Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation

David Montani[1,2,3,14], Barbara Girerd[1,2,3,14], Xavier Jaïs[1,2,3], Pierantonio Laveneziana[4,5], Edmund M.T. Lau[6], Amir Bouchachi[3,7], Sébastien Hascoët[3,8], Sven Günther[9], Laurent Godinas[1,2,3], Florence Parent[1,2,3], Christophe Guignabert[1,3], Antoine Beurnier[3,10], Denis Chemla[3,10], Philippe Hervé[3,11], Mélanie Eyries[12,13], Florent Soubrier[12,13], Gérald Simonneau[1,2,3], Olivier Sitbon[1,2,3], Laurent Savale[1,2,3] and Marc Humbert[1,2,3]

[1]School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [2]Service de Pneumologie et Soins Intensifs Respiratoires, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [3]INSERM UMRS 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [4]INSERM UMRS 1158, Neurophysiologie Respiratoire Expérimentale et Clinique, Sorbonne Université, Paris, France. [5]Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée, Département Médico-Universitaire "APPROCHES", Hôpitaux Universitaires Pitié-Salpêtrière, Tenon et Saint-Antoine, AP-HP, Sorbonne Université, Paris, France. [6]Dept of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, Australia. [7]Service de Cardiologie, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [8]Pôle de Cardiologie Pédiatrique et Congénitale, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [9]Service de Physiologie, AP-HP, Georges Pompidou European Hospital, Paris, France. [10]Service de Physiologie, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [11]Service de Chirurgie Thoracique, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [12]Département de Génétique, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France. [13]INSERM UMRS 1166, Sorbonne Université and Institute for Cardiometabolism and Nutrition (ICAN), Paris, France. [14]These two authors contributed equally to this work.

Corresponding author: Marc Humbert (marc.humbert@aphp.fr)

Shareable abstract (@ERSpublications)
Asymptomatic *BMPR2* mutation carriers have a 2.3% per year risk of developing PAH. DELPHI-2 provides the platform for future international multicentre studies to refine multimodal screening algorithms in *BMPR2* mutation carriers. http://bit.ly/3oi2KJ1

Cite this article as: Montani D, Girerd B, Jaïs X, *et al*. Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation. *Eur Respir J* 2021; 58: 2004229 [DOI: 10.1183/13993003.04229-2020].

This article has supplementary material available from erj.ersjournals.com

This article has an editorial commentary: https://doi.org/10.1183/13993003.00286-2021

Received: 18 Nov 2020
Accepted: 17 Dec 2020

Abstract

Background Heritable pulmonary arterial hypertension (PAH) is most commonly due to heterozygous mutations of the *BMPR2* gene. Based on expert consensus, guidelines recommend annual screening echocardiography in asymptomatic *BMPR2* mutation carriers. The main objectives of this study were to evaluate the characteristics of asymptomatic *BMPR2* mutation carriers, assess their risk of occurrence of PAH and detect PAH at an early stage in this high-risk population.

Methods Asymptomatic *BMPR2* mutation carriers underwent screening at baseline and annually for a minimum of 2 years (DELPHI-2 study; ClinicalTrials.gov: NCT01600898). Annual screening included clinical assessment, ECG, pulmonary function tests, 6-min walk distance, cardiopulmonary exercise testing, chest radiography, echocardiography and brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP level. Right heart catheterisation (RHC) was performed based on predefined criteria. An optional RHC at rest and exercise was proposed at baseline.

Results 55 subjects (26 males; median age 37 years) were included. At baseline, no PAH was suspected based on echocardiography and NT-proBNP levels. All subjects accepted RHC at inclusion, which identified two mild PAH cases (3.6%) and 12 subjects with exercise pulmonary hypertension (21.8%). At long-term follow-up (118.8 patient-years of follow-up), three additional cases were diagnosed, yielding a PAH incidence of 2.3% per year (0.99% per year in males and 3.5% per year in females). All PAH cases remained at low-risk status on oral therapy at last follow-up.

Conclusions Asymptomatic *BMPR2* mutation carriers have a significant risk of developing incident PAH. International multicentre studies are needed to confirm that refined multimodal screening programmes with regular follow-up allow early detection of PAH.