Familial pulmonary arterial hypertension by \textit{KDR} heterozygous loss of function

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KDR mutations were identified in two families with a particular form of PAH characterised by low DLCOc and radiological evidence of parenchymal lung disease http://bit.ly/30npPPn


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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 \textit{KDR} gene was found in a large genetic association study.

We prospectively analysed the \textit{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 \textit{KDR} gene. These two index cases were clinically characterised by low diffusing capacity for carbon monoxide adjusted for haemoglobin (DLCOc) and interstitial lung disease. In one family, segregation analysis revealed that variant carriers are either presenting with PAH associated with low DLCOc, or have only decreased DLCOc, whereas non-carrier relatives have normal DLCOc. In the second family, a single affected carrier was alive. His carrier mother was unaffected with normal DLCOc.

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