

Genetic Counseling and Testing in Pulmonary Arterial Hypertension

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ABSTRACT: A subgroup of patients diagnosed with pulmonary arterial hypertension (PAH) carry transmissible pathogenic gene mutations. For many of these patients, the heritable nature of their disease can only be uncovered by genetic testing. Because identification of PAH patients who carry pathogenic gene mutations has important implications for other family members, genetic counseling and testing should be offered to patients diagnosed with idiopathic or familial PAH. This review describes the current state of genetic counseling and testing for patients diagnosed with PAH.

INTRODUCTION

World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH) is a rare but important disorder that narrows pulmonary arterioles and leads to increased pulmonary vascular resistance, right ventricular failure, and death. The diagnosis of PAH requires demonstration of precapillary pulmonary hypertension (PH), defined by a mean pulmonary artery pressure > 20 mm Hg, pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) > 3 Wood units (WU) not attributable to other disorders. The current classification of group 1 PAH includes seven subclasses (see PAH clinical classification in the review by Beshay et al. in this issue).

Over the past six decades, US investigators occasionally recognized families with multiple members diagnosed with PAH. In 1987, the first registry of US patients diagnosed with what was then called "primary pulmonary hypertension" (PPH) identified more than one affected family member in 13 of 187 (6%) patients with PPH.¹ Two decades later, investigators for the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) identified 97 of 1,742 (6%) patients with diagnostic features of PPH who had more than one family member diagnosed with PAH.^{2,3} Neither the National Institutes of Health PPH Registry nor REVEAL investigators used genetic tests to identify heritable PAH (HPAH) or heritable pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (HPVOD/PCH). Genetic testing can identify HPAH and HPVOD/PCH in patients when the family history does not provide evidence of heritable PH.

In 2020, investigators for the United States Pulmonary Hypertension Scientific Registry (USPHSR) provided data from the first US PAH patient registry to include genetic information.⁴

Genetic testing identified pathogenic or suspected pathogenic variants in 67 of 499 (13%) USPHSR participants and reclassified 40 of 218 (18%) patients diagnosed with idiopathic PAH (IPAH) and 13 of 256 (5%) patients diagnosed with associated PAH (APAH) to HPAH.

HERITABLE PULMONARY ARTERIAL HYPERTENSION

Physicians recognized HPAH (formerly familial PPH) before molecular causes of HPAH were discovered. In 1954, David Dresdale, MD, described a mother, sister, and son who displayed characteristic features of PPH.⁵ Thirty years later, Jim Loyd, MD, reported that autosomal dominant inheritance characterized familial PPH.⁶ In addition, Dr. Loyd described incomplete penetrance when he observed that not all obligate carriers of the causative gene mutation developed PPH. Other investigators suggested that many sporadic (idiopathic) cases of PPH were inherited,^{7,8} and in 2001, John Newman, MD, reported a common pathogenic mutation in several members of a multigenerational family that already had 12 members who were previously diagnosed with sporadic (idiopathic) PPH.⁹

Physicians identified other HPAH phenotypes and inheritance patterns. In 1972, Erik Trelle, MD, described patients with PAH and hereditary hemorrhagic telangiectasia (HHT).¹⁰ Once again, a pattern of autosomal dominant inheritance was present, and penetrance was incomplete. In 1988, David Langleben, MD, identified a family affected by pulmonary capillary hemangiomatosis (PCH).¹¹ In this case, the autosomal recessive inheritance pattern and complete penetrance of PCH differed from familial PPH even though the two disorders shared many clinical features.

Discoveries of pathogenic gene mutations followed these seminal clinical observations. In 2000, two independent teams of investigators identified mutations in *BMPR2*, a gene

that encodes bone morphogenetic protein receptor II, as a cause of familial PPH.^{12,13} Within months, another team showed that many patients with sporadic (idiopathic) PPH carried pathogenic *BMPR2* mutations.¹⁴ One year later, Richard Trembath, FRCP, reported that mutations in the gene encoding activin receptor-like kinase 1 (*ALK1*) caused PAH in patients with HHT.¹⁵ Discoveries of additional genes with mutations that caused HPAH followed over the next two decades (Figure 1).¹⁶ Although defects in several molecular pathways underlie HPAH, many of the genes implicated caused defects in the transforming growth factor beta pathway.¹⁷

Recently, members of the genetics task force of the 6th World Symposium on Pulmonary Hypertension identified 17 genes with evidence of harboring mutations that cause PAH. These causal genes encode a variety of proteins that affect pulmonary vascular structure and function (Table 1).¹⁶ Pathogenic mutations in *BMPR2* are the most common cause of HPAH in both adults and children.^{4,18,19} However, the nature of causal gene mutations found in children with PAH differs significantly from the nature of those found in adults with PAH.¹⁸ De novo mutations, those not inherited from parents, are more likely to cause PAH in children than adults. Furthermore, the prevalence of genes with causal mutations identified in children with PAH differs significantly from the prevalence of causal gene mutations identified in adults with PAH. For example, mutations in *TBX4*, a transcription factor in the T-box gene family that modulates limb and lung development, are found more commonly in children than adults with PAH.²⁰

GENETIC TESTING

Discoveries of gene mutations that cause PAH and advances in molecular diagnostic testing permit clinicians to use genetic tests to identify which patients diagnosed with PAH

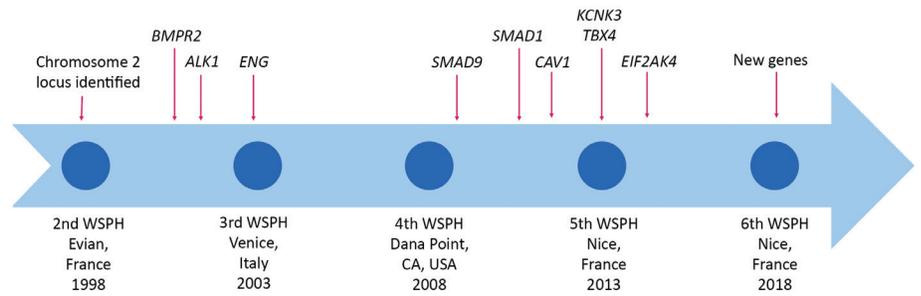


Figure 1.

Discovery of gene mutations that caused heritable pulmonary arterial hypertension (PAH) began with the localization of a causative gene to chromosome 2 at the time of the 2nd World Symposium on Pulmonary Hypertension and continued as important scientific advances were reported at successive World Symposia on Pulmonary Hypertension (WSPH). Genes with mutations that cause PAH include *BMPR2* (bone morphogenetic protein receptor type II), *ALK1* (activin A receptor type II-like 1), *ENG* (endoglin), *SMAD1* (mothers against decapentaplegic homologue 1), *SMAD9* (mothers against decapentaplegic homologue 9), *CAV1* (caveolin 1), *KCNK3* (potassium channel subfamily K, member 3), *TBX4* (T-box 4), and *EIF2AK4* (eukaryotic translation initiation factor 2 α kinase 4). Reproduced with permission of the © ERS 2021: European Respiratory Journal Jan 2019, 53 (1) 1801899; DOI: 10.1183/13993003.01899-2018.¹⁶

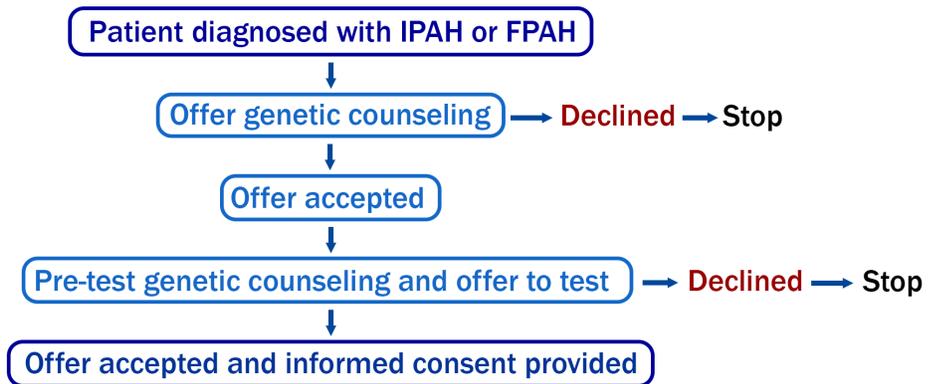


Figure 2.

A simple algorithm for genetic counseling followed by informed consent to perform genetic testing of patients diagnosed with idiopathic pulmonary arterial hypertension (IPAH) or familial pulmonary arterial hypertension (FPAH).

have HPAH; furthermore, they allow clinicians to offer genetic counseling and testing to family members when a pathogenic mutation is found.

Genetic Counseling

An offer of genetic counseling (Figure 2) is the first step for patients diagnosed

with IPAH or familial PAH and for those diagnosed with idiopathic or familial PAH with overt features of venous/capillary involvement. Patients in other PAH subgroups—including PAH associated with drugs, a connective tissue disease, or congenital heart disease—may also benefit from genetic counseling and testing.²¹

GENE	PREVALENCE (%)*	PHENOTYPE	
<i>BMPR2</i>	15.3	PAH	Autosomal dominant with incomplete penetrance
<i>TBX4</i>	1.3	PAH	Autosomal dominant with incomplete penetrance More common in children
<i>KCNK3</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>GDF2</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>KLF2</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>SMAD4</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>ATP13A3</i>	1.1	PAH	Autosomal dominant with incomplete penetrance
<i>BMPR1B</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>KCNA5</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>SMAD1</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>SMAD9</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>SOX17</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>AQP</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>CAV1</i>	<1.0	PAH	Autosomal dominant with incomplete penetrance
<i>ACVRL1</i>	<1.0	HHT	Autosomal dominant with incomplete penetrance
<i>ENG</i>	<1.0	HHT	Autosomal dominant with incomplete penetrance
<i>EIF2AK4</i>	<1.0	PVOD, PCH	Autosomal recessive with complete penetrance

Table 1.

Genes with mutations reported to cause heritable pulmonary arterial hypertension (PAH). Adapted from Morrell NW et al. Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J.* 2019 Jan;53(1). doi: 10.1183/13993003.01899-2018.¹⁶ HHT: hereditary hemorrhagic telangiectasia; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary hemangiomatosis

The purpose of genetic counseling is to inform the patient about HPAH and disclose the risks and benefits of genetic testing (Table 2). Potential benefits of genetic testing include informed decisions about reproduction and facilitation of early diagnosis and treatment of family members who develop HPAH. Potential risks of genetic testing include anxiety for family members who carry a pathogenic mutation and feelings of guilt in family members who do not carry a mutation.^{16,22} In the United States, genetic counselors should address the Genetic Information Nondiscrimination Act of 2008,²³ which protects employment and health insurance but does not protect life or long-term disability insurance.

Experts recommend that family members who are diagnosed with PAH, the probands, undergo testing for pathogenic mutations in genes known to cause HPAH before unaffected family members are tested.¹⁶ Genetic testing of family members is unnecessary if a pathogenic mutation cannot be identified in the proband. Patients can inform their families when a genetic test suggests HPAH so that other family members can seek genetic counseling and testing. Guideline authors recommend annual evaluations for asymptomatic family members whose mutation status remains unknown or for asymptomatic carriers of pathogenic mutations.²⁴⁻²⁶

Gene Panels

Genetic tests may include a gene panel, which analyzes multiple genes at once, or whole exome sequencing, which examines all gene-coding regions. Gene panels are the preferred initial test for mutations commonly responsible for HPAH. Next-generation sequencing (NGS) gene panels provide the most rapid turnaround time (weeks), and NGS gene panel tests are most likely to be covered by insurance. NGS panels for PAH may not all examine the same genes. For example, the current PAH NGS panel at Associated Regional

Describe disease characteristics, mutation detection techniques, and the inheritance pattern of disease transmission.
Describe potential implications of genetic test results for the patient.
Describe implications and possible consequences for the patient's family members.
Describe prevention and treatment possibilities.
Obtain informed consent for genetic testing.
Provide individual consultation for asymptomatic high-risk relatives.
Table 2. Guidelines for genetic counseling.

and University Pathologists laboratories examines *ACVRL1*, *BMP2*, *CAV1*, *EIF2AK4*, *KCNA5*, *KCNK3*, and *SMAD9* (with the possible addition of *TBX4* next year), but other expanded PAH gene panels examine up to 14 additional genes.²¹

If gene panel testing of a PAH patient's DNA identifies a pathogenic mutation, then family members can undergo a lower-cost targeted genetic test for the specific mutation. Conversely, if pathogenic mutations are not identified in a PAH gene panel, then whole exome sequencing may be ordered if the clinical suspicion for HPAH remains high.

Interpreting Genetic Test Results

The complexity of clinical genetic tests for HPAH warrants interpretation by a board-certified clinical molecular geneticist or molecular genetic pathologist. Reports of genetic tests for HPAH identify mutations as “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” according to standards and guidelines of the American College of Medical Genetics and Genomics.²⁷ As with all genetic tests, interpretation may differ and require additional counseling and consultation.²⁸

Post-Test Genetic Counseling

Post-test genetic counseling is essential for patients who undergo tests to detect and characterize HPAH. Genetic test results are used to characterize an individual family member's lifetime risk of developing PAH and to identify at-risk members of a family. For example, a family member who does not carry a disease-causing *BMP2* mutation has the same risk as the general population (ie, about one chance in a million) of developing IPAH. In contrast, a first-order relative who carries a disease-causing *BMP2* mutation has approximately one chance in five of developing PAH. Furthermore, available data suggest that the lifetime risk of developing PAH is approximately 14% for men and 42% for women who carry a pathogenic *BMP2* mutation.²⁹

CONCLUSION

Careful clinical observations, basic molecular discoveries, and advances in laboratory technology have made genetic counseling and testing possible for patients diagnosed with group 1 PAH. Genetic counseling and testing offer PAH patients with other affected family members, those diagnosed with IPAH, and those with familial or idiopathic PVOD/PCH the opportunity to plan their families and avoid the tragedy of undiagnosed and untreated PAH in other family members.

KEY POINTS

- Current evidence suggests that 10% to 15% of patients diagnosed with idiopathic pulmonary arterial hypertension (PAH) will be found to have heritable PAH after genetic testing.
- Genetic counseling is necessary to inform patients about heritable PAH and to disclose the risks and benefits of genetic testing.
- Genetic test results can diagnose heritable pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, influence family planning, and facilitate earlier detection of heritable PAH.

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The author has completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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