

Pulmonary Arterial Hypertension (*BMPR2*) Sequencing and Deletion/Duplication

TO DETERMINE THE ETIOLOGY OF FAMILIAL OR IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (PAH)

Disease Overview

- PAH is caused by widespread occlusion/destruction of the smallest pulmonary arteries. As resistance to blood flow increases, the right ventricle must work increasingly hard, leading to right ventricular hypertrophy. Heart failure results when the right ventricle can no longer maintain sufficient pressure to generate blood flow.
- Symptoms include: shortness of breath, fatigue, syncope, chest pain, palpitation, and edema.
- Diagnosis of PAH requires exclusion of other common causes of pulmonary hypertension, such as lung disease, pulmonary embolism, heart disease, connective tissue disease, cirrhosis, and HIV. Additionally, a diagnosis of PAH requires clinical documentation of a mean pulmonary artery pressure of greater than 25 mmHg at rest or greater than 30 mmHg during exercise.
- Average age of diagnosis is 36 years. Although the median survival for untreated individuals was less than three years after diagnosis in the 1980s, given the recent development of combination therapy with multiple new drugs, the median survival may now be extended 10 years or more after diagnosis.
- Individuals diagnosed with PAH should be followed in a center specializing in PAH diagnosis and therapy.
- Affected individuals should avoid high altitude and all drugs causing vasoconstriction, such as fenfluramine, dexfenfluramine, amfepramone, cocaine, amphetamines, and possibly estrogen compounds such as oral contraceptives and hormone-replacement therapy.
- Only 5 percent of those diagnosed with PAH have a known family history.
- At-risk family members should undergo echocardiographic screening every three to five years to enable early detection and treatment.

Epidemiology/Incidence

One to two new cases per million individuals per year.

Genetics

- *BMPR2*-related PAH is autosomal dominant.
- The penetrance of *BMPR2*-related PAH is 20 percent.
- Pathogenic *BMPR2* gene mutations are detected in approximately 70 percent of familial PAH cases. Of detectable mutations, 52 percent are identified by sequencing and 48 percent by large deletion/duplication analysis.
- Approximately 14 percent of idiopathic PAH patients have detectable *BMPR2* mutations.

Indication for Ordering

Individuals with a primary diagnosis of PAH, especially those with a known family history.

Contraindications

- Prenatal testing.
- Testing relatives for a known familial *BMPR2* mutation (please order [Familial Mutation, Targeted Sequencing, ARUP test #2001961](#)).

Interpretation

- Lack of a detectable *BMPR2* gene mutation does not rule out a hereditary cause of PAH, since *BMPR2* deep intronic and promoter mutations, as well as other genes that may predispose to familial PAH, are not interrogated.
- Detection of a pathogenic *BMPR2* gene mutation in a symptomatic individual is indicative of *BMPR2*-related PAH.
- Detection of a pathogenic *BMPR2* gene mutation in an asymptomatic individual indicates a 20 percent risk for developing PAH.
- Sequencing may reveal novel mutations of uncertain clinical significance.

Limitations

- Genes associated with familial PAH, other than *BMPR2*, will not be tested.
- Deep intronic and regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Breakpoints of large *BMPR2* deletions or duplications will not be determined.

Methodology

- PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *BMPR2* gene.
- Multiplex ligation-dependent probe amplification (MLPA) of the entire coding region.
- For familial PAH, the clinical sensitivity of *BMPR2* sequencing is 37 percent, while clinical sensitivity of MLPA is 34 percent.
- For idiopathic PAH, the clinical sensitivity of *BMPR2* sequencing and MLPA is approximately 14 percent.
- Analytical sensitivity and specificity of sequencing are 99 percent.
- Analytic sensitivity and specificity of MLPA are 99 percent.

Related Tests

- [Pulmonary Arterial Hypertension \(BMP2\) Sequencing \(2003410\)](#)
- [Pulmonary Arterial Hypertension \(BMP2\) Deletion/Duplication \(2003401\)](#)
- [Familial Mutation, Targeted Sequencing \(2001961\)](#)
- [Hereditary Hemorrhagic Telangiectasia \(ACVRL1 and ENG\) Sequencing & Deletion/Duplication \(0051382\)](#)

References

- Cogan JD, et al. High frequency of BMP2 exonic deletions/duplications in familial pulmonary arterial hypertension. *Am J Respir Crit Care* 2006;174(5):590–8.
- Machado RD, et al. BMP2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. *Am J Hum Genet* 2001;68:92–102.
- Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet* 2003;361:1533–44.
- Thomson JR, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMP2-II, a receptor member of the TGF-beta family. *J Med Genet* 2000;37:741–5.

Test Information

2003405 Pulmonary Arterial Hypertension (BMP2) Sequencing and Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.