**EIF2AK4** genetic mutations cause a recessive form of rare and deadly lung disease, pulmonary veno-occlusive disease

**References**


Pulmonary veno-occlusive disease (PVOD) is a recessive and a specific rare form of pulmonary hypertension affecting mostly children and young adults. It occurs as a result of progressive obstruction of small pulmonary veins. This leads to elevation in pulmonary vascular
resistance and right ventricular failure, resulting in severe postcapillary pulmonary hypertension. It accounts for 5–10% of cases initially classified as idiopathic pulmonary arterial hypertension (PAH), and occurs in the population at a male: female ratio of 6:1. The etiology remains unknown and it generally carries a very poor prognosis, with some studies reporting a 72% mortality rate within 1 year of diagnosis (1). A definite diagnosis of PVOD necessitates a surgical biopsy, but because it represents a high-risk procedure in these patients, it is contraindicated. Lung transplantation remains the only proven therapy. Therefore, the identification of the genetic causes of PVOD will allow for a non-invasive genetic diagnosis and a more accurate clinical classification of PVOD. Also, the identification of the genetic causes of PVOD might offer insight into the pathophysiology of the disease and the identification of potential novel therapeutic targets.

Eyries and colleagues performed genetic linkage mapping, whole-exome sequencing and Sanger sequencing on 12 PVOD families and 20 sporadic cases. PVOD was diagnosed histologically after lung transplantation or lung biopsy or on the basis of clinical and paraclinical data. PVOD families had at least two affected siblings and unaffected parents, suggesting that the disease is a recessive trait. Their study identified recessive mutations in eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) coding sequences in all 12 families and in 5/20 sporadic cases (25%). As a control measure, Eyries et al. investigated the entire EIF2AK4 coding sequence in 26 patients with no histologically proven PVOD and 9 patients from PAH families without BMPR2 mutations, and found no EIF2AK4 mutations. Immunohistochemistry analyses detected the EIF2AK4 protein in smooth muscle cells of the vessel wall and interstitial tissue and in macrophages in control lung tissue and in a lung tissue from a PVOD patient without EIF2AK4 mutations. On the contrary, no EIF2AK4 protein was detected in the lung tissue of PVOD patient with EIF2AK4 mutations, suggesting that EIF2AK4 mutations are loss of function mutations. This study also observed that EIF2AK4 mutations were associated with younger age at onset of PVOD.

In conclusion, mutations in EIF2AK4 have been identified as the major cause of PVOD (Fig. 2). EIF2AK4 mutations accounted for all familial cases of PVOD and a quarter of sporadic cases in the study. This allows for the genetic diagnosis of PVOD and offers insight into the pathophysiology of PVOD, which could facilitate the development of novel therapeutic strategies. Clinically, the genetic diagnosis of PVOD will offer the opportunity for genetic counseling to affected families, including prenatal and pre-implantation genetic diagnosis, newborn and carrier screening.

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