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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

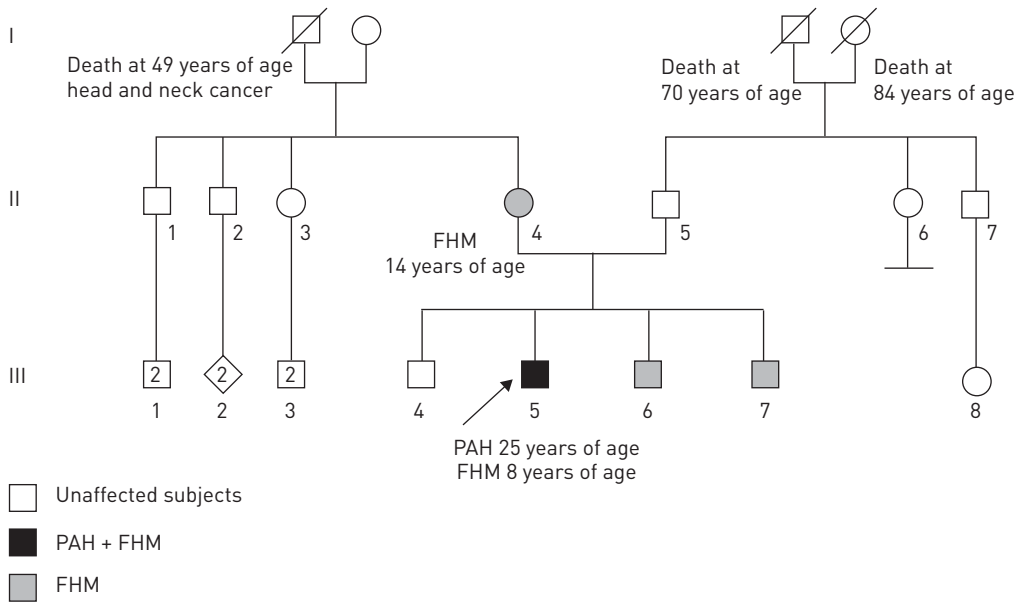

FIGURE 1 Family tree. Ages indicated are those at pulmonary arterial hypertension (PAH) diagnosis or the beginning of familial hemiplegic migraine (FHM) symptoms. Arrow: proband.

various types of epileptic seizures and intellectual deficit; permanent cerebellar signs may be present in patients carrying a *CACNA1A* mutation [6]. FHM has an estimated prevalence of one in 20 000, 20–30% of cases carrying an *ATP1A2* mutation [6]. In France, only 216 FHM patients (126 families) carry an *ATP1A2* mutation (unpublished data).

The association of two rare diseases (PAH and FHM) supports the hypothesis of a potential common pathophysiological link. It is important to note that the presence and the activity of the α2-subunit of the Na^+/K^+-ATPase in lung and, more particularly, in pulmonary vascular smooth muscle cells have been previously reported [7]. In addition, several studies have reported substantial decreases in expression and/or activity of different types of K^+ channels in pulmonary arterial smooth muscle cells of patients displaying idiopathic PAH, together with abnormalities in resting membrane potential and Ca^{2+} homeostasis [8]. Furthermore, pulmonary hypertension improvement has been demonstrated by restoring the expression of K^+ channels in a chronic hypoxic pulmonary hypertension rodent model (by treatment with a voltage-gated K^+ (Kv) channel activator or by gene transfer using adenovirus carrying the human Kv1.5 gene (*KCNA5*)) [9, 10]. The chemical gradient produced by the normal activity of the Na^+/K^+-ATPase is important for restoration of low intracellular Ca^{2+} concentration. Inhibition of K^+ channels leads to an increase in intracellular Ca^{2+} concentration, which is a major stimulus for cell growth, migration and vasoconstriction [11]. Notably, inhibition of the Na^+/K^+-ATPase by ouabain rapidly activates the Ras/mitogen-activated protein kinase (MAPK) signalling pathway, leading to the proliferation of cultured vascular smooth cells [12, 13]. Interestingly, we have reported eight cases of neurofibromatosis type 1 and one case of Cowden syndrome associated with pre-capillary pulmonary hypertension [14]. Neurofibromatosis type 1 and Cowden syndrome are due to mutations in the *NF1* and *PTEN* genes, respectively, leading to the activation of the Ras/MAPK signalling pathway and proliferation. Finally, it has been demonstrated that a decreased activity of K^+ channels can inhibit apoptosis by attenuating the activity of intracellular caspases [11]. Altogether, these observations support a possible role of mutations in *ATP1A2* gene in the development of PAH through the disturbance of intracellular Ca^{2+} and K^+ concentrations.

We thus suggest that mutations in the *ATP1A2* gene may contribute to pulmonary arterial remodelling and PAH. However, we must emphasise that our report of a single family remains hypothesis-generating and requires future additional information. Importantly, no other families with mutations in *ATP1A2* with a history of PAH have been reported to date. In addition, within the present family, the phenotype of FHM segregates with the *ATP1A2* mutation, but only one member has PAH. While this family is intriguing, it remains possible that PAH is unrelated to the *ATP1A2* mutation or FHM. Although these are both rare diseases, there is a small number of patients who do have coincidental rare diseases. In the future, our task will be to demonstrate the presence of *ATP1A2* mutations in other individuals with PAH and/or functionally demonstrate how the mutation may affect the pulmonary vasculature. Similarly, patients displaying hereditary haemorrhagic telangiectasia and PAH have been very rarely reported in the past.

Currently, <50 heritable PAH cases have been reported in *ACVRL1* mutation carriers, while most mutation carriers develop hereditary haemorrhagic telangiectasia by the age of 60 years, emphasising that a single gene may cause different vascular diseases, alone or in combination, with markedly different penetrance [15]. In conclusion, our present case report reinforces the potential interest of ion channels in the pathogenesis of PAH.

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