Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is caused by widespread occlusion or destruction of the smallest pulmonary arteries, leading to increased blood flow resistance, right ventricular hypertrophy, and heart failure. Genetic testing is most appropriate when no obvious etiology for pulmonary hypertension is found or if a family history of PAH exists.

Disease Overview

Symptoms

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

Epidemiology

Incidence: 1-2/million

Inheritance

- Autosomal dominant: *ACVRL1*, *BMPR2*, *CAV1*, *ENG*, *KCNA5*, *KCNK3*, and *SMAD9*
- Autosomal recessive: *EIF2AK4*

Test Description

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

- 75-80% for familial cases[1,2]
- ~25% for simplex cases[1,2]

Limitations

- A negative result does not exclude a heritable form of pulmonary arterial hypertension.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *KCNA5*
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing

Tests to Consider

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

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Preferred test to confirm a 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 lab report documenting the known familial variant is required

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is required

- Deletions/duplications less than 1kb in the targeted genes by array
- Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions

- Low-level somatic variants
- Single exon deletions/duplications in the following exons:
  - *EIF2AK4* (NM_001013703) 2, 5, 29, 34, 35

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	MIM Number	Disorder	PAH Attributable to Gene
ACVRL1	601284	HHT type 2	1%
BMPR2	600799	*BMPR2*-related PAH; PAH1; PVOD type 1	~75% of familial cases; ~25% of simplex cases
CAV1	601047	PAH3	~1%
EIF2AK4	609280	PVOD2	>10%
ENG	131195	HHT type 1	~1%
KCNA5	176267	Familial atrial fibrillation-7	Unknown
KCNK3	603220	PAH4	~1-3%
SMAD9	603295	PAH2	Unknown

HHT, hereditary hemorrhagic telangiectasia; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiotomatosis; PVOD, pulmonary veno-occlusive disease

References

1. Austin ED, Loyd JE. The genetics of pulmonary arterial hypertension. Circ Res. 2014;115(1):189-202. PubMed

2. Garcia-Rivas G, Jerjes-Sánchez C, Rodriguez D, et al. A systematic review of genetic mutations in pulmonary arterial hypertension. BMC Med Genet. 2017;18(1):82. PubMed

Additional Resources

Austin ED, Loyd JE, Phillips JA III. Heritable pulmonary arterial hypertension. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2021. [Last update: Jun 2015; Accessed: Feb 2020]

Ma L, Chung WK. The role of genetics in pulmonary arterial hypertension. J Pathol. 2017;241(2):273-280. PubMed

Ma L, Roman-Campos D, Austin ED, et al. A novel channelopathy in pulmonary arterial hypertension. N Engl J Med. 2013;369(4):351-361. PubMed

Prins KW, Thenappan T. World Health Organization group I pulmonary hypertension: epidemiology and pathophysiology. Cardiol Clin. 2016;34(3):363-374. PubMed

Scientific Leadership Council. Genetic testing and counseling for idiopathic and familial pulmonary arterial hypertension (PAH). Pulmonary Hypertension Association. [Last revised: Nov 2008; Accessed: Nov 2018]

Related Information

Pulmonary Arterial Hypertension - PAH

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