

Genetic Testing and Counseling for Idiopathic and Familial Pulmonary Arterial Hypertension (PAH)

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A brief description of the disease and genetic testing is provided here, and sources for more extensive information are cited at the end.

What is familial PAH?

In idiopathic pulmonary arterial hypertension (IPAH), formerly called primary pulmonary hypertension (PPH), there is blockage to blood flow through the small arteries in the lungs. The disease occurs more often in women and may begin at any age. Most IPAH patients have no known affected relatives, and are said to have **sporadic IPAH**. IPAH patients who have one or more blood relatives with IPAH are said to have **familial PAH (FPAH)**. It is estimated that a few hundred families in the US have FPAH. Sometimes it is difficult to recognize that PAH has a familial basis, because the disease can skip generations, which happens when the parents or grandparents of a patient do not have PAH.

What causes familial PAH?

In most families, FPAH is caused by an inherited change (mutation) in the genetic directions for making a protein called bone morphogenetic protein receptor 2 (BMPR2). The BMPR2 protein helps regulate the growth of cells in the walls of the small arteries of the lungs. Other factors, probably genetic or environmental, are also needed to produce disease because only about 20% of individuals with a BMPR2 mutation ever develop IPAH. FPAH can occur at any age and affects women almost 3 times more often than men. Some individuals in families with a different genetic condition called Hereditary Hemorrhagic Telangiectasia (HHT) may also develop IPAH, due to a mutation in a different gene, called ALK1. Knowledge about genes that cause IPAH is still growing, so it is possible that other genes may contribute and will be discovered in the future.

[Learn what genetics can teach us about PAH \(www.phassociation.org/GeneticsandPAH\)](http://www.phassociation.org/GeneticsandPAH)

What is a gene?

Genes are units of genetic information that are passed from parents to children. Each gene contains the directions to make one or more proteins that the body needs. Genes control everything about us, including the way that our body grows and functions. All of us receive a full set of about 30,000 genes from each of our parents. Therefore, we have a pair of genes, one from each parent, to make each protein, including the BMPR2 protein.

How is familial PAH inherited?

Each normal person has a pair of BMPR2 genes in each cell in our bodies. One copy is inherited from our father and the other is inherited from our mother. The copy of the BMPR2 gene which we inherit from each parent occurs by random chance, like flipping a coin. A mutation in only one copy (from mother or father) of the pair of BMPR2 genes is enough to cause FPAH in a child.

By simple observation it can be seen that any person in the bloodline of a family with FPAH has an overall risk of about 1 in 10, or 10%, of developing FPAH during their lifetime. When a parent has a BMPR2 gene mutation, each child has a 50% chance to inherit the abnormal gene, and a 50% chance to inherit the normal gene. If a child inherits the normal gene, then that child's risk is similar to that of the general population, which is about one in a million for developing PAH. If a child inherits the abnormal disease gene, that does not necessarily mean they will develop FPAH. The likelihood for a person with a BMPR2 mutation to develop FPAH is estimated to be about 20%, though the actual risk may be different in each family. In other words, 80 out of 100 people who inherit a BMPR2 mutation will never develop IPAH.

Identification of a genetic mutation in a patient who already has PAH does not affect their medical care, so this result has importance only to their family.

The gene for BMPR2 is very large, and many different mutations (>100) have been found in it. In each FPAH family, one specific mutation in BMPR2 is the cause of FPAH in every patient in that family, and every patient within that family has that same specific mutation. Different families have different BMPR2 mutations. Knowing which specific mutation is present in a family is important because it makes it much easier to perform genetic testing for any person in that family. Testing one part of the large BMPR2 gene for a known mutation is far easier than testing for changes in the entire gene. In other words, searching for a mistake in an entire phone book would take a very long time and the mistake could be missed, but looking up the spelling of a specific name (testing for a known mutation) is accurate and easy to do.

What is the cause of sporadic IPAH?

The cause of most sporadic IPAH is not known, but BMPR2 mutations have been found to cause sporadic IPAH in 10% to 40% of IPAH patients. Children of IPAH patients with BMPR2 mutations have the same risks as the children of individuals with familial PAH. So far, most people with sporadic IPAH do not have a detectable BMPR2 mutation.

What testing is available for people at risk for familial PAH?

Medical testing shows whether a person has signs of PAH at the time of testing. One simple test, an echocardiogram, is a noninvasive and painless sound wave test of the heart that is often used to screen for PAH. However, it may be expensive, is not always accurate, and does not predict whether a person will develop IPAH in the future.

Genetic testing is laboratory testing of DNA, usually from a blood specimen. It searches for a mutation in a gene. The results of genetic testing can better define the actual risk for another family member to develop FPAH, especially when a BMPR2 mutation has been identified in a PAH patient in the same family. Genetic testing does not tell whether a person has any signs of PAH.

At present, BMPR2 mutations have been identified in about 80% of the families with FPAH. Information about which specific mutation is present in each family may be available from the research team. If information is not available about which particular BMPR2 mutation causes disease in a specific family, then DNA from a patient with FPAH in that family is needed to try to identify a specific mutation for their family.

My family is involved in a research project on familial PAH. Can I get my genetic test result from the research laboratory?

By law, diagnostic testing for genetic mutations can be provided only by specially licensed clinical laboratories (CLIA approval). These regulations assure rigorous quality control at all stages of sample analysis and ensure that the test is performed by fully trained personnel. At present, most university institutional review boards (IRB) prohibit disclosure of results obtained in a research lab to unaffected family members. Thus, most research laboratories cannot reveal genetic test results for specific individuals, but the labs may provide information which they discovered about the location and type of BMPR2 mutation in a specific family.

How can I get genetic testing for familial PAH?

Because there can be unexpected risks, counseling by experts (genetics counselors) is necessary to be fully informed. Counselors will discuss all of the benefits, drawbacks, and limitations before a person makes a decision about genetic testing.

If a family has participated in a research study, they may want to contact the coordinator or the director of the research study to determine whether a BMPR2 mutation has been identified in their family.

If a BMPR2 gene mutation has been identified, the research study coordinator can help to arrange genetic counseling. The genetics counselor can help contact a clinical laboratory that provides genetic testing for BMPR2 mutations. The cost of testing will vary. A blood sample from a relative with IPAH or FPAH may be needed. The accuracy of testing will usually be greater than 99%.

If a BMPR2 gene mutation has not been identified, the laboratory can examine the entire gene and try to find a mutation. If a mutation is found, then this information can be used to test any family member. If a BMPR2 gene mutation cannot be found in a specific family, then genetic testing will not provide any information for unaffected family members. Another gene that has not yet been found could be responsible for PAH in that family.

If a family is not involved with a research group, they may wish to contact their primary care provider or a genetics counselor (see list below or the [National Society of Genetic Counselors website \(www.nsgc.org\)](http://www.nsgc.org)). Information about IPAH and laboratories which provide testing [can be found online \(www.ncbi.nlm.nih.gov/sites/GeneTests/\)](http://www.ncbi.nlm.nih.gov/sites/GeneTests/).

Who should have genetic testing?

This decision is very personal. After counseling, each person should decide what is in their own best interest. Some people may find it helpful to read over the “pros and cons” of testing that are listed below. These will be explained further and discussed in detail during genetic counseling.

Some possible benefits of genetic testing for familial PAH

- The risk for a person to develop FPAH is more accurate, which may decrease uncertainty about their health. Their children's risk estimates are also more accurate.
- If a person is found to not have the BMPR2 mutation which is known to cause FPAH in their family, they may feel relieved and can safely stop medical screening for FPAH.
- Knowing the result may help with planning a person's family or financial decisions.

Some possible drawbacks or limitations of genetic testing for familial PAH

- If a person has the BMPR2 mutation which causes FPAH in their family, they still do not know whether or when they will develop FPAH. Recommendations for medical screening are the same as before they had genetic testing.
- If a person has the familial BMPR2 mutation, they may feel anxious, depressed or upset.
- A person might have trouble buying life or health insurance if their health record showed that they inherited the familial BMPR2 mutation.
- A person might feel guilty because they did not inherit the familial BMPR2 mutation and escaped the disease, while their relatives suffered from FPAH.
- In some cases, genetic test results can cause anger, resentment, or other problems which can affect family relationships.

Can children have genetic testing for FPAH or IPAH?

Genetic testing in children who are under 18 presents serious ethical issues because legally they are not able to make an informed decision. Yet genetic testing can have a profound effect on their future. For example, the results of genetic testing can alter the child's self-image and future aspirations. It can also affect the relationship between child and parents.

For these reasons, many experts strongly recommend that genetic testing in childhood be avoided except when results will provide significant medical benefits. Both the American Academy of Pediatrics and the American Society of Human Genetics have published statements regarding the ethical issues involved.

In IPAH, there is no proof so far that genetic testing in childhood improves the long term medical outcome. If a person feels strongly that testing would be beneficial for their child, they may wish to discuss their concerns with a genetic counselor and a pediatric pulmonary hypertension physician or other expert.

Genetic testing has many important effects upon medical, social, and emotional aspects of a person's life. For this reason, professional counseling before and after testing is very important, and is required by testing centers.

At present only a few centers offer genetic testing and professional counseling for patients with pulmonary arterial hypertension and their families. At this time, these centers include:

- Columbia University
- LDS Hospital and the University of Utah
- Vanderbilt University

To learn more about genetic testing and PAH you may contact:

Columbia University

Wendy Chung, MD, PhD, Director
212-851-5313
wkc15@columbia.edu

LDS Hospital / University of Utah

Janet Williams, M.S.
Genetic Counselor
801-408-5057
janet.williams@intermountainmail.org

Vanderbilt University

Vickie Hannig, M.S.
Genetics Counselor
615-322-7601
Vickie.Hannig@Vanderbilt.edu

Counseling is strongly recommended and often required prior to testing. Testing is available at the following clinical laboratories:

Columbia University Molecular Biology Laboratory

New York, NY
Mahesh M Mansukhani, MD, Director
212-305-2546

LDS Hospital

Salt Lake City, Utah
John Carlquist, PhD, Director
801-408-1028

Vanderbilt University Molecular Genetics Laboratory

Nashville, TN
Cindy Vnencak-Jones, PhD, Director
615-343-9074

Ambry Genetics Corp

Alisa Viejo, CA
James Thompson, MD, PhD, Director
949-900-5517

[Find a genetic counselor in your area \(www.genetests.org\)](http://www.genetests.org)

GINA-Genetic Information Non-Discrimination Act

Signed into law May 21, 2008 and forbids employers and insurance companies to deny employment, promotions, and/or health coverage based on genetic information.

H. R. 493 details can be found at the [Library of Congress website \(www.loc.gov\)](http://www.loc.gov). Click on Thomas and enter the bill number.

Policy statements:

ASHG/ACMG policy statement. Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet 1995;57:1233-1241.

American Academy of Pediatrics Committee on Bioethics. Policy statement: ethical issues with genetic testing in pediatrics. Pediatrics 2001;107:1451-1455.

References and Resources:

[GeneTests web site \(www.PHAssociation.org/GeneTests\)](http://www.PHAssociation.org/GeneTests): This site contains summaries of many genetic conditions including PPH. It also has contact information for genetics clinics and laboratories with links to a list of the tests that each lab performs.

[National Society of Genetic Counselors Web Site \(www.PHAssociation.org/GeneticCounselors\)](http://www.PHAssociation.org/GeneticCounselors): This site provides contact information for genetic counselors in your area.

American Lung Association

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New York, NY 10019

Phone: 212-315-8700

Email: infor@lungusa.org

[Fact Sheet: Primary Pulmonary Hypertension \(PPH\) \(www.PHAssociation.org/UnderstandingPPH\)](http://www.PHAssociation.org/UnderstandingPPH)

DISCLAIMER:

This information is for general information only. These guidelines may not apply to your individual situation. You should rely on the information and instructions given specifically to you by your PH specialist and/or the nurses at your PH Center. This information is general in nature and may not apply to your specific situation. It is not intended as legal, medical or other professional advice, and should not be relied upon as a substitute for consultations with qualified professionals who are familiar with your individual needs.