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
- 25% for simplex cases

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
  - 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:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate(^a) (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

\(^a\) 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

<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>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>
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<td>SMAD9</td>
<td>603295</td>
<td>PAH2</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

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

REFERENCES
