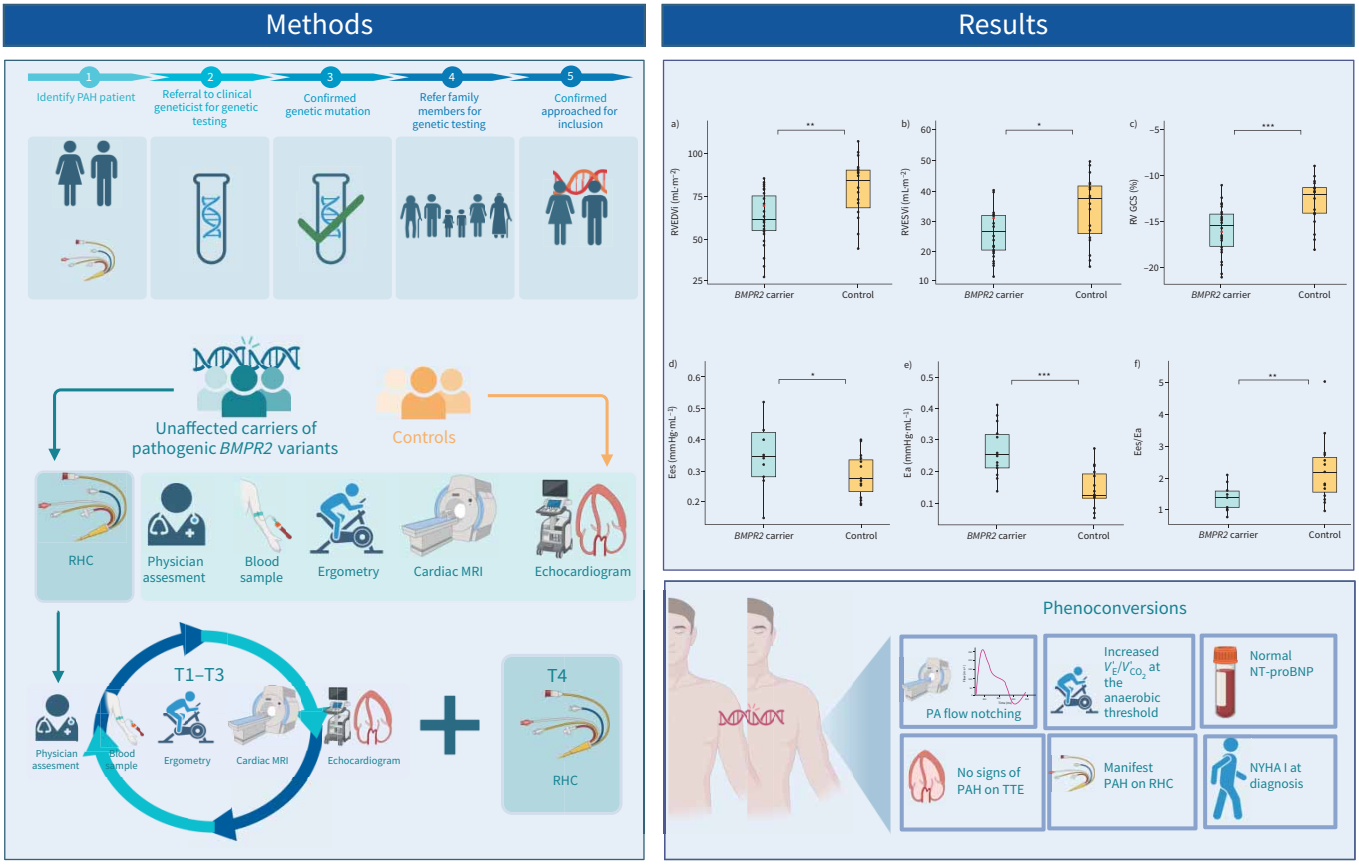
Deep phenotyping of unaffected carriers of pathogenic *BMPR2* variants screened for pulmonary arterial hypertension

Eszter N. Tóth, Lucas R. Celant, Marili Niglas, Samara Jansen, Jelco Tramper, Nicoleta Baxan, Ali Ashek, Jeroen N. Wessels, J. Tim Marcus, Lilian J. Meijboom, Arjan C. Houweling, Esther J. Nossent, Jurjan Aman, Julien Grynblat, Frédéric Perros, David Montani, Anton Vonk Noordegraaf, Lan Zhao, Frances S. de Man and Harm Jan Bogaard



GRAPHICAL ABSTRACT Summary of study protocol and main study findings. Unaffected carriers (UCs) of pathogenic *BMPR2* variants and healthy family members (controls) were recruited for study participation after genetic counselling. A multimodality screening approach was employed with UCs undergoing an additional right heart catheterisation (RHC) at baseline and at the 4-year follow-up (T4). Main study findings include lower indexed right ventricular (RV) end-systolic volume (ESVi) and RV end-diastolic volume (EDVi) in UCs as well as a higher RV global circumferential strain (GCS) (red dots indicate phenoconverters). Haemodynamic and pressure–volume loop analysis showed higher RV end-systolic elastance (Ees), RV afterload (arterial elastance (Ea)) and altered RV pulmonary artery (PA) coupling (Ees/Ea) in UCs. During the study, two participants developed pulmonary arterial hypertension (PAH). MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; TTE: transthoracic echocardiography; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production.

Link to published version: https://doi.org/10.1183/13993003.00442-2024

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
E.N. TÓTH ET AL.

Deep phenotyping of unaffected carriers of pathogenic *BMPR2* variants screened for pulmonary arterial hypertension

Eszter N. Tóth [1,2,11], Lucas R. Celant [1,2,11], Marili Niglas [3], Samara Jansen[1,2], Jelco Tramper[1,2], Nicoleta Baxan[3], Ali Ashek[3], Jeroen N. Wessels [1,2], J. Tim Marcus[2,4], Lilian J. Meijboom [2,4], Arjan C. Houweling[5], Esther J. Nossent [1], Jurjan Aman [1], Julien Grynblat [6,7,8,9], Frédéric Perros[10], David Montani [6,7,8], Anton Vonk Noordegraaf [1,2], Lan Zhao [3], Frances S. de Man[2] and Harm Jan Bogaard[1,2]

[1]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Pulmonary Medicine, Amsterdam, The Netherlands. [2]Amsterdam Cardiovascular Sciences, Pulmonary Hypertension and Thrombosis, Amsterdam, The Netherlands. [3]Imperial College London, National Heart and Lung Institute, London, UK. [4]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Radiology and Nuclear Medicine, Amsterdam, The Netherlands. [5]Amsterdam UMC location AMC, Department of Human Genetics, Amsterdam, The Netherlands. [6]INSERM UMR_S 999 "Pulmonary Hypertension: Pathophysiology and Novel Therapies", Marie Lannelongue Hospital and Bicêtre Hospital, Le Plessis-Robinson, France. [7]AP-HP, Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Bicêtre Hospital, Le Kremlin-Bicêtre, France. [8]Université Paris-Saclay, School of Medicine Gif-sur-Yvette, Gif-sur-Yvette, France. [9]M3C-Necker, Hôpital Necker-Enfants Malades, AP-HP, Université de Paris Cité, Cardiologie Congénitale et Pédiatrique, Paris, France. [10]CarMeN Laboratory, INSERM U1060, INRAE U1397, Université Claude Bernard Lyon 1, Pierre-Bénite, France. [11]Contributed equally.

Corresponding author: Harm Jan Bogaard (hj.bogaard@amsterdamumc.nl)

Shareable abstract (@ERSpublications)
Unaffected *BMPR2* mutation carriers have an altered cardiac phenotype, with slightly increased right ventricular contractility. In the screening of individuals susceptible to developing PAH, echocardiography and NT-proBNP are insufficient. https://bit.ly/3xtcD0w

Cite this article as: Tóth EN, Celant LR, Niglas M, *et al*. Deep phenotyping of unaffected carriers of pathogenic *BMPR2* variants screened for pulmonary arterial hypertension. *Eur Respir J* 2024; 64: 2400442 [DOI: 10.1183/13993003.00442-2024].

This article has an editorial commentary: https://doi.org/10.1183/13993003.01369-2024

Received: 4 March 2024
Accepted: 19 June 2024

Abstract

Introduction Pathogenic variants in the gene encoding for *BMPR2* are a major genetic risk factor for heritable pulmonary arterial hypertension. Owing to incomplete penetrance, deep phenotyping of unaffected carriers of a pathogenic *BMPR2* variant through multimodality screening may aid in early diagnosis and identify susceptibility traits for future development of pulmonary arterial hypertension.

Methods 28 unaffected carriers (44±16 years, 57% female) and 21 healthy controls (44±18 years, 48% female) underwent annual screening, including cardiac magnetic resonance imaging, transthoracic echocardiography, cardiopulmonary exercise testing and right heart catheterisation. Right ventricular pressure–volume loops were constructed to assess load-independent contractility and compared with a healthy control group. A transgenic $Bmpr2^{\Delta 71Ex1/+}$ rat model was employed to validate findings from humans.

Results Unaffected carriers had lower indexed right ventricular end-diastolic (79.5±17.6 $mL \cdot m^{-2}$ *versus* 62.7±15.3 $mL \cdot m^{-2}$; p=0.001), end-systolic (34.2±10.5 $mL \cdot m^{-2}$ *versus* 27.1±8.3 $mL \cdot m^{-2}$; p=0.014) and left ventricular end-diastolic (68.9±14.1 $mL \cdot m^{-2}$ *versus* 58.5±10.7 $mL \cdot m^{-2}$; p=0.007) volumes than control subjects. $Bmpr2^{\Delta 71Ex1/+}$ rats were also observed to have smaller cardiac volumes than wild-type rats. Pressure–volume loop analysis showed that unaffected carriers had significantly higher afterload (arterial elastance 0.15±0.06 *versus* 0.27±0.08 $mmHg \cdot mL^{-1}$; p<0.001) and end-systolic elastance (0.28±0.07 *versus* 0.35±0.10 $mmHg \cdot mL^{-1}$; p=0.047) in addition to lower right ventricular pulmonary artery coupling (end-systolic elastance/arterial elastance 2.24±1.03 *versus* 1.36±0.37; p=0.006). During the 4-year follow-up period, two unaffected carriers developed pulmonary arterial hypertension, with normal N-terminal pro-brain natriuretic peptide and transthoracic echocardiography indices at diagnosis.

Conclusion Unaffected *BMPR2* mutation carriers have an altered cardiac phenotype mimicked in $Bmpr2^{\Delta 71Ex1/+}$ transgenic rats. Future efforts to establish an effective screening protocol for individuals at risk for developing pulmonary arterial hypertension warrant longer follow-up periods.