Hypomorphic mutation in SFTPB leads to adult pulmonary fibrosis


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 affect 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.