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Heritable Pulmonary Arterial Hypertension Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding genetic causes of heritable pulmonary arterial hypertension (HPAH) and related genetic counseling issues.

The goals of this overview are the following:

Goal 1

Describe the clinical characteristics of HPAH.

Goal 2

Review the genetic causes of HPAH.

Goal 3

Provide an evaluation strategy to identify the genetic cause of HPAH in a proband (when possible).

Goal 4

Inform genetic risk assessment and surveillance of at-risk relatives for detection of early treatable manifestations of HPAH.

Goal 5

Review a high-level view of management of HPAH.

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1. Clinical Characteristics of Heritable Pulmonary Arterial Hypertension

Heritable pulmonary arterial hypertension (HPAH) includes familial PAH (i.e., PAH that occurs in ≥2 family members) and simplex PAH (i.e., a single occurrence in a family) when a pathogenic variant in one of the known genes has been identified.

Note: Pulmonary hypertension (PH) is a general designation for increased blood pressure in the lungs from any cause and is classified into five groups by the World Symposium of PH (WSPH) [Simonneau et al 2019]. PAH is classified as Group 1, and it is a clinical diagnosis that is established by excluding the others, including PH resulting from heart disease (Group 2), PH resulting from lung disease or hypoxia (Group 3), PH from chronic thromboembolic PH (Group 4), and a variety of miscellaneous causes, metabolic disorders, sarcoidosis, or splenectomy (Group 5).

The diagnosis of HPAH is established clinically [Morrell et al 2019] by the following in a proband:

- Confirmation of the presence of PAH (i.e., mean pulmonary artery pressure >20 mm Hg at rest during cardiac catheterization [Simonneau et al 2019])
- Exclusion of other known causes of PAH; see Differential Diagnosis of HPAH.
- Identification of a heterozygous pathogenic (or likely pathogenic) variant in one of the genes known to be associated with HPAH (Table 1) and/or confirmation of PAH in one or more of the proband's family members

  Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Clinical Symptoms

Clinical symptoms of HPAH include dyspnea, fatigue, chest pain, palpitation, syncope, or edema. HPAH affects all ages, including the very young and the elderly; the mean age at diagnosis is 34.9±14.9 years [Larkin et al 2012].

Females are twice as likely to be affected as males; survival is worse in males than in females [Kozu et al 2018].

The clinical course varies considerably, but untreated individuals gradually deteriorate, with a mean survival of 2.8 years after diagnosis. The variability in survival across individuals is broad, ranging from sudden death to decades (rare). The physiologic stress of pregnancy in an individual with HPAH is significant and maternal mortality is believed to be substantial, with risk variable according to pulmonary arterial pressure and right ventricular dysfunction [Ballard et al 2021].

Clinical Examination

Because the symptoms of HPAH are nonspecific and develop slowly, affected individuals often mistakenly attribute their initial symptoms to aging, poor physical conditioning, or being overweight. Some individuals report no symptoms, and diagnosis is suspected on an incidental basis because of signs (abnormal findings on physical examination) including:

- Accentuation of the pulmonic component of the second heart sound;
- Right ventricular heave or cardiac murmur such as tricuspid regurgitation resulting from right ventricular dilatation;

- Signs of right ventricular failure such as increased venous pressure, edema, or hepatomegaly (later in the course).

Clinical Testing to Confirm PAH

The approach to the individual with suspected PAH has been carefully described by several international guidelines [Galiè et al 2016]. Note: It is generally advised, when possible, to involve a specialty pulmonary hypertension referral center during the diagnostic work up.

Once symptoms or signs concerning for PAH are identified on clinical exam, the following evaluations are recommended:

- Electrocardiogram
- Transthoracic echocardiogram
- Laboratory work to include complete blood count, comprehensive metabolic panel, brain natriuretic peptide, antinuclear antibody, Rh factor, HIV testing, and coagulation studies
- Computed tomography of the chest and likely a ventilation/perfusion scan and pulmonary function studies

Ultimately, the diagnosis of PAH is formally made at the time of cardiac catheterization at rest, which is recommended for all individuals with suspected PAH.

- Specifically, cardiac catheterization is used to confirm the diagnosis of PAH by directly measuring pulmonary artery pressures and excluding other cardiac abnormalities.
- Challenge testing with vasodilators (i.e., inhaled nitric oxide) or fluid loading, or both, during catheterization is important to assess physiologic responses to guide appropriate therapy.

Differential Diagnosis of HPAH

Other cardiopulmonary causes of PH are far more common than PAH. Importantly, causes of PH associated with related conditions need to be excluded before the diagnosis of PAH can be established. Other causes of PH include connective tissue diseases, cirrhosis, HIV infection, treatment with appetite suppressants, and the following acquired and hereditary disorders [Badesch et al 2010]:

- **Heart disease (WSPH Group 2).** Most advanced cardiac conditions, including left ventricular dysfunction, congenital heart disease, valvular disease, and cardiomyopathy, can cause PH. Heart diseases are detected by physical examination, electrocardiogram, echocardiography, and cardiac catheterization.
- **Lung disease or hypoxia (WSPH Group 3).** The advanced stages of all lung diseases may cause PH. Most lung diseases that cause PH are identified by detection of abnormal lung sounds on physical examination, pulmonary function testing, and/or high-resolution computed tomographic lung imaging.
- **Pulmonary embolism / disease of large pulmonary vessels (WSPH Group 4).** Pulmonary embolism or disease of large pulmonary vessels is detected by imaging procedures; traditionally, screening by lung perfusion scanning with confirmation by pulmonary arteriography. Although CT angiography has improved greatly, nuclear medicine perfusion scanning still has a role in screening for chronic thromboembolic pulmonary hypertension (CTEPH), a disorder in which pulmonary emboli are not resorbed normally by fibrinolysis. It is important to correctly diagnose CTEPH because surgical pulmonary thromboendarterectomy is highly effective under the appropriate medical circumstances [Kim et al 2013].
- **Acquired pulmonary venoocclusive disease and pulmonary capillary hemangiomatosis.** These conditions are typically acquired but may be hereditary on rare occasion (most often associated with biallelic pathogenic variants in *EIF2AK4*) [Best et al 2014, Eyries et al 2014].

2. Genetic Causes of Heritable Pulmonary Arterial Hypertension

To date, ten genes are convincingly known to be associated with heritable pulmonary arterial hypertension (HPAH), although more discoveries will likely emerge over the next few years. Table 1 lists the percentage of HPAH caused by pathogenic variants in each of these genes based on data from 2572 individuals with World Symposium of Pulmonary Hypertension (WSPH) Group1 PAH (including 1211 individuals with a clinical diagnosis of "familial" or "idiopathic" PAH prior to genetic testing) enrolled in the PAH Biobank as reported in Zhu et al [2019].

Of note:

- *BMPR2*-releated HPAH is associated with decreased penetrance: lifetime risk of developing PAH with a *BMPR2* pathogenic variant in a male is 14% and 42% in a female.
- *TBX4*-related HPAH is associated with a variable phenotype with digit-limb-girdle abnormalities, developmental lung disease, developmental delay, and congenital heart disease, in addition to PAH (OMIM 147891).

Table 1. Heritable Pulmonary Arterial Hypertension (HPAH): Genes and Distinguishing Clinical Features

Gene [1]	% of Individuals w/ Pathogenic Variant in Gene [2]	Allelic Disorders	Reference
ACVRL1	Rare (16/2572)	Hereditary hemorrhagic telangiectasia	Girerd et al [2010]
BMPR1B	Rare (4/2572)	• Acromesomelic chrondrodysplasia w/ genital anomalies (OMIM 609441) • Brachydactyly (OMIM 112600 & 616849)	Chida et al [2012]
BMPR2	75% of HPAH cases [3] & 201/2572 PAH cases in the US PAH Biobank	• Congenital heart disease [4] • Fenfluramine-assoc pulmonary arterial hypertension (fen-PAH) [5] • Hereditary hemorrhagic telangiectasia • Pulmonary venoocclusive disease (OMIM 265450)	Cogan et al [2006]
CAV1	Rare (10/2572)	• Congenital generalized lipodystrophy (OMIM 612526) • Type 3 partial lipodystrophy, congenital cataracts, & neurodegeneration syndrome (OMIM 606721)	Austin et al [2012]
ENG	Rare (6/2572)	Hereditary hemorrhagic telangiectasia	Girerd et al [2010]
KCNK3	Rare (3/2572)	None	Ma et al [2013]
KDR	Rare (4/2572)	None	Swietlik et al [2020]
SMAD9	Rare (13/2572)	None	Shintani et al [2009]
TBX4	Rare (23/2572)	Posterior amelia w/pelvic & pulmonary hypoplasia syndrome (OMIM 601360)	Kerstjens-Frederikse et al [2013]

Table 1. continued from previous page.

Gene [1]	% of Individuals w/ Pathogenic Variant in Gene [2]	Allelic Disorders	Reference
TET2	Rare (10/2572)	Myelodysplastic syndrome, somatic (OMIM 614286)	Potus et al [2020]

Based on data from the National Biological Sample and Data Repository for Pulmonary Arterial Hypertension (PAH Biobank) [Zhu et al 2019]
Note: HPAH caused by pathogenic variants in the genes listed in Table 1 is inherited in an autosomal dominant manner.
1. Genes are listed alphabetically.
2. Out of 2572 individuals with World Symposium of Pulmonary Hypertension (WSPH) Group 1 PAH
3. Since the discovery of *BMPR2* [Aström et al 1999], numerous studies consistently show that among families with two or more individuals with confirmed PAH, approximately 75% have a detectable pathogenic germline variant in *BMPR2*.
4. Roberts et al [2004] described six individuals with complete type C atrioventricular canal, atrial septal defect, patent ductus arteriosus, partial anomalous pulmonary venous return, and aortopulmonary window with a ventricular septal defect.
5. In a retrospective study, the records of all persons with a diagnosis of fen-PAH evaluated from 1986 to 2004 were studied. The median duration of fenfluramine exposure was six months, with a median of 4.5 years between exposure & onset of symptoms. Nine (22.5%) of the 40 persons evaluated had a *BMPR*2 pathogenic variant [Souza et al 2008].

3. Evaluation Strategies to Identify the Genetic Cause of Heritable Pulmonary Arterial Hypertension in a Proband

Establishing a specific genetic cause of heritable pulmonary arterial hypertension (HPAH):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, and molecular genetic testing.

Medical history and physical examination. No particular findings in the medical history or on physical examination distinguish among the various genetic causes of HPAH; however, skeletal anomalies (e.g., patellar irregularities), tracheal and/or bronchial diverticulosis (noted by CT scan or bronchoscopy), developmental delay, and congenital heart disease can be suggestive of *TBX4* syndrome [Austin & Elliott 2020].

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of HPAH and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing). Gene-targeted testing requires the clinician to hypothesize which genes are likely involved, whereas genomic testing does not.

A multigene panel that includes the genes listed in Table 1 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which genes are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Genetic Risk Assessment and Surveillance of At-Risk Relatives

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Clarification of the genetic status of first-degree family members of an individual with heritable pulmonary arterial hypertension (HPAH) can allow early detection of HPAH and prompt initiation of treatment, and improve long-term outcome. A basic view of HPAH genetic risk assessment and surveillance for at-risk relatives is presented in this section; issues that may be specific to a given family or genetic cause of HPAH are not comprehensively addressed.

Note: Given the complexity of the genetics and surveillance recommendations for HPAH, health care providers should consider referring at-risk asymptomatic relatives to a Pulmonary Hypertension Specialty Referral Center, or to a Cardiovascular Genetics Center or genetic counselor specializing in cardiac or cardiopulmonary genetics (see NSGC – Find a Genetic Counselor or ABGC Find a Certified Genetic Counselor search tools).

Mode of Inheritance

HPAH is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with HPAH have an affected parent.
- Some individuals diagnosed with HPAH have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with HPAH caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case) and has a known HPAH-causing pathogenic variant, molecular genetic testing is recommended for the parents of the proband.
- If the proband has a known HPAH-associated pathogenic variant that is not identified in either parent, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with HPAH may appear to be negative because of failure to recognize the disorder in affected family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or

molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the HPAH-associated pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Because of the significant possibility of reduced penetrance of PAH in an individual who is heterozygous for a PAH-associated pathogenic variant (and the possibility that an individual's sex may influence penetrance), a sib who inherits the pathogenic variant identified in the proband may or may not develop clinically expressed PAH. For example, approximately 14% of males and 42% of females with a known *BMPR2* pathogenic variant will express PAH clinically in their lifetime [Larkin et al 2012].
- If the proband has a known HPAH-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be approximately 1.3% or less because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk that a sib of a proband with a known PAH-associated pathogenic variant has inherited the pathogenic variant is assumed to be 50% for clinical screening purposes (see Clinical Surveillance for Relatives at Risk).

Offspring of a proband. Each child of an individual with an HPAH-related pathogenic variant is at a 50% risk of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Clinical Surveillance for Relatives at Risk

Asymptomatic family members of an affected individual in whom the specific genetic cause of HPAH has not been identified. The WSPH, American College of Cardiology, and American Heart Association recommend serial screening by echocardiography of at-risk family members every three to five years to enable early detection and treatment.

Asymptomatic family members of an affected individual who has a known pathogenic variant in an HPAH-associated gene. If a definitive pathogenic variant is identified in the affected individual, molecular genetic testing can be performed in at-risk relatives to clarify their genetic risk:

- Those identified as heterozygous for the pathogenic variant present in the affected family member and thus at high risk for developing HPAH should be screened each year with a clinical evaluation and echocardiogram [McLaughlin et al 2009a, McLaughlin et al 2009b, Morrell et al 2019].
- Those without the familial HPAH-associated pathogenic variant are no longer considered to be at increased risk and thus may be discharged from cardiac surveillance.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **PHAWARE**

  www.phaware.global

- **Pulmonary Hypertension Association (PHA)**

8401 Colesville Road
Suite 00
Silver Spring MD 20910
Phone: 301-565-3004
Fax: 301-565-3994
Email: PHA@PHAssociation.org
www.phassociation.org

- **American Heart Association**
  What is Pulmonary Hypertension?
- **American Lung Association**
  Phone: 800-586-4872 (Toll-free HelpLine)
  Fax: 202-452-1805
  Email: info@lung.org
  www.lung.org
- **MedlinePlus**
  Pulmonary arterial hypertension

5. Management of Heritable Pulmonary Arterial Hypertension

See Abman et al [2015] (full text) and Galiè et al [2016] (full text) for evidence-based treatment algorithms for pediatric and adult populations respectively.

Referral centers specializing in diagnosis and therapy of pulmonary arterial hypertension (PAH) are available across the US (see Pulmonary Hypertension Association website). Consultation is encouraged for all persons suspected of having PAH because of the complexity and continuing evolution of diagnosis and treatment.

Unprecedented approval of medications for PAH by the FDA in the last two decades has led to availability of a dozen therapies which all demonstrate some efficacy. However, substantial limitations remain: none of them cures the disease, nor is effective in all patients, nor stops or reverses the underlying pathogenesis (obstruction of the pulmonary arteries).

The most effective among them, continuous IV prostacyclin or prostanoids, delivered by continuous IV or subcutaneous delivery, are the most complicated to administer as they require patient management of a pump for continuous infusion, with a myriad of possible problems, including sepsis related to chronic central venous catheters. Patient preference often dictates the route of medication administration (continuous IV or subcutaneous, aerosol, oral) or side effects determine which agents are personally acceptable.

There are no different therapeutic approaches for pregnant women with PAH; standard PAH-directed care remains a crucial component of care in addition to high-risk obstetric approaches.

Continuous patient monitoring for progression of disease and medication adjustment requires a dedicated multidisciplinary team that communicates seamlessly with multiple specialty pharmacies and insurers.

Chapter Notes

Author Notes

Genetic and genomic discovery efforts in PAH are rapidly progressing. Some sites of interest include the following:

- PAH Biobank
- National Cohort Study of Idiopathic and Heritable PAH
- UK Biobank
- Chung Lab at Columbia

Pulmonary Hypertension Clinical & Research Team
Vanderbilt Research Registry of PAH Families, Idiopathic PAH Cases, and other PAH Forms
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- 23 December 2020 (ha) Comprehensive update posted live; scope changed to overview
- 11 June 2015 (me) Comprehensive update posted live
- 20 December 2012 (cd) Revision: pathogenic varaints in *ACVRL1*, *BMPR1B*, *CAV1*, *ENG*, and *SMAD9* found in rare cases to cause FPAH
- 29 March 2011 (me) Comprehensive update posted live
- 15 November 2007 (cd) Revision: prenatal diagnosis available
- 18 July 2007 (me) Comprehensive update posted live
- 24 March 2006 (jl) Revision: duplication/deletion testing using Southern blot clinically available
- 29 June 2005 (jl) Revision: sequence analysis clinically available
- 2 November 2004 (me) Comprehensive update posted live
- 8 December 2003 (jl) Revision: Summary
- 18 July 2002 (me) Review posted live
- 14 January 2002 (jl) Original submission

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