Pulmonary Arterial Hypertension Panel

Panel Gene List: *ACVRL1, BMPR2, CAV1, EIF2AK4, ENG, GDF2, KCNK3, SMAD9*
Additional genes from our cardiology test menu may be added to this panel by selecting test code 696C.

Clinical Features:

Pulmonary arterial hypertension (PAH) is characterized by high blood pressure in the pulmonary artery and occurs when the small arteries throughout the lungs narrow in diameter. This increases the resistance to blood flow through the lungs, causing hypertension in the pulmonary artery as the right ventricle compensates to preserve pulmonary blood flow. Progressive heart failure develops when the right ventricle can no longer compensate for the higher resistance. Initial symptoms include dyspnea, fatigue, syncope, chest pain, palpitation, and edema. Idiopathic PAH is diagnosed clinically by pulmonary arterial hypertension (>25 mmHg at rest or >30 mmHg during exercise) in the absence of other known causes of pulmonary hypertension. The average age of diagnosis is approximately 36 years.[1] Genetic anticipation has been reported, with earlier ages of diagnosis in successive generations in families with PAH, but the mechanism remains unclear.[2,3] Approximately 6% of affected individuals have been reported to have an affected first degree relative.[4,5] Females are twice as likely to be affected as males.[6]

Inheritance Pattern/Genetics: Autosomal Dominant or Autosomal Recessive

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the PAH Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined PAH and a family history of disease. The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events.

It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Gene	Protein	Inheritance	Disease Association(s)
ACVRL1	ACTIVIN A RECEPTOR TYPE II-LIKE 1	AD	HHT, PAH
BMPR2	BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE II	AD	PAH
CAV1	CAVEOLIN 1	AD	PAH, lipodystrophy
EIF2AK4	EUKARYOTIC TRANSLATION INITIATION FACTOR 2-ALPHA KINASE 4	AR	PVOD2, PCH, PAH
ENG	ENDOGLIN	AD	HHT +/- PAH
GDF2	GROWTH/DIFFERENTIATION FACTOR 2	AD	HHT +/- PAH
KCNK3	POTASSIUM CHANNEL, SUBFAMILY K, MEMBER 3	AD	PAH
SMAD9	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 9	AD	PAH

Abbreviations: AD – Autosomal dominant; AR – Autosomal recessive; HHT – Hereditary hemorrhagic telangiectasia; PAH – Pulmonary arterial hypertension; PVOD2 - Pulmonary veno-occlusive disease 2; PCH - Pulmonary capillary hemangiomatosis

References:

1. Loyd JE, Phillips JA III. Heritable Pulmonary Arterial Hypertension. 2002 Jul 18 [Updated 2012 Dec 20]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1485/
2. Loyd et al. (1995) American Journal Of Respiratory And Critical Care Medicine 152 (1):93-7 (PMID: 7599869)
3. Sztrymf et al. (2005) Revue Des Maladies Respiratoires 22 (5 Pt 1):796-805 (PMID: 16272982)
4. O'Callaghan et al. (2012) European Respiratory Review : An Official Journal Of The European Respiratory Society 21 (125):218-22 (PMID: 22941886)
5. Rich et al. (1987) Ann. Intern. Med. 107 (2):216-23 (PMID: 3605900)
6. Austin et al. (2009) The European Respiratory Journal 34 (5):1093-9 (PMID: 19357154)