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
  o 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
    o One variant detected in EIF2AK4 gene
      ▪ Indicates carrier status for an EIF2AK4-related disorder

• Negative
  o 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
  o Variants of unknown clinical significance may be identified

Limitations

• Not determined or evaluated
  o Variants in genes not listed
  o Deep intronic or regulatory region variants
  o 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

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

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