First identification of *Krüppel-like factor 2* mutation in heritable pulmonary arterial hypertension

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Background: Heritable pulmonary arterial hypertension (HPAH) is an autosomal dominantly inherited disease caused by mutations in the *bone morphogenic protein receptor 2* gene and/or genes of its signalling pathway in about 85% of patients.

Objectives: Our main objective was to identify the genetic cause of the disease in this family using an next generation sequencing based PAH specific gene panel including all so far known PAH and further candidate genes.

Methods: We clinically and genetically analysed a HPAH family without mutations in previously described PAH genes. Clinical assessment included electrocardiogram, lung function, blood gas analysis, chest X-ray, laboratory testing, echocardiography and right heart catheterisation in case of suspected disease. Genetic diagnostics were performed using a PAH specific gene panel including all known 12 PAH genes and 20 further candidate genes by next-generation-sequencing.

Results: HPAH was invasively confirmed in two sisters and their father who died aged 32 years. No signs of HPAH were detected in five first degree family members. Both sisters were lung transplanted and remained stable during a follow-up of >20 years. We detected a novel missense mutation in the *Krüppel-like factor 2* (*KLF2*) likely leading to a disruption of gene function. The same *KLF2* mutation has been described as a recurrent somatic mutation in B-cell lymphoma. Neither the healthy family members carried the mutation nor >120,000 controls.

Conclusions: These findings point to *KLF2* as a new PAH gene. Further studies are needed to assess frequency and implication of *KLF2* mutations in PAH patients.

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