Cardiovascular Diseases Genetic Testing Program

Pulmonary Arterial Hypertension Panel

Pulmonary Arterial Hypertension (PAH) is characterized by the obstruction or obliteration of vessels within the pulmonary arteries, leading to increased resistance of blood flowing to the lungs. As a result, the right ventricle must pump harder to maintain blood flow to the lungs, and this may eventually lead to progressive heart failure. The prevalence of PAH is estimated to be 1-2/1,000,000, with more females being affected than males.

BMPR2 is the most common gene associated with PAH. Causative mutations or deletions/duplications in *BMPR2* can be identified in 80% of individuals with familial PAH. Mutations have also been identified in the *ACVRL1* gene in approximately 3% of cases. Other genes reported to be associated with PAH include *ENG*, *SMAD4*, *SMAD9*, *ABCA3*, *CAV1*, *KCNK3*, and *KCNA5*. Pulmonary hypertension is one of the pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (HHT). Genes associated with HHT (*ENG*, *ACVRL1*, *SMAD4*, *GDF2*) are included in this panel.

PAH has an autosomal dominant pattern of inheritance. The average penetrance of *BMPR2* mutations is estimated to be 20% overall and is sex dependent, with 14% in male and 42% in female.

Indication

The Pulmonary Arterial Hypertension Panel is indicated for confirmation of a diagnosis of PAH in patients with clinically evident disease. Genetic testing may also allow for early identification and diagnosis of individuals at greatest risk (e.g. family members) prior to the expression of typical clinical manifestations.

Pulmonary Arterial Hypertension Panel includes sequencing of:

- *BMPR2*
- *ACVRL1*
- *ENG*
- *SMAD4*
- *SMAD9*
- *ABCA3*
- *CAV1*
- *KCNK3*
- *GDF2*
- *KCNA5*

Molecular Genetics Laboratory

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Molecular Genetics Lab
Cincinnati Children's Hospital
3333 Burnet Ave. NRB 1042
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373

Methodology:

Next Generation Sequencing: All coding exons, as well as their flanking regions, of the genes listed in the panel are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Sensitivity & Accuracy:

Validation testing indicates an analytic sensitivity of greater than 99% and an analytic specificity of 100%.

References:

1) Deng Z, et al. Familial primary pulmonary hypertension (gene *PPH1*) is caused by mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet*. 2000;67:737-744.
2) Trembath RC, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med*. 2001;345:325-334.
3) Thomson JR et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding *BMPR-II*, a receptor member of the TGF-beta family. *J Med Genet*. 2000;37:741-745.
4) Lane KB, et al. Heterozygous germline mutations in *BMPR2*, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. *Nat Genet*. 2000;26:81-84.
5) Machado RD, et al. *BMPR2* haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. *Am J Hum Genet*. 2001;68:92-102.
6) Machado RD, et al. Mutations of the TGF-beta type II receptor *BMPR2* in pulmonary arterial hypertension. *Hum Mutat*. 2006;27:121-132.
7) Soubrier F, et al. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62:D13-21.
8) Remillard CV, et al. Function of KV1.5 channels and genetic variations of *KCNA5* in patients with idiopathic pulmonary arterial hypertension. *American journal of physiology. Cell physiology*. 2007;292:C1837-1853.
9) Wang G, et al. Early onset severe pulmonary arterial hypertension with 'two-hit' digenic mutations in both *BMPR2* and *KCNA5* genes. *Int J Cardiol*. 2014;177:e167-169.
10) Kunig AM, et al. *ABCA3* deficiency presenting as persistent pulmonary hypertension of the newborn. *J Pediatr*. 2007;151:322-324.
11) Danhaive O, et al. *ABCA3* mutation and pulmonary hypertension: A link with alveolar capillary dysplasia. *J Pediatr*. 2008;152:891-892.
12) Austin ED, et al. (Updated [January 12, 2012]). Heritable pulmonary arterial hypertension. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1993-2013. Available at http://www.genetests.org. Accessed [7/27/2015].

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Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact us at 513-636-4474

Turnaround Time:

Full Panel Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Panel Analysis: 81405 x3, 81406 x5, 81407, 81408
Known Mutation Analysis: 81403

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