GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

BMPR2-Related Pulmonary Arterial Hypertension

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Initial Posting: July 18, 2002.
Last Revision: November 15, 2007.

Summary

Disease characteristics. *BMPR2*-related pulmonary arterial hypertension (PAH) caused by mutations in the gene *BMPR2*, is characterized by widespread obstruction and obliteration of the smallest pulmonary arteries. When a sufficient number of vessels are occluded, the resistance to blood flow through the lungs increases, and the right ventricle attempts to compensate by generating higher pressure to maintain pulmonary blood flow. When the right ventricle can no longer compensate for the increased resistance, progressive heart failure ensues. Initial symptoms include dyspnea (60%), fatigue (19%), syncope (8%), chest pain (7%), palpitation (5%), and edema (3%). The mean age at diagnosis is 36 years. Mean survival after diagnosis is 2.8 years. Individuals who have *BMPR2*-related PAH have identical symptoms, signs, and clinical course as those with idiopathic PAH. The time from onset of symptoms to diagnosis may be shorter in individuals with *BMPR2*-related PAH, possibly because of familial awareness of the disease.

Diagnosis/testing. The diagnosis of PAH can be established clinically by confirming the presence of pulmonary arterial hypertension (i.e., mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg during exercise) and excluding other known causes of pulmonary hypertension (PH). The presence of a *BMPR2* mutation in an individual with PAH confirms the diagnosis of *BMPR2*-related PAH. Molecular genetic testing of *BMPR2* is available on a clinical basis.

Management. *Treatment of manifestations:* Referral centers specializing in PAH diagnosis and therapy are available across the US; continuous intravenous epoprostenol, the most effective therapy to date, is standard for individuals with serious or life-threatening PAH; newly approved medications include treprostinil (Remodulin®) subcutaneous, treprostinil (Remodulin®) intravenous, bosentan (Tracleer®), sildenafil (Revatio®), and inhalation iloprost (Ventavis®); a minority of individuals respond to oral calcium channel blockers; chronic anticoagulation therapy, diuretics, and supplemental oxygen are used routinely as needed; lung transplantation is effective, but age restrictions for potential transplant recipients apply and long-term survival is usually limited by chronic rejection. *Agents/circumstances to avoid:* appetite suppressants, such as fenfluramine/phentermine, dexfenfluramine, and amfepramone (diethylpropion); cocaine, amphetamines, and related compounds causing vasoconstriction; hypoxia (including that associated with high altitude); possibly estrogen compounds used as

oral contraceptives or hormone replacement therapy. *Testing of relatives at risk:* Recommendations for surveillance of asymptomatic at-risk family members are controversial: echocardiographic screening of at-risk family members every three to five years is recommended to enable earlier detection and treatment. The possible role of molecular genetic testing for early diagnosis of at-risk family members is yet to be established. *Other:* Anecdotal reports of onset of PAH with pregnancy raise concern about risks of pregnancy, but no consensus exists regarding the best approach to birth control in women with PAH.

Genetic counseling. *BMPR2*-related PAH is inherited in an autosomal dominant manner. The average penetrance of *BMPR2* mutations is approximately 20%. If a parent of a proband has *BMPR2*-related PAH, the risk to each sib of inheriting the gene mutation is 50%; however, because of reduced penetrance the risk to a sib of developing PAH is approximately 10% (50% x ~20%). Similarly, each child of an affected individual is at a 50% risk of inheriting the mutant allele; however, because of reduced penetrance the risk to offspring of developing PAH is approximately 10% (50% x ~20%). Prenatal testing for pregnancies at increased risk is available if the disease-causing mutation has been identified in the family.

Diagnosis

Clinical Diagnosis

The diagnosis of pulmonary arterial hypertension (PAH) may be suspected in individuals with the following if other causative diseases are absent:

- Symptoms: dyspnea, fatigue, chest pain, palpitation, syncope, or edema [Rich et al 1987]
- Signs (abnormal findings on physical examination):
  - 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)

PAH can be established clinically by the following:

- Confirmation of the presence of pulmonary arterial hypertension (i.e., mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg during exercise)
- Excludion of other known causes of pulmonary hypertension (PH) (see Differential Diagnosis) [McGoon 2001].

The presence of a *BMPR2* mutation in an individual with PAH confirms the diagnosis of *BMPR2*-related PAH.

In individuals with PAH:

- **Electrocardiography (ECG)** may reveal changes suggestive of right atrial or right ventricular hypertrophy. In individuals with PH associated with cardiac causes, ECG may reveal additional changes.
- **Pulmonary function testing** may show mild restriction or be normal. In individuals with PH associated with parenchymal lung diseases, pulmonary function testing may reveal evidence of obstructive and/or restrictive disorders.

- **Chest radiography** shows normal parenchyma and may show cardiomegaly. In those with PH associated with parenchymal lung disease, chest radiography may reveal changes of other lung diseases.
- **Perfusion lung scanning** is normal or mottled, or may reveal segmental or larger perfusion defects suggestive of pulmonary embolism.
- **Chest CT** shows normal lung parenchyma. In individuals with PH associated with parenchymal disease, high-resolution imaging may show changes of interstitial lung diseases or emphysema.

  CT angiography has improved greatly and is noninvasive; thus it may be helpful in the evaluation of most individuals with PH. The angiographic features of chronic thromboembolic pulmonary hypertension (CTEPH) include pouching deformities and intravascular webs, which are distinctly different from the intraluminal filling defects of thrombus, as seen in acute pulmonary embolism.
- **Echocardiography,** a noninvasive procedure, provides estimates of systolic pulmonary artery pressure and/or reveals changes in the right ventricle. Echocardiography is also used to screen for valvular or left ventricular disease as an alternative cause of PH.
- **Cardiac catheterization** is used to confirm the diagnosis of PAH by directly measuring pulmonary artery pressures and excluding other cardiac abnormalities. Because increased wedge pressure resulting from LV diastolic dysfunction may be a cryptic cause requiring different treatments, catheterization is appropriate for all individuals with suspected PH.
- **Lung biopsy** shows occlusion of small pulmonary arteries and in some cases plexiform lesions, but is otherwise normal. Several pathophysiologic features may contribute to small pulmonary artery occlusion: proliferation of the intima and media of the vessel wall, vasospasm, and microthrombosis. Lung biopsy is rarely indicated for individuals in whom the other tests mentioned are compatible with PAH, but on rare occasions it reveals other conditions [Palevsky et al 1989].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *BMPR2* is the only gene currently known to be associated with *BMPR2*-related pulmonary arterial hypertension.

Clinical testing. *BMPR2* mutations are detected in about 80% of individuals with familial PAH [Cogan et al 2006]. Of those mutations detected, 37% were point mutations in the coding region and 48% were intragenic deletion/duplications detected by MLPA or other comparable methods. Therefore, among all individuals with familial PAH, an estimated 30% of mutations are detectable by sequence analysis and 34% by deletion/duplication analysis.

- **Sequence analysis.** Sequence analysis detects mutations in 30% of individuals with *BMPR2*-related PAH [Cogan et al 2006].
- **Deletion/duplication analysis.** About 34% of individuals with familial PAH have a detectable duplication or deletion [Cogan et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *BMPR2*-Related Pulmonary Arterial Hypertension

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*BMPR2* sequence variants	30% [2]	Clinical Testing
Deletion/duplication analysis	*BMPR2* deletion or duplication	34% [3]	

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. Deng et al 2000, Lane et al 2000, Thomson et al 2000, Machado et al 2001, Cogan et al 2006
3. Cogan et al 2006

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis of *BMPR2*-related pulmonary arterial hypertension in a proband, it is necessary to perform moleuclar genetic testing.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Mutation of *BMPR2* is also reported in the following:

- One family with pulmonary veno-occlusive disease [Runo et al 2003]
- Five individuals with appetite suppressant-related PH [Humbert et al 2002]
- Six individuals with congenital heart disease (complete type C atrioventricular canals, atrial septal defect, patent ductus arteriosus, partial anomalous pulmonary venous return, and aortopulmonary window with a ventricular septal defect) [Roberts et al 2004]

Clinical Description

Natural History

The clinical characteristics and natural history of pulmonary arterial hypertension (PAH) were reported in a multicenter study [Rich et al 1987] before the recent introduction of new therapies. The study, involving 32 US centers, included 194 affected individuals in whom other causes of PH (e.g., pulmonary embolism) were excluded.

Initial symptoms were dyspnea (60%), fatigue (19%), syncope (8%), chest pain (7%), near syncope (5%), palpitations (5%), and leg edema (3%). Ten percent (95% of whom were female) reported Raynaud phenomenon. The mean age at diagnosis was 36 years.

The clinical course varies considerably, but most untreated individuals gradually deteriorate, with a mean survival of 2.8 years. The variability in survival is broad, ranging from sudden death to (rarely) decades. Clinical functional capacity correlated directly with survival, such that individuals in New York Heart Association (NYHA) class IV had a mean survival of six months.

Family history was positive in 6%. Individuals with a family history of PAH had symptoms, signs, and clinical course identical to those in individuals with no family history of PAH.

Because the symptoms of PAH are nonspecific and develop slowly, affected individuals often attribute initial symptoms to aging, poor conditioning, or overweight. Diagnosis is often delayed, in part because PAH is uncommon and thus rarely considered. The time to diagnosis from onset of symptoms may be shorter in familial PAH, probably because of familial awareness of the disease.

PAH affects all ages, including the very young and the elderly. Females are twice as likely to be affected as males; however, disease severity and outcome are similar in males and females.

The physiologic stress of pregnancy in an affected woman with PAH is significant and maternal mortality is believed to be substantial; newer effective therapies may decrease this risk.

Anecdotal reports suggest a possible association between familial or idiopathic PAH and pregnancy or exogenous estrogen therapy [Humbert et al 2001].

Pathophysiology. PAH is caused by widespread obstruction and obliteration of the smallest pulmonary arteries [Runo & Loyd 2003, Hoeper & Rubin 2006]. When a sufficient number of vessels are occluded, the resistance to blood flow through the lungs increases and the right ventricle attempts to compensate by generating higher pressure to maintain pulmonary blood flow. When the right ventricle can no longer compensate for the increased resistance, progressive heart failure ensues.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been established in *BMPR2*-related pulmonary arterial hypertension.

Penetrance

Penetrance (i.e., the presence of symptoms in an individual with a pathogenic *BMPR2* mutation) is 20% [Newman et al 2001].

Anticipation

It appears that subsequent generations experience earlier onset of disease in some families with familial PAH. Loyd et al (1995) observed that the mean age at death decreased from 45±11 years to 36±13 years to 24±11 years in three successive generations. Anticipation was also observed in a recent report of familial PAH in France [Sztrymf et al 2005].

Nomenclature

At the World Congress on PAH, Venice 2003 [Simmoneau et al 2004], it was suggested that the term "idiopathic pulmonary arterial hypertension" (IPAH) be used when no underlying genetic cause for PAH could be determined and that the term "familial PAH" be used when the disease occurs in families and/or a disease-causing mutation is detected.

Prevalence

To date, more than 100 families with familial PAH (including one family with 23 affected individuals) are known in the US [Newman et al 2001, Thomas et al 2001].

The number of new cases of PAH is estimated at 1-2:1,000,000 population per year. Because survival has improved with modern therapies [Barst 2001, Runo & Loyd 2003], the prevalence is increasing.

Insufficient information is available to determine whether specific populations have different frequencies of PAH, but the distribution of reported families with PAH (including some with causative *BMPR2* mutations) is worldwide.

Several factors may lead to under-recognition of *BMPR2*-related PAH [Thomas et al 2001]:

- Reduced penetrance (20%) with transmission via unaffected obligate heterozygotes [Newman et al 2001]
- Inadequate family histories
- Incorrect diagnosis of other affected family members
- Inability of currently available test methods to detect *BMPR2* mutations, such as those occurring in its promoter region or introns

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Other cardiopulmonary causes of pulmonary hypertension (PH) are far more common than pulmonary arterial hypertension (PAH). Importantly, causes of PH associated with related conditions need to be excluded before the diagnosis of PAH can be established. Causes of PH include lung disease, pulmonary embolism, heart disease, connective tissue diseases, cirrhosis, HIV infection and others [Humbert et al 2001, McGoon 2001].

- **Lung disease.** 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.** Pulmonary embolism or disease of large pulmonary vessels is detected by imaging procedures, traditionally including screening by lung perfusion scanning with confirmation by pulmonary arteriography. CT angiography has improved greatly, replacing these techniques in many centers. Chronic thromboembolic pulmonary hypertension (CTEPH) is a disorder in which pulmonary emboli are not resorbed normally by fibrinolysis, in contrast to what is observed in the vast majority of survivors of pulmonary embolism. CTEPH is of special importance because surgical correction is possible and highly effective for most affected individuals [Fedullo et al 2001].
- **Heart disease.** Most advanced cardiac conditions, including congenital heart disease, valvular disease, and cardiomyopathy, can cause PH. Heart diseases are detected by physical examination, ECG, echocardiography, and cardiac catheterization.
- **Hereditary hemorrhagic telangiectasia (HHT).** When HHT is associated with PH, mutations of another TGF beta receptor, *ALK 1*, appear to be causative [Trembath et al 2001, Harrison et al 2003, Abdalla et al 2004].
- **Other** causes of PH include connective tissue disease [Galie et al 2005], cirrhosis, HIV infection, and treatment with appetite suppressants [Abenhaim et al 1996, Humbert et al 2001]. Pulmonary veno-occlusive disease [Holcomb et al 2000] and pulmonary capillary hemangiomatosis [Slovis et al 1998], two other disorders that are limited to the vessels of the lungs, were previously classified as pathologic subsets of PH, but are now generally accepted as distinct conditions. Both disorders are, on rare occasion, familial. Anecdotal reports suggest that an association may exist between PAH and pregnancy or exogenous estrogen therapy [Humbert et al 2001].

Management

Evaluations Following Initial Diagnosis

Because pulmonary arterial hypertension (PAH) is a diagnosis by exclusion, the necessary evaluations are all completed as part of establishing the diagnosis.

Treatment of Manifestations

Referral centers specializing in diagnosis and therapy of PAH are available across the US (see Pulmonary Hypertension Association Web site).

Epoprostenol (Flolan®). A randomized controlled trial of continuous intravenous infusion of epoprostenol, an analog of prostacyclin, in individuals with PAH demonstrated substantial benefit in symptoms, functional status, and survival [Barst et al 1996]. Because continuous intravenous epoprostenol appears to be the most effective therapy tested so far, it has become standard for individuals with serious or life-threatening PAH and is approved for individuals who are NHYA class III and IV. Epoprostenol is effective for most individuals with PAH, but it is expensive and its administration is difficult because it requires continuous infusion via a portable infusion pump and a chronic central venous catheter. Dosing of epoprostenol is complicated by tachyphylaxis and a serious discontinuation response; if the infusion is stopped, sudden worsening or even death may occur.

Treprostinil (Remodulin®) subcutaneous. A randomized controlled trial of continuous subcutaneous infusion of treprostinil, an analog of prostacyclin, demonstrated efficacy and is now FDA approved. Pain at the subcutaneous infusion site limits dose escalation in some individuals [Simonneau et al 2002, McLaughlin 2003].

Treprostinil (Remodulin®) intravenous. Continuous intravenous use of treprostinil is also effective and has been FDA approved.

Bosentan (Tracleer®). A randomized control trial of oral bosentan, a nonselective (A and B receptors) endothelin blocker, demonstrated efficacy and is now FDA approved [Rubin et al 2002].

Sildenafil (Revatio®). A randomized trial of oral sildenafil, a phosphodiesterase inhibitor, demonstrated efficacy and is now FDA approved.

Inhalation iloprost (Ventavis®). Inhalation of this prostacyclin analog circumvents the need for parenteral administration and is now FDA approved.

Calcium channel blockers. A minority of those with PAH have a favorable long-term clinical response to oral calcium channel blockers. Such responders may be identified by a significant acute pulmonary vasodilator response assessed during cardiac catheterization. Some evidence suggests that individuals with *BMPR2*-related PAH are less likely to demonstrate an acute pulmonary vasodilator response [Elliott et al 2006].

Adjunctive agents. Chronic anticoagulation therapy, diuretics, and supplemental oxygen are also used routinely in PAH as needed.

Lung transplantation is an effective treatment for many individuals with PAH [Trulock 2001]. Typical age restrictions for potential transplant recipients are age 50-55 years for heart-lung transplantation, 55-60 years for bilateral lung transplantation, and 60-65 years for single lung transplantation. Insufficient availability of donor lungs is a problem.

Long-term survival is limited by chronic rejection for most recipients, such that mean survival after lung transplantation is about four years.

Surveillance

The clinical course of PAH is highly variable, with a broad range from rapid progression to long periods of stable clinical status. The appropriate surveillance measures and timing are determined by the relative stability of the patient's clinical condition. Patients who are declining should be in frequent contact with their health care providers so that therapies may be changed or added.

Agents/Circumstances to Avoid

Appetite-suppressant medications, such as fenfluramine/phentermine, dexfenfluramine, and amfepramone (diethylpropion) have been associated with PH [Abenhaim et al 1996, Abramowicz et al 2003].

Cocaine, amphetamines, and related compounds causing vasoconstriction have anecdotal association with PH and could be risk factors [Humbert et al 2001].

Other medications that have anecdotal suggestion of risk include estrogen compounds used as oral contraceptives or hormone replacement therapy. Anecdotal reports associating pregnancy with onset of PH raise some concern about the risks involved with pregnancy; however, there is no published consensus regarding the best approach to birth control in women with PAH.

The hypoxia that accompanies high altitude is associated with pulmonary vasoconstriction and PH in susceptible individuals. Individuals with PAH should avoid hypoxia.

Testing of Relatives at Risk

Recommendations for surveillance of asymptomatic at-risk family members are controversial. The 1998 WHO Symposium suggested echocardiographic screening of at-risk family members every three to five years to enable earlier detection and treatment. However, many health insurers do not provide coverage for screening tests for asymptomatic individuals. No studies describe the frequency of compliance with the 1998 WHO recommendation.

The possible role of molecular genetic testing for early diagnosis of at-risk family members is yet to be established [Newman et al 2001]. However, the use of *BMPR2* molecular genetic testing oto clarify the genetic status of at-risk relatives could permit individuals in some families with *BMPR2*-related PAH to safely forego clinical screening.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Several well-designed multicenter trials aim to identify adjunctive or alternative therapies for PAH:

- Randomized trials with two different selective (A receptor) endothelin blockers [Hoeper & Rubin 2006] were recently completed and are being reviewed by the FDA.
- Trials of combination therapy using selected combinations of the six FDA-approved therapies mentioned in Treatment of Manifestations are in progress and appear promising.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Several investigations are actively seeking new treatment directions or compounds, and many have shown promising results in experimental models or pilot studies in affected individuals, including the following:

- Rho kinase inhibitors
- Serotonin transporter inhibitors
- Overexpression of survivin (an inhibitor of apoptosis)
- Concepts that target growth factor signaling, including a tyrosine kinase inhibitor with effects to block platelet-derived growth factor signaling

Human and animal studies using bone marrow-derived endothelial progenitor cells also appear promising [Hoeper & Rubin 2006].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

BMPR2-related pulmonary arterial hypertension (PAH) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals with an identified *BMPR2* mutation inherited the mutation from a parent. Because penetrance is reduced, only about 20% of those parents with the mutation are affected with PAH.
- *De novo* mutations have been reported to occur [Thomson et al 2000].
- It is appropriate to evaluate both parents for manifestations of PAH by performing a comprehensive clinical examination and an echocardiogram. If a disease-causing mutation in *BMPR2* has been identified in the proband, molecular genetic testing of both parents is also appropriate.

Sibs of a proband

- The risk to sibs of the proband depends on the genetic status of the proband's parents.
- If a parent has *BMPR2*-related PAH, the risk to the sibs of inheriting the disease-causing mutation is 50%; however, because of reduced penetrance [Newman et al 2001], the risk to a sib of developing PAH is approximately 10% (50% x ~20%).
- A sib known to have inherited the *BMPR2* mutation has a 20% chance of developing PAH.

Offspring of a proband

- Each child of an individual with *BMPR2*-related PAH is at a 50% risk of inheriting the mutant allele; however, because of reduced penetrance [Newman et al 2001], the risk to offspring of developing PAH is approximately 10% (50% x ~20%)
- An offspring known to have inherited the *BMPR2* mutation has a 20% chance of developing PAH.

Other family members of a proband

- The risk to other family members depends on the status of the proband's parents.
- If a parent is heterozygous for a *BMPR2* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Genetic counseling for family members at risk for *BMPR2*-related PAH is complicated because of decreased penetrance and variable age of onset.

Family planning. The optimal time for determination of genetic risk is before pregnancy. Similarly, decisions regarding the use of echocardiography or molecular genetic testing to determine the status of at-risk asymptomatic family members are best made before pregnancy.

Testing of at-risk asymptomatic adults for *BMPR2*-related PAH is available using echocardiography and/or molecular genetic testing. Testing for cardiac changes in the absence of definite symptoms of the disease detects mild or presymptomatic cases.

Testing of at-risk asymptomatic adults for a *BMPR2* mutation is available using the same techniques described in Molecular Genetic Testing. Such testing is not useful in predicting whether symptoms will occur, or if they do, what the age of onset, severity and type of symptoms, or rate of disease progression in asymptomatic individuals will be. When testing at-risk individuals for *BMPR2*-related PAH, an affected family member should be tested first to confirm the molecular diagnosis in the family.

At-risk asymptomatic adult family members may seek testing in order to plan early treatment and/or make personal decisions regarding reproduction, financial matters, and career planning. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and education discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant

when the sensitivity of currently available testing is less than 100%. See Testing for laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as *BMPR2*-related PAH that do not affect intellect and have treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of BMPR2-Related Pulmonary Arterial Hypertension

Gene Symbol	Chromosomal Locus	Protein Name
BMPR2	2q33	Bone morphogenetic protein receptor type-2

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for BMPR2-Related Pulmonary Arterial Hypertension

178600	PULMONARY HYPERTENSION, PRIMARY; PPH1
265400	PULMONARY HYPERTENSION, PRIMARY, AUTOSOMAL RECESSIVE
600799	BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE II; BMPR2

Table C. Genomic Databases for BMPR2-Related Pulmonary Arterial Hypertension

Gene Symbol	Entrez Gene	HGMD
BMPR2	659 (MIM No. 600799)	BMPR2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *BMPR2* gene comprises 13 exons [Machado et al 2001].

Pathologic allelic variants: Over 140 unique mutations have been reported. Approximately 30% of mutations localize to exon 12 [Machado et al 2003].

Normal gene product: Bone morphogenetic protein receptor type-2 (BMPR-2) is a member of the transforming growth factor β (TGF-β) superfamily of cell-signaling molecules. BMPR-2, with different reported protein isoforms, forms a heterodimer with BMPR1 to transduce BMP signaling via SMAD proteins. Foletta et al (2003) analyzed interactions with BMPR-2 and discovered the ability of LIMK1 to phosphorylate cofilin, which could then be alleviated by addition of BMP4. A BMPR-2 mutant containing the smallest COOH-terminal truncation described in an individual with *BMPR2*-related PAH failed to bind or inhibit LIMK1. This study identified the first function of the BMPR-2 tail domain and suggests that the deregulation of actin dynamics may contribute to the etiology of *BMPR2*-related PAH. Tctex-1, a light chain of the motor complex dynein, interacts with the cytoplasmic domain of BMPR-2 and is phosphorylated by BMPR-2 [Machado et al 2003]. BMPR-2 and Tctex-1 colocalize to endothelium and smooth muscle within the media of pulmonary arterioles, key sites of vascular remodeling in PAH.

Abnormal gene product: Haploinsufficiency of BMPR-2 is reported to be a molecular mechanism of *BMPR2*-related PAH [Machado et al 2001]. Fifty-eight percent of reported mutations lead to truncated BMPR-2 protein product. Machado et al (2003) determined that phosphorylation of Tctex-1 is disrupted by disease-causing mutations within exon 12. Nishihara et al (2002) determined that missense mutations within the extracellular and kinase domains of BMPR-2 abrogated its signal-transducing abilities.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Primary pulmonary hypertension

Pulmonary Hypertension Association
801 Roeder Rd Ste 400
Silver Spring MD 20910
Phone: 800-748-7274; 301-565-3004
Fax: 301-565-3994
Email: candibleifer@earthlink.com
www.phassociation.org

American Lung Association
1740 Broadway
New York NY 10019
Phone: 212-315-8700
Email: infor@lungusa.org
Fact Sheet: Primary Pulmonary Hypertension (PPH)

Familial Primary Pulmonary Hypertension Registry
National Familial PPH Registry

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Author Notes

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Revision History

- 15 November 2007 (cd) Revision: prenatal diagnosis available
- 18 July 2007 (me) Comprehensive update posted to live Web site
- 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 to live Web site
- 8 December 2003 (jl) Revision: Summary
- 18 July 2002 (me) Review posted to live Web site
- 14 January 2002 (jl) Original submission