The next step for our study will be direct determination, such as faecal *H. pylori* antigens or *H. pylori* determination in BAL (*i.e.* DNA PCR or culture), in a wide population of IPF patients. The effects of IPF pharmacological treatments on *H. pylori* infection remain to be established.

@ERSpublications
***Helicobacter pylori* infection in IPF patients is associated with higher rates of mortality and PFTs decline** http://ow.ly/qKb3K

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Combined pulmonary fibrosis and emphysema syndrome associated with *ABCA3* mutations

To the Editor:

Herein, we present the first report of combined pulmonary fibrosis and emphysema (CPFE) in an adult patient who was compound heterozygous for mutations of the ATP-binding cassette subfamily A member 3 gene (*ABCA3*, MIM 601615).

A 41-year-old nonsmoking male presented with dyspnoea on mild exertion. The patient's medical history indicated neonatal respiratory distress, gastro-oesophageal reflux and pneumonia 8 years previously that resolved with antibiotics. His physical examination revealed a mild pectus excavatum, finger clubbing and bilateral basal crackles. High-resolution computed tomography (HRCT) of the chest showed voluminous

emphysema in the upper zones of the lungs associated with honeycomb fibrosis and ground-glass opacity in lower lobes, predominating in left lung (fig. 1). The bronchoalveolar lavage differential cell count was 67% macrophages, 22% neutrophils and 8% lymphocytes. Pulmonary function tests showed: total lung capacity of 75%, vital capacity (VC) of 50%, residual volume of 134%; forced expiratory volume in 1 s (FEV_1) of 49%, diffusing capacity of the lung for carbon monoxide of 38% predicted, FEV_1/VC of 74%, and arterial oxygen tension at room air was 96 mmHg. During a 6-min walk test the peripheral oxygen saturation decreased from 96% at rest to 90% after 630 m (80% of predicted value). A lung biopsy was not performed. Doppler echocardiography showed normal heart cavities, with estimated systolic pulmonary arterial pressure of 37 mmHg. Serum α_1-antitrypsin levels, autoimmune markers (including anti-nuclear antibody and rheumatoid factor), and immunoglobulin pattern were normal.

This clinical presentation of CPFE in a young patient prompted us to screen mutations in genes causing surfactant dysfunction. After informed consent was obtained, sequencing analysis of the surfactant protein C gene (*SFTPC*, MIM 178620) revealed no mutation. Sequence analysis of the *ABCA3* gene identified two mutations: 1) c.3081_3092delinsCG resulting in a serine to valine change at codon 1028 with the creation of a stop codon 103 amino acids downstream (p.Ser1028Valfs*103); and 2) the common mutation c.875A>T changing a glutamic acid to a valine at codon 292 (p.Glu292Val). None of these mutations were found in either the public polymorphism database or our controls. 2 years after presentation, chest HRCT as well as lung function worsened and azithromycin (250 mg every other day) was initiated.

Pulmonary surfactant, a complex mixture of lipids and specific proteins located at the air–liquid interface, lowers alveolar surface tension thereby preventing alveolar collapse at the end of expiration. It is synthesised by alveolar type II cells, stored in lamellar bodies, and secreted by exocytosis. ABCA3 is expressed in the lamellar bodies of alveolar type II cells and is crucial to pulmonary surfactant storage and homeostasis. Several studies indicated a role of genes involved in surfactant metabolism in the development of diffuse lung diseases [1].

CPFE is a syndrome characterised by the coexistence of emphysema and pulmonary fibrosis in the same patient [2]. It typically occurs in male smokers and is associated with dyspnoea, upper lobe emphysema, lower lobe fibrosis and abnormalities of gas exchange. In the absence of the *SFTPC* mutation, previously associated with CPFE [3], we decided to analyse other genes involved in surfactant metabolism, such as *ABCA3*. Recessive loss-of-function mutations in *ABCA3* present as lethal surfactant deficiency in the newborn, whereas other recessive mutations in *ABCA3* can result in interstitial lung disease in older children [4]. Previous studies showed that homozygous or compound heterozygous *ABCA3* mutations led

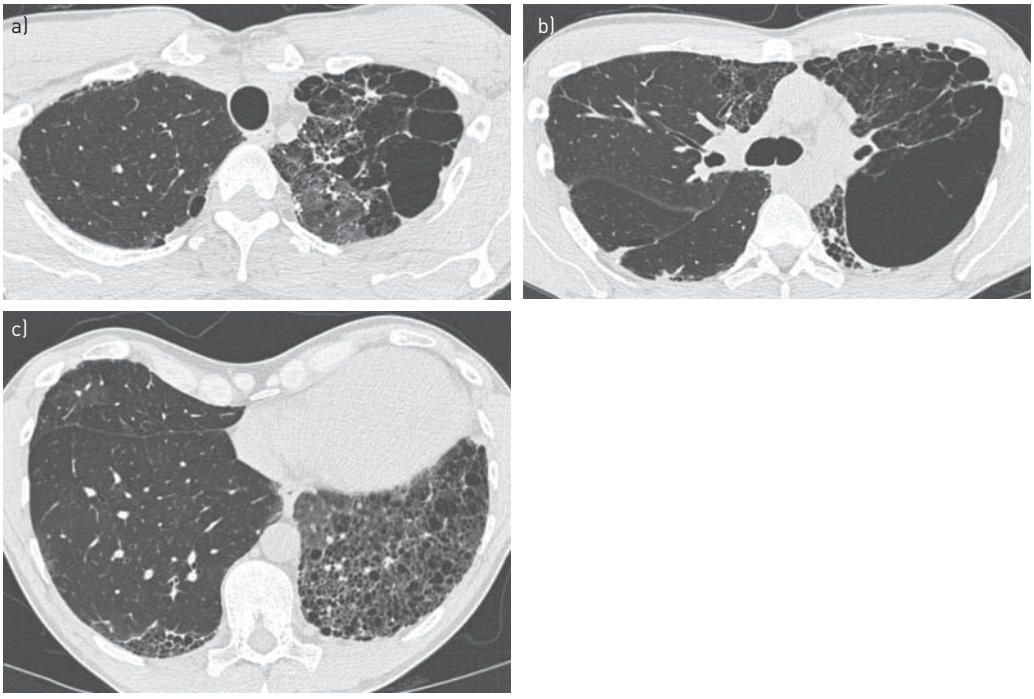

FIGURE 1 High-resolution computed tomography of the chest showing a, b) left upper lobe predominant emphysema associated with a, c) ground-glass opacities and c) asymmetric honeycomb pattern in the lower zones.

to abnormal processing and/or trafficking of the ABCA3 protein [5], alterations in ABCA3 protein functions such as ATPase activity [6], or impaired lipid transport [7]. As previously described, our patient had a less severe phenotype than is usually associated with *ABCA3* mutations [4]. These variations in the clinical and radiological features may be related to the nature of the mutation. Our patient was found to be compound heterozygous for *ABCA3* mutations. The first is the common mutation p.Glu292Val, which is found in heterozygous form with a frequency of $<1\%$ [8] and has been previously reported to be associated with mild lung disease. The second has not yet been described but is expected to be a disease-causing mutation as it introduces a premature termination codon, likely to be associated with markedly reduced mRNA levels due to nonsense-mediated degradation. Such a ''null'' allele precludes any functional ABCA3 from being made resulting in abnormal lamellar bodies, but should be less deleterious in combination with the mild mutation p.Glu292Val. Interactions with variants in other genes and/or with external factors such as viral or bacterial infections, as observed in our case, may also influence the observed phenotype [9].

The phenotype of our patient is very similar to that observed in the case reported by COTTIN *et al.* [3] carrying *SFTPC* mutations. Our patient is a nonsmoker and the emphysematous lesions were voluminous and localised, mostly in the upper lobes, whereas asymmetric fibrosis lesions were predominant in the lower lobes.

There is no specific treatment for CPFE syndrome. Supported immunosuppressive therapy was not indicated in this case without evidence of active inflammation. Improvement of severe interstitial lung disease in a young patient with ABCA3 deficiency has been reported after treatment with azithromycin, an azalide macrolide antibiotic characterised by a nitrogen in the macrolide ring [10]. Although, there is no evidence of efficacy of azithromycin in CPFE, the worsening of our patient's respiratory status together with the safety of this drug incited us to initiate this treatment in our patient.

To our knowledge, this is the first report of a phenotype of CPFE syndrome in an adult patient carrying mutations of the *ABCA3* gene. Although further studies are needed to confirm the role of surfactant metabolism in CPFE, this result suggests that this syndrome may have an underlying genetic predisposition.

@ERSpublications
The first report of combined pulmonary fibrosis and emphysema in an adult carrying compound heterozygote ABCA3 mutations http://ow.ly/rm0Dd

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Pulmonary arterial hypertension in familial hemiplegic migraine with ATP1A2 channelopathy

To the Editor:

Pulmonary arterial hypertension (PAH) has been the focus of major research in recent years [1]. Involvement of mutations in genes encoding for members of the transforming growth factor-β signalling pathway (*BMPR2*, *ACVRL1*, *ENG* and *SMAD8*) has been demonstrated in the development of heritable PAH, allowing novel experimental and clinical approaches [2–4]. However, ~30% of familial forms of PAH remain without any identification of genetic mutations. Recently, mutations of the *KCNK3* gene (encoding K^+ channel subfamily K member 3) have been reported in patients with familial and sporadic PAH [5]. KCNK3 belongs to a family of mammalian K^+ channels, and are involved in the regulation of resting membrane potential, pulmonary vascular tone and in vascular remodelling. This result paves the way to the involvement of novel signalling pathways in the development of heritable PAH. Herein, we describe a novel association of PAH and a channelopathy due to mutation in *ATP1A2* (encoding the α2-subunit of the Na^+/K^+-ATPase), a mutation known to cause familial hemiplegic migraine (FHM), a rare autosomal dominant disease [6].

A 24-year-old male was referred with a 1-year history of progressive exertional dyspnoea. Since the age of 8 years, he has reported recurrent episodes of hemiplegic migraine associated with muscle weakness and pain. The proband's mother (II4) (fig. 1) and two of his brothers (III6 and III7) had recurrent hemiplegic migraine with aura. There was no familial history of PAH. On admission, the patient was in New York Heart Association (NYHA) functional class III. His 6-min walk distance (6MWD) was 409 m. Pulmonary function tests were normal except for decreased diffusing capacity of the lungs for carbon monoxide. Doppler transthoracic echocardiography revealed signs of severe pulmonary hypertension with an estimated systolic pulmonary artery pressure of 75 mmHg, right ventricular dilatation and hypertrophy, and mild pericardial effusion. Right heart catheterisation confirmed pre-capillary pulmonary hypertension, with a mean pulmonary artery pressure (mPAP) of 51 mmHg, a pulmonary capillary wedge pressure of 12 mmHg, a right atrial pressure of 7 mmHg, a cardiac index of 1.90 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance (PVR) of 12.3 Wood units. No acute vasodilator response to nitric oxide was observed. Screening for other causes of pulmonary hypertension was negative. The patient was treated with a combination of intravenous epoprostenol, an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i). The patient stopped taking the PDE5i after a few days because of side-effects, including increased symptoms of migraine. 4 months later, re-evaluation showed moderate clinical (NYHA functional class II and 6MWD 518 m) and haemodynamic improvement (mPAP 43 mmHg, cardiac index 2.29 $L \cdot min^{-1} \cdot m^{-2}$ and PVR 8.4 Wood units). The patient is still alive 1 year after diagnosis on intravenous epoprostenol and an ERA.

According to our local procedures, the patient underwent genetic counselling and gave written informed consent for genetic screening. No point mutations or large rearrangements of the *BMPR2* and *ACVRL1* genes were identified. To date, three genes (*CACNA1A*, *ATP1A2* and *SCNA1*) encoding ion transporters are known to be associated with FHM. Genetic analysis revealed a nucleotide substitution in the coding sequence of the *ATP1A2* gene (c.2819C>T; p.S940L) located on chromosome 1 (1q23). This mutation, which was not found in 200 control chromosomes, and was absent from the dbSNP, 1000 Genomes and Exome Sequencing Project data, affects a highly conserved amino acid, but has never been reported before. The patient's brothers, III4 and III6, were screened for the familial *ATP1A2* mutation. Patient III4 did not carry the familial mutation and, as suggested by the clinical symptoms, the mutation was identified in patient III6 (fig. 1). Mutations of the *ATP1A2* gene are known to cause FHM, a rare autosomal dominant disease characterised by migraine with motor weakness and aura [6]. Other neurological symptoms include