults with pulmonary fibrosis (PF) due to a new homozygous *SFTPB* mutation.

Methods

The synonymous mutation c.582G>A p.(Gln194=) was predicted *in silico* to affected splicing, we analyzed *in vitro* the transcription. Constructs of genomic *SFTPB* sequence spanning exon 4 to 6, WT or mutated, were transiently expressed in A549 cells. cDNA obtained was analyzed by sequencing and electrophoresis. In parallel, Haematoxylin & eosin stainings and immunostaining targeting SP-B and SP-C were assessed on biopsy of native lung explant of the proband.

Results

The proband and his son, both being born from consanguineous union, presented a progressive PF. The proband required lung transplantation at 51 year-old. *In silico* studies of the predicted transcripts highlighted three abnormal transcripts, however with the preservation of the expression of a small proportion of normal *SFTPB* transcripts

Lung biopsy of proband showed a usual interstitial pneumonia pattern. Immunostainings showed an almost complete loss of SP-B expression and an abnormal expression of SP-C compared to healthy controls.

Conclusions

We first report two adult patients with a fibrosing ILD due to a hypomorphic splice mutation of *SFTPB*. The preservation of a small proportion of normal transcript may have allowed a residual SP-B production and could explain the long-term survival of the patients. This observation extends to *SFTPB* the surfactant related genes mutations involved in adult PF.