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Pulmonary arterial hypertension in familial hemiplegic migraine with ATP1A2 channelopathy

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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 TGF-β signaling pathway has been demonstrated in the development of heritable PAH (*BMPR2*, *ACVRL1*, *ENG*, *Smad8*) allowing novel experimental and clinical approaches [2–4]. However, around 30% of familial forms of PAH remain without any identification of genetic mutations. Recently, mutations of the *KCNK3* gene (encoding for potassium channel subfamily K, member 3) have been reported in patients with familial and sporadic PAH [5]. KCNK3 belongs to a family of mammalian potassium (K^+) channels, and are involved in the regulation of resting membrane potential, pulmonary vascular tone and in vascular remodeling. This result paves the way to the involvement of novel signaling pathways in the development of heritable PAH. Herein, we describe a novel association of PAH and a channelopathy due to *ATP1A2* mutation encoding for an 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 man was referred with a one-year history of progressive exertional dyspnea. Since the age of 8, he has reported recurrent episodes of hemiplegic migraine associated with muscle weakness and pain. The proband's mother (II4, **Figure 1**) and two of his brothers (III6 and III7) had recurrent hemiplegic migraine with aura. There was no familial history of PAH. At admission, the patient was in New York Heart Association (NYHA) functional class III. The 6-minute walk distance was 409 m. Pulmonary function tests were normal except for decreased diffusing capacity of the lungs for carbon monoxide (DLCO). Doppler transthoracic echocardiography revealed signs of severe pulmonary hypertension with an estimated systolic pulmonary artery pressure of 75 mmHg, a right ventricular dilatation and hypertrophy, and mild pericardial effusion. Right heart catheterization confirmed precapillary 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 (CI) of 1.90 L/min/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, endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE5i). The patient stopped PDE5i after a few days because of side effects, including increased symptoms of migraine. Four months later, reevaluation showed moderate clinical (NYHA functional class II, 6-MWD 518 m) and haemodynamic improvement (mPAP 43 mmHg, CI 2.29 L/min/m^2 and PVR of 8.4 wood units). The patient is still alive one year after diagnosis on intravenous epoprostenol and ERA.

According to our local procedures, the patient underwent genetic counseling and signed written informed consent for genetic screening. No point mutations or large rearrangements of *BMPR2* and *ACVRL1* genes were identified. To date, 3 genes (*CACNA1A*, *ATP1A2,* and *SCNA1*) coding for 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) localized on chromosome 1 (1q23). This mutation, not found in 200 control chromosomes, was absent from the Single Nucleotide Polymorphism Database (dbSNP), 1000 genome and Exome Sequencing Project (ESP) data, affects a highly conserved amino acid, but has never been reported before. His 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 (**Figure 1**). Mutations of *ATP1A2* gene are known to cause FHM, a rare autosomal dominant disease characterized by migraine with motor weakness and aura [6]. Other neurological symptoms include 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 1/20,000,

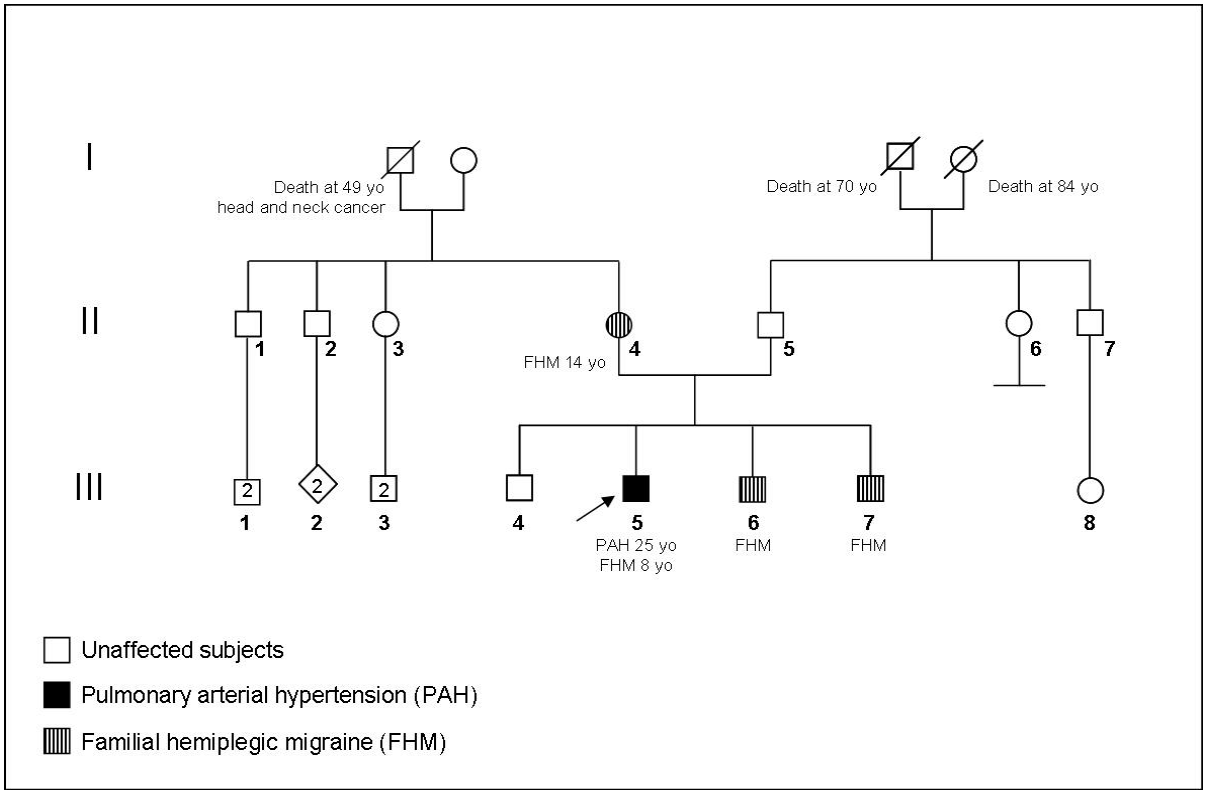
20-30% of which carry an *ATP1A2* mutation [6]. In France, only 216 FHM patients (126 families) carry an *ATP1A2* mutation (personal data).

The association of two rare diseases (PAH and MHF) supports the hypothesis of a potential common pathophysiological link. It is important to note that the presence and the activity of 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 decrease in expression and/ or activity of different types of K^+ channels in pulmonary arterial smooth muscle cells (PASMCs) of patients displaying idiopathic PAH, together with abnormalities in resting membrane potential and calcium 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 Kv channel activator or by gene transfer using adenovirus carrying human Kv1.5 gene) [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 of intracellular Ca^{2+} concentration which is a major stimulus for cell growth, migration and vasoconstriction [11]. Of note, inhibition of Na^+, K^+-ATPase by ouabain rapidly activates the Ras/MAPK signaling pathway, leading to the proliferation of cultured vascular smooth cells [12, 13]. Interestingly, we have reported 8 cases of neurofibromatosis type 1 and one case of Cowden syndrome associated with precapillary pulmonary hypertension [14]. Neurofibromatosis type 1 and Cowden syndrome are due to mutations in *NF1* and *PTEN* genes, respectively, leading to the activation of the Ras/ MAPK signaling 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 *ATPIA2*

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 remodeling and PAH. However, one must emphasize that our report of a single family remains hypothesis-generating and requires future additional information. Importantly, no other families with mutations in *ATP1A2* have been reported to date with a history of PAH. 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 are 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 hemorrhagic telangiectasia and PAH have been very rarely reported in the past. Currently, less than 50 heritable PAH cases have been reported in *ACVRL1* mutation carriers, while most mutation carriers develop hereditary hemorrhagic telangiectasia by the age of 60, emphasizing 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.

<u>Figure 1</u>: Family tree. Arrows identify proband. Age indicated are age at PAH diagnosis or the beginning of FHM symptoms.



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