Title Page

**Title:**

Response to Letter Regarding Article: “Phenotypic Characterization of EIF2AK4 Mutation Carriers in a Large Cohort of Patients Diagnosed Clinically With Pulmonary Arterial Hypertension”

**First author’s surname:**

Hadinnapola

**Authors:**

Charaka Hadinnapola MB BChir Department of Medicine, University of Cambridge, Cambridge, UK

Stefan Gräf PhD Department of Medicine, University of Cambridge, Cambridge, UK

Nicholas W Morrell MD FRCP FMedSci Department of Medicine, University of Cambridge, Cambridge, UK

**Corresponding author:**

Prof Nicholas Morrell, Department of Medicine,

University of Cambridge School of Clinical Medicine

Box 157, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, UK

Tel: +44 1223 331666

Fax: +44 1223 336846

Email: nmw23@cam.ac.uk

Twitter: @Cambridgecardio

Word count: 386

We thank Subias et al. for their response to our recent article 1. In this study we demonstrated that the clinical, radiological and histological features in patients with pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis (PVOD/PCH) (including those carrying biallelic *EIF2AK4* mutations) can show significant overlap with idiopathic pulmonary arterial hypertension (PAH). In our study, none of the patients found to have a molecular diagnosis (biallelic *EIF2AK4* mutations) consistent with PVOD/PCH, but classified by expert clinicians as idiopathic PAH, developed pulmonary oedema in response to pulmonary artery vasodilator therapies. This may account for the apparent increased survival reported in our study compared to Montani et al. who ascertained cases of clinically obvious cases of PVOD/PCH 2. Indeed, Tejedor et al. also show a better prognosis in Romani patients carrying a founder mutation in *EIF2AK4*, who were tolerant of pulmonary artery vasodilator therapies 3.

As eloquently described by Miller and Faber in the editorial accompanying our article the key question is how this impacts clinical practice 4. We would assert that clinical genetic testing is of value in the early identification of PVOD/PCH. We showed that the diagnostic yield of biallelic *EIF2AK4* mutations was 53% in patients aged less than 50 years with a diffusion coefficient for carbon monoxide less than 50% of predicted. Although the presence of biallelic *EIF2AK4* mutations is not of prognostic significance in cohorts of patients with PVOD/PCH, it might well be in patients diagnosed with idiopathic PAH. In our manuscript we show a worse prognosis in patients with an apparent clinical diagnosis of idiopathic PAH even though they were “tolerant” of pulmonary artery vasodilator therapies. Therefore, early identification of these patients may facilitate early transplant assessment and careful monitoring when initiating pulmonary artery vasodilatory therapies.

Specific information regarding consanguinity was not collected as part of our study. However, of the 7 patients with homozygous rare and predicted deleterious *EIF2AK4* mutations, 5 (71%) were of South Asian descent, perhaps pointing towards a shared kinship.

Being an ultra-rare disease, further study of distinct subgroups requires international collaboration to obtain sufficient numbers. Only with such large prospective studies can we validate and build upon these preliminary but intriguing observations. Pulmonary venopathy is an important aspect of pulmonary hypertension associated with connective tissue disease and left heart disease. As such these questions may have much wider clinical relevance.

1. Hadinnapola C, Bleda M, Haimel M, Screaton N, Swift A, Dorfmuller P, Preston SD, Southwood M, Hernandez-Sanchez J, Martin J, Treacy C, Yates K, Bogaard H, Church C, Coghlan G, Condliffe R, Corris PA, Gibbs S, Girerd B, Holden S, Humbert M, Kiely DG, Lawrie A, Machado R, MacKenzie Ross R, Moledina S, Montani D, Newnham M, Peacock A, Pepke-Zaba J, Rayner-Matthews P, Shamardina O, Soubrier F, Southgate L, Suntharalingam J, Toshner M, Trembath R, Vonk Noordegraaf A, Wilkins MR, Wort SJ, Wharton J, Gräf S and Morrell NW. Phenotypic Characterization of EIF2AK4 Mutation Carriers in a Large Cohort of Patients Diagnosed Clinically With Pulmonary Arterial Hypertension. *Circulation*. 2017;136:2022-2033.

2. Montani D, Girerd B, Jais X, Levy M, Amar D, Savale L, Dorfmuller P, Seferian A, Lau EM, Eyries M, Le Pavec J, Parent F, Bonnet D, Soubrier F, Fadel E, Sitbon O, Simonneau G and Humbert M. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med*. 2017;5:125-134.

3. Navas Tejedor P, Palomino Doza J, Tenorio Castano JA, Enguita Valls AB, Rodriguez Reguero JJ, Martinez Menaca A, Hernandez Gonzalez I, Bueno Zamora H, Lapunzina Badia PD and Escribano Subias P. Variable Expressivity of a Founder Mutation in the EIF2AK4 Gene in Hereditary Pulmonary Veno-occlusive Disease and Its Impact on Survival. *Rev Esp Cardiol (Engl Ed)*. 2018;71:86-94.

4. Miller DP and Farber HW. Pulmonary Veno-Occlusive Disease: Welcome to the PAHty (Bostonian for Party). *Circulation*. 2017;136:2034-2036.

Disclosures: None