Familial pulmonary arterial hypertension by *KDR* heterozygous loss of function

Mélanie Eyries[1,2,13], David Montani[3,4,5,13], Barbara Girerd[3,4], Nicolas Favrolt[6], Marianne Riou[7], Laurence Faivre[8], Grégoire Manaud[5], Frédéric Perros[5], Stefan Gräf[9,10,11], Nicholas W. Morrell[9,12], Marc Humbert[3,4,5] and Florent Soubrier[1,2]

Affiliations: [1]Hôpital Pitié-Salpêtrière, Département de génétique, Assistance Publique-Hôpitaux de Paris, Paris, France. [2]UMR_S1166-ICAN, Sorbonne Université, INSERM, Paris, France. [3]Univ. Paris–Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin Bicêtre, France. [4]Assistance Publique Hôpitaux de Paris, Service de Pneumologie, Centre de Référence de l'Hypertension Pulmonaire, Hôpital Bicêtre, Le Kremlin Bicêtre, France. [5]UMR_S 999, Univ. Paris–Sud, INSERM, Hôpital Marie Lannelongue, Le Plessis Robinson, France. [6]Service de Pneumologie et Soins Intensifs Respiratoires, Centre de référence constitutif des maladies pulmonaires rares de l'adulte, Centre de compétence de l'hypertension pulmonaire, CHU Dijon-Bourgogne, Dijon, France. [7]Service de pneumologie, Nouvel hôpital civil, Strasbourg, France. [8]Centre de génétique, FHU TRANSLAD, Institut GIMI et UMR INSERM 1231, CHU de Dijon et Université de Bourgogne, Dijon, France. [9]NIHR Bioresource – Rare Diseases, Cambridge Biomedical Campus, Cambridge, UK. [10]Dept of Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK. [11]Dept of Haematology, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK. [12]Dept of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Royal Papworth Hospitals, Cambridge, UK. [13]Equally contributing authors.

Correspondence: Florent Soubrier, UMR_S 1166 ICAN, Paris 75634, France. E-mail: florent.soubrier@sorbonne-universite.fr

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ABSTRACT Beyond the major gene *BMPR2*, several new genes predisposing to PAH have been identified during the last decade. Recently, preliminary evidence of the involvement of the *KDR* gene was found in a large genetic association study.

We prospectively analysed the *KDR* gene by targeted panel sequencing in a series of 311 PAH patients referred to a clinical molecular laboratory for genetic diagnosis of PAH.

Two index cases with severe PAH from two different families were found to carry a loss-of-function mutation in the *KDR* gene. These two index cases were clinically characterised by low diffusing capacity for carbon monoxide adjusted for haemoglobin (D_{LCO}c) and interstitial lung disease. In one family, segregation analysis revealed that variant carriers are either presenting with PAH associated with low D_{LCO}c, or have only decreased D_{LCO}c, whereas non-carrier relatives have normal D_{LCO}c. In the second family, a single affected carrier was alive. His carrier mother was unaffected with normal D_{LCO}c.

We provided genetic evidence for considering *KDR* as a newly identified PAH-causing gene by describing the segregation of *KDR* mutations with PAH in two families. In our study, *KDR* mutations are associated with a particular form of PAH characterised by low D_{LCO}c and radiological evidence of parenchymal lung disease including interstitial lung disease and emphysema.