Pulmonary Arterial Hypertension Panel, Sequencing and Deletion/Duplication

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.

Clinical Sensitivity

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

Tests to Consider

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

Familial Targeted Sequencing 3005867
Method: Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.
Analytic Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate(^a) (%) and 95% Credibility Region (%)</th>
<th>Analytic Specificity (NPA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp(^b)</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp(^b)</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM Number</th>
<th>Disorder</th>
<th>PAH Attributable to Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACVRL1</td>
<td>601284</td>
<td>HHT type 2</td>
<td>1%</td>
</tr>
<tr>
<td>BMPR2</td>
<td>600799</td>
<td>BMPR2-related PAH; PAH1; PVOD type 1</td>
<td>~75% of familial cases; ~25% of simplex cases</td>
</tr>
<tr>
<td>CAV1</td>
<td>601047</td>
<td>PAH3</td>
<td>~1%</td>
</tr>
<tr>
<td>EIF2AK4</td>
<td>609280</td>
<td>PVOD2</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>ENG</td>
<td>131195</td>
<td>HHT type 1</td>
<td>~1%</td>
</tr>
<tr>
<td>GDF2</td>
<td>615506</td>
<td>HHT type 5</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

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
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<tr>
<td>KCNA5</td>
<td>176267</td>
<td>Familial atrial fibrillation 7</td>
<td>Unknown</td>
</tr>
<tr>
<td>KCNK3</td>
<td>603220</td>
<td>PAH4</td>
<td>~1-3%</td>
</tr>
<tr>
<td>SMAD9</td>
<td>603295</td>
<td>PAH2</td>
<td>Unknown</td>
</tr>
<tr>
<td>TBX4</td>
<td>147891; 601360</td>
<td>ICPPS, PAPPAS</td>
<td>Unknown</td>
</tr>
</tbody>
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References


Additional Resources


Related Information

Pulmonary Arterial Hypertension Panel, Sequencing and Deletion/Duplication

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Content Review May 2022 | Last Update November 2022

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