Targeted exome sequencing in routine clinical practice can help to elucidate pulmonary veno-occlusive disease in patients with pulmonary artery hypertension

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Pulmonary veno-occlusive disease (PVOD) is a rare disease which is very difficult to recognize. It characterized with recessive inheritance. Morphological confirmation can be performed only postmortem or after lung transplantation, so the true disease prevalence is unknown. We performed NGS in 54 patients with idiopathic and family forms of pulmonary artery hypertension (PAH) in Moscow pulmonary hypertension expert center. Four patients had mutations in EIF2AK4 gene: 2 - biallelic mutations, and 2 – in combination with mutations in other PAH genes. None of them had clinical signs of PVOD. Patients with EIF2AK4 biallelic mutations died. The first one (female, PAH manifestation at the age of 47 and died at the age of 55). There were 2 cases of fatal PAH in her family (at the same generation). We found the previously described PVOD-related pathological EIF2AK4 variant (c.C2965T) in the heterozygous state, resulting in non-synonymous substitution in position 989 of the protein (p.Arg989Trp), and previously non-described (according to HGMD, COSMIC, ClinVar, 1000 GenomesProject, dbSNP, ExomeVariantServer databases) EIF2AK4 variant (c.859+1G>A) in the heterozygous state, leads to violation of the splice site. Lung tissue histologic examination demonstrated intimal fibroelastosis of pulmonary vein brunches with narrowing or complete obliteration of vein lumen, which confirmed PVOD. The second patient (male, PAH manifestation at the age of 17, died shortly after lung transplantation). Previously described variant EIF2AK4 p.Arg463* (stop gain) and the non-described variant (EIF2AK4 p.Val1142Met) were found. The histologic examination demonstrated intimal fibroelastosis of the pulmonary vein and artery brunches and fibrous and atheromatous plaques in segmental lung arteries. In the other two patients, EIF2AK4 mutations were found in combination with mutations in SMAD9 and TOPBP1 genes. We speculated that it can promote PAH penetration. So targeted exome sequencing included in the PAH examination algorithms can be used as a "molecular biopsy".