Pulmonary Arterial Hypertension Panel, Sequencing and Deletion/Duplication

Content Review: May 2022 Last Update: December 2023

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

Genetics

Genes

See Genes Tested table for genes included in the panel.

Epidemiology

Incidence:1-2/million

Approximately 80% of PAH is idiopathic and 20% is heritable.

Inheritance

- Autosomal dominant: *ACVRL1*, *BMPR2*, *CAV1*, *ENG*, *GDF2*, *KCNA5*, *KCNK3*, and *SMAD9*
- Autosomal recessive: *EIF2AK4*, *TBX4*

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Featured ARUP Testing

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

Method: Massively Parallel Sequencing

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

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Clinical Sensitivity

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

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

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 (excluding the 5' untranslated region of *ENG*, and a region of *ACVRL1* intron 9 encompassing the CT-rich variant hotspot region)
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Single exon deletions/duplications in the following exons:
    - *ENG* (NM_001114753) 1
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic 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

HHT, hereditary hemorrhagic telangiectasia; ICPPS, Ischiocoxopodopatellar syndrome; PAH, pulmonary arterial hypertension; PAPPAS, posterior amelia with pelvic and pulmonary hypoplasia syndrome; PCH, pulmonary capillary hemangiotomatosis; PVOD, pulmonary veno-occlusive disease

Gene	MIM Number	Disorder	PAH Attributable to Gene
CAV1	601047	PAH3	~1%
EIF2AK4	609280	PVOD2	>10%
ENG	131195	HHT type 1	~1%
GDF2	615506	HHT type 5	Unknown
KCNA5	176267	Familial atrial fibrillation 7	Unknown
KCNK3	603220	PAH4	~1-3%
SMAD9	603295	PAH2	Unknown
TBX4	147891; 601360	ICPPS; PAPPAS	Unknown

HHT, hereditary hemorrhagic telangiectasia; ICPPS, Ischiocoxopodopatellar syndrome; PAH, pulmonary arterial hypertension; PAPPAS, posterior amelia with pelvic and pulmonary hypoplasia syndrome; 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.

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.

Related Information

Pulmonary Arterial Hypertension Panel, Sequencing and Deletion/Duplication

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com