EIF2AK4-Associated Disorders

Indications for Ordering

- Confirm diagnosis and genetic etiology of pulmonary capillary hemangiomatosis (PCH) or pulmonary veno-occlusive disease (PVOD) in a symptomatic individual
- Predictive testing for at-risk relatives of an individual with an *EIF2AK4*-associated disorder
- Carrier testing for the reproductive partner of an individual known to carry one or more *EIF2AK4* gene variants

Test Description

Polymerase chain reaction followed by bidirectional sequencing of the entire *EIF2AK4* gene coding region and intron/exon boundaries

Tests to Consider

Primary test

EIF2AK4-Associated Disorders (*EIF2AK4*) Sequencing 2010696

- Preferred test to confirm diagnosis or assess carrier status for an *EIF2AK4*-associated disorder, pulmonary capillary hemangiomatosis (PCH), and pulmonary veno-occlusive disease (PVOD), especially when molecular testing for variants in other genes associated with pulmonary arterial hypertension (PAH) has not identified a cause

Related test

Pulmonary Arterial Hypertension (PAH) Panel, Sequencing and Deletion/Duplication, Multigene 2009345

- Preferred test to confirm diagnosis of pulmonary arterial hypertension (PAH), especially in those with known family history
  - Genes – ACVRL1, BMPR2, CAV1, EIF2AK4, ENG, KCNK3

Disease Overview

Incidence – rare

Symptoms

- Progressive dyspnea
- Cough
- Hemoptysis
- Fatigue
- Weight loss
- Pulmonary arterial hypertension

Diagnostic issues

Variable presentation depending on the affected lung structures

- PCH may mimic idiopathic PAH, PVOD, or pulmonary hemosiderosis

Pathophysiology

Two different histological patterns of disease currently associated with *EIF2AK4* variants – PCH and PVOD

- PCH –uncontrolled proliferation of capillaries in the pulmonary interstitium
  - Capillary invasion may impact the pulmonary veins or arteries, alveolar walls and alveolar space, intralobular fibrous septa and bronchi, pericardium, pleura, and/or mediastinal lymph nodes
- PVOD
  - Occlusion or narrowing of pulmonary veins and venules by fibrous tissue
  - Dilatation of alveolar capillaries and capillary proliferation may be noted
  - Dilatation of lymphatics can occur

Genetics

Gene – *EIF2AK4*

Inheritance – autosomal recessive

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - >90% for heritable *EIF2AK4*-related disorders
  - <10% for PAH
- Analytical sensitivity/specificity – 99%

Results

- Positive
  - Two pathogenic variants identified on opposite chromosomes
    - Confirms a diagnosis of PCH/PVOD
  - One pathogenic variant identified
    - Individual is at least a carrier of an *EIF2AK4*-associated disorder
- Negative – no pathogenic *EIF2AK4* gene variant detected
  - Reduces but does not exclude the possibility of a hereditary form of PAH, PCH, or PVOD
- Inconclusive – one or more gene variants detected, but whether pathogenic or benign is unclear

Limitations

- Not detected
  - Deep intronic and regulatory region mutations
  - Large exonic deletions and duplications
- Diagnostic errors can occur due to rare sequence variations