Pulmonary Arterial Hypertension

Indication for Ordering

Confirm diagnosis of pulmonary arterial hypertension (PAH), especially in those with known family history

Test Description

- Next generation sequencing
  - Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Sequence variants reported are confirmed by Sanger sequencing
- Deletion/duplication analysis by custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary test

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

- Preferred test to confirm diagnosis of PAH
- Genes – *ACVRL1, BMPR2, CAV1, EIF2AK4, ENG, KCNK3*

Related tests

Pulmonary Arterial Hypertension (*BMPR2*) Sequencing and Deletion/Duplication 2003405

- Acceptable test for individuals with clinical symptoms of PAH
- If negative, consider 2009345

Pulmonary Arterial Hypertension (*BMPR2*) Sequencing 2003410

- Alternate test for individuals with clinical symptoms of PAH
- Large deletions and duplications will not be detected

EIF2AK4-Associated Disorders (*EIF2AK4*) Sequencing 2010696

- Confirm diagnosis or assess carrier status for an *EIF2AK4*-related disorder, especially when testing for other genes associated with PAH has not identified a cause

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – 1-2/million

Symptoms

- Shortness of breath
- Fatigue
- Syncope
- Chest pain
- Palpitations
- Edema

Physiology

- Widespread occlusion/destruction of the smallest pulmonary arteries
- Right ventricle has increased work due to increased blood flow resistance
  - Right ventricle hypertrophy occurs
- Heart failure ensues when the right ventricle can no longer maintain sufficient pressure to generate blood flow

Diagnosis

- Exclude other common causes of symptoms
  - Heart disease
  - Pulmonary disease
    - Asthma
  - Pulmonary embolism
  - Connective tissue disease
  - Cirrhosis
  - HIV
- Document mean pulmonary artery pressure >25 mm Hg at rest or >30 mm Hg with exercise

Genetics

See table

Test Interpretation

Clinical sensitivity

- 75-80% for familial cases
- ~25% for simplex cases

Results

- Positive
  - One copy of a pathogenic variant detected in *ACVRL1, BMPR2, CAV1, ENG,* or *KCNK3* gene **OR**
  - Two pathogenic variants detected in *EIF2AK4* gene
    - Associated with risk for PAH and, in some cases, additional vascular abnormalities
  - One variant detected in *EIF2AK4* gene
    - Indicates carrier status for an *EIF2AK4*-related disorder
- Negative
  - No pathogenic variant detected in *ACVRL1, BMPR2, CAV1, EIF2AK4, ENG,* or *KCNK3* gene
    - Diminishes but does not rule out the likelihood of familial PAH
- Inconclusive
  - Variants of unknown clinical significance may be identified

Limitations

- Not determined or evaluated
  - Variants in genes not listed
  - Deep intronic or regulatory region variants
  - Breakpoints of large deletions/duplications
- Small deletions or insertions may not be detected by massively parallel sequencing
- Copy number variants <1,000 base pairs may not be detected in the targeted genes
- Diagnostic errors can occur due to rare sequence variations

Gene Symbol	Gene Description	NM #	OMIM #	Condition[1]	Inh.[2]	PAH Attributable to Gene	Variant Identification	Penetrance
ACVRL1	Activin receptor-like kinase 1	000020	601284	HHT type 2/ HHT2	AD	~1%	90% by sequencing; 10% by large del/dup analysis	<1% for PAH >95% for HHT
BMPR2	Bone morphogenetic protein receptor, type II	001204	600799	*BMPR2*-related PAH/PAH1	AD	75% of familial cases; 25% of simplex cases	52% by sequencing; 48% by large del/dup analysis	20%
CAV1	Caveolin 1	001753	601047	PAH3	AD	~1%	Unknown	Unknown
EIF2AK4	Eukaryotic translation initiation factor 2 alpha kinase 4	001013703	609280	PAH, PCH, PVOD	AR	>10%	To date, all known variants are detected by sequencing	Unknown
ENG	Endoglin	001114753	131195	HHT type 1/ HHT1	AD	~1%	90% by sequencing; 10% by large del/dup analysis	<1% for PAH >95% for HHT
KCNK3	Potassium channel, subfamily K, member 3	002246	603220	PAH4	AD	Unknown	Unknown	Unknown

[1]HHT = hereditary hemorrhagic telangiectasia; PAH = pulmonary arterial hypertrophy; PCH = pulmonary capillary hemangiomatosis; PVOD = pulmonary veno-occlusive disease
[2]Inh. = inheritance; AD = autosomal dominant; AR = autosomal recessive