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Widening the landscape of heritable pulmonary hypertension mutations in paediatric and adult cases

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Gene panel sequencing unravels the genetic architecture of pulmonary hypertension in adult and paediatric cases, emphasises the importance of *BMPR2*, *EIF2AK4*, *BMP9* and *TBX4* mutations, and suggests *BMP10* as a new gene for the disease http://ow.ly/Oxes30mXnrI

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ABSTRACT

Background: Heritable forms of pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis (PVOD/PCH) diverge by lung histopathological lesions, clinical and para-clinical presentation, their responsible genes, and mode of transmission. Since the identification of the *BMPR2* gene in families affected by PAH, mutations in several other genes have been discovered for both forms. The mutation landscape in these new genes is not yet well known.

Methods: We set up a next-generation sequencing-based targeted sequencing gene panel allowing known genes for PAH and PVOD/PCH to be analysed simultaneously. Genetic analysis was prospectively performed on 263 PAH and PVOD/PCH patients (adult and paediatric cases).

Results: Pathogenic mutations were identified in 19.5% of sporadic PAH patients (n=180), 54.5% of familial PAH patients and 13.3% of PVOD/PCH patients. *BMPR2* was the most frequently mutated gene, followed by *TBX4* in both paediatric and adult PAH. *BMP9* mutations were identified in 1.2% of adult

PAH cases. *EIF2AK4* biallelic mutations were restricted to PVOD/PCH. A truncating mutation and a predicted loss-of-function variant were also identified in *BMP10* in two severely affected sporadic PAH female patients.

Conclusion: Our results confirm that mutations are found in genes beyond *BMPR2* in heritable PAH, emphasise the role of *TBX4* and *BMP9*, and designate *BMP10* as a new PAH gene.