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EIF2AK4-Associated Disorders

Two disorders are currently associated with *EIF2AK4* variants: pulmonary capillary hemangiomatosis (PCH) and pulmonary veno-occlusive disease (PVOD). Both disorders result in pulmonary arterial hypertension and are progressive, leading to death. Presentation is variable, depending on the affected lung structures as well as other genetic modifiers and environmental factors. PCH may mimic idiopathic pulmonary arterial hypertension (PAH), PVOD, or pulmonary hemosiderosis.

PCH is a rare disease caused by proliferation of multiple layers of capillaries that infiltrate multiple structures or tissues within the lungs. PVOD is characterized by a buildup of abnormal fibrous tissue in the small veins in the lungs, resulting in occlusion of the pulmonary veins that carry oxygenated blood from the lungs to the heart.

DISEASE OVERVIEW

	PCH	PVOD	PAH
Age of onset	Variable but often in third to fourth decades	Variable but most often in third to fifth decades	Fourth to fifth decade
Gender difference	None	None	Females>males
Symptoms	PAH, clubbing of digits more common	PAH, clubbing of digits more common	PAH, clubbing of digits uncommon
	Progressive dyspnea	Progressive dyspnea	Dyspnea
	Syncope	Syncope	Syncope
	Hemoptysis – in 40%	Hemoptysis – rare	Hemoptysis – rare
	Pericardial effusions – rare	Pericardial effusions – rare	Pericardial effusions
	Pleural effusion in 25%	Pleural effusion in 20%	Pleural effusion in 15%
	Increased pulmonary artery pressure with normal wedge	Increased pulmonary artery pressure with normal wedge	Increased pulmonary artery pressure with normal wedge
Clinical Course	Shorter time from onset of symptoms to death	Shorter time from onset of symptoms to death	Slower progression from onset of symptoms to death

Table adapted from Chaisson, 2016

Incidence

Rare

Inheritance

Autosomal recessive

TEST DESCRIPTION

Clinical Sensitivity

- >90% for autosomal recessive *EIF2AK4*-related disorders (Chaisson, 2016; Galle, 2016; Ma, 2015)
- <10% for PAH

TESTS TO CONSIDER

EIF2AK4-Associated Disorders (EIF2AK4) Sequencing 2010696
Method: Polymerase Chain Reaction/Sequencing

Preferred test to confirm diagnosis or assess carrier status for an *EIF2AK4*-associated disorder, PCH, and PVOD, especially when previous molecular testing for variants in other genes associated with PAH did not identify a cause.

Related Tests

Pulmonary Arterial Hypertension (PAH) Panel, Sequencing and Deletion/Duplication 2009345
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Preferred test to confirm diagnosis of PAH, especially in those with a family history of PAH.

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

Recommended test if there is a known familial sequence variant previously identified in a family member. A copy of the family member's test result documenting the known familial variant is required.

Analytical Sensitivity/Specificity

99%

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