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

**ARUP test code 2003405**

**BMPR2 FGA Specimen**  
Whole Blood

**PAH (BMPR2) Interpretation**

| Positive | *
| --- | ---
| **TEST PERFORMED** | 2003405
| **TEST DESCRIPTION** | Pulmonary Arterial Hypertension (BMPR2) Sequencing and Deletion/Duplication
| **INDICATION FOR TEST** | Not Provided

**RESULT**
One pathogenic variant was detected in the BMPR2 gene.

**DNA VARIANT**
- **Classification:** Pathogenic
- **Gene:** BMPR2
- **Nucleic Acid Change:** c.1128+1G>A; Heterozygous

**INTERPRETATION**
One copy of a pathogenic variant, c.1128+1G>A, was detected in the BMPR2 gene by sequencing. No pathogenic variants were detected by deletion/duplication analysis. Individuals with BMPR2 pathogenic variants are at 20 percent risk for being affected with pulmonary arterial hypertension (PAH). This disorder is characterized by widespread occlusion and destruction of the smallest pulmonary arteries, leading to right ventricular hypertrophy and eventual heart failure. This individual's offspring have a 50 percent risk of inheriting the causative pathogenic variant, but due to reduced penetrance, only a 10 percent risk for developing BMPR2-related PAH.

Evidence for variant classification: The BMPR2 c.1128+1G>A variant (rs863223420) is reported in the literature in individuals affected with idiopathic pulmonary arterial hypertension (Machado 2006, Wang 2019), and a similar variant with a different nucleotide change, c.1128+1G>T, was also reported in two affected families (Cogan 2006, Koelher 2004, Pfarr 2011, Kindermann 2003). The c.1128+1G>A variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 212811), and is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron 8. Functional assays show that the c.1128+1G>T variant results in a stable transcript with an in-frame skipping of exons 8 and 9 (Cogan 2006). Based on available information, the c.1128+1G>A variant is considered to be pathogenic.

**RECOMMENDATIONS**
Genetic consultation is indicated, including a discussion of...
medical screening and management. At-risk adult family members and symptomatic children should be offered targeted testing for the identified variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_001204.6 (BMPR2)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report, but are available upon request.

REFERENCES
Rindermann M et al. Primary pulmonary hypertension may be a heterogeneous disease with a second locus on chromosome 2q31. J Am Coll Cardiol. 2003 Jun 18;41(12):2237-44.

This result has been reviewed and approved by Hunter Best, Ph.D.

BACKGROUND INFORMATION: Pulmonary Arterial Hypertension (BMPR2) Sequencing and Deletion/Duplication

CHARACTERISTICS: Primary pulmonary arterial hypertension (PAH) is caused by widespread occlusion/destruction of the smallest pulmonary arteries that increases resistance to blood flow.
INCIDENCE: 1 to 2 new cases per million individuals per year.
INHERITANCE: Autosomal dominant.
PENETRANCE: Approximately 20 percent.
CAUSE: Pathogenic BMPR2 mutations.
CLINICAL SENSITIVITY: Approximately 70 percent for familial PAH and 15 percent for idiopathic PAH.
METHODOLOGY: Bidirectional sequencing of the entire BMPR2 coding region and intron-exon boundaries and Multiplex Ligation-dependent Probe Amplification (MLPA) to detect large BMPR2 coding region deletions and duplications.
ANALYTICAL SENSITIVITY AND SPECIFICITY FOR SEQUENCING: 99 percent.
ANALYTICAL SENSITIVITY AND SPECIFICITY FOR MLPA: 99 percent.
LIMITATION: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations will not be detected. Breakpoints of large deletions/duplications will not be determined. Mutations in genes other than BMPR2 are not evaluated.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS
### VERIFIED/REPORTED DATES

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**END OF CHART**

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*H=High, L=Low, *=Abnormal, C=Critical*