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Genetics and Genomics of Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a rare disorder that may be hereditable (HPAH), idiopathic (IPAH), or associated with either drug-toxin exposures or other medical conditions. Familial cases have long been recognized and are usually due to mutations in the bone morphogenetic protein receptor type 2 gene (*BMPR2*), or, much less commonly, 2 other members of the transforming growth factor-β superfamily, activin-like kinase-type 1 (*ALK1*) and endoglin (*ENG*), which are associated with hereditary hemorrhagic telangiectasia. In addition, approximately 20% of patients with IPAH carry mutations in *BMPR2*. We provide a summary of *BMPR2* mutations associated with HPAH, most of which are unique to each family and are presumed to result in loss of function. We review the finding of missense variants and variants of unknown significance in *BMPR2* in IPAH/HPAH, fenfluramine exposure, and PAH associated with congenital heart disease. Clinical testing for *BMPR2* mutations is available and may be offered to HPAH and IPAH patients but should be preceded by genetic counseling, since lifetime penetrance is only 10% to 20%, and there are currently no known effective preventative measures. Identification of a familial mutation can be valuable in reproductive planning and identifying family members who are not mutation carriers and thus will not require lifelong surveillance. With advances in genomic technology and with international collaborative efforts, genome-wide association studies will be conducted to identify additional genes for HPAH, genetic modifiers for *BMPR2* penetrance and genetic susceptibility to IPAH. In addition, collaborative studies of *BMPR2* mutation carriers should enable identification of environmental modifiers, biomarkers for disease development and progression, and surrogate markers for efficacy end points in clinical drug development, thereby providing an invaluable resource for trials of PAH prevention. (J Am Coll Cardiol 2009;54:S32–42) © 2009 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a rare disorder with an estimated incidence of approximately 2 cases per million per year (1,2). It is characterized by a sustained increase in mean pulmonary artery pressure (>25 mm Hg at rest or 30 mm Hg with exercise), normal pulmonary capillary wedge pressure, and increased pulmonary vascular resistance. For adults, mean age at presentation ranges from 36 to 50 years, although individuals of any age can be affected (2,3). Prior to the advent of modern therapies, life expectancy for adults with idiopathic pulmonary arterial hypertension (IPAH) was <3 years from diagnosis; for children, it was <10 months (4).

Pulmonary arterial hypertension may be heritable (HPAH), idiopathic, or associated with drug or toxin exposures (fenfluramine derivatives or toxic oil syndrome), or other medical conditions, including connective tissue diseases, human immunodeficiency virus infection, congenital heart disease, and portal hypertension. Familial cases have long been recognized (5), and in 2000, bone morphogenetic protein receptor type 2 (*BMPR2*) was identified following linkage analysis (6–8) as the gene responsible for more than 70% of HPAH and approximately 20% of IPAH cases (9–12). Crude indirect estimates of the population carrier frequency for *BMPR2*

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mutations lie in the frequency range of 0.001% to 0.01% (13). Two further receptor members of the transforming growth factor (TGF)-β cell signaling superfamily are also recognized as uncommon causes of HPAH. Heterozygous mutations in activin-like kinase-type 1 (*ALK1*) (14) and endoglin (*ENG*) (15) cause hereditary hemorrhagic telangiectasia (HHT) and may rarely lead directly to the development of PAH.

Heritable PAH is inherited as an autosomal dominant trait with incomplete penetrance and an estimated lifetime risk of 10% to 20% (16). The disease is more frequent in women, with a ratio of at least 1.7:1 women to men (2,17,18). Both incomplete penetrance and the significantly skewed gender ratio suggest interactions between *BMPR2* disease mutations and environmental exposures that may include hormones, together with a role for modifying genes. The latest classification scheme now replaces the term *familial PAH* with HPAH, at least in part to recognize the fact that up to 20% of cases previously thought to be IPAH harbor identifiable mutations in *BMPR2* and therefore pose a hereditary risk to other family members. Only 6% of PAH patients reported a family history of PAH in the prospective National Institutes of Health registry (18). A family history of PAH may go unrecognized in IPAH cases with *BMPR2* mutations, as a consequence of either incomplete penetrance or de novo (spontaneous) mutations. Heterozygous *BMPR2* sequence variants have been identified in a small subset of patients with PAH associated with relatively brief exposure to fenfluramine (13,19) or with congenital heart disease (20), raising the question as to whether such factors represent disease triggers in the face of inherited susceptibility in some patients. In contrast, *BMPR2* mutations have not been identified in PAH associated with the scleroderma-spectrum of disease or with human immunodeficiency virus (21,22).

HPAH and IPAH have a similar clinical course. HPAH is associated with a slightly younger age of onset and a slightly more severe hemodynamic impairment at diagnosis, but with similar survival (23). Patients with PAH and disease-causing *BMPR2* mutations are, however, less likely to respond to acute vasodilator testing during right heart catheterization and are unlikely to benefit from treatment with calcium channel blockade (23–25).

Genetic Anticipation

Families with *BMPR2* mutations have been reported to have genetic anticipation, or earlier age of diagnosis in subsequent generations (17). However, no systematic population-based study has been performed to avoid the ascertainment bias that could result in the recruitment and study of families associated with earlier-onset disease in more recent generations. Furthermore, the usual genetic mechanisms for anticipation, including trinucleotide repeat expansions, are not present in *BMPR2*. The question of genetic anticipation can be better addressed in future registries in which all patients with HPAH and IPAH can be genetically characterized and unbiased family studies can be performed.

Abbreviations and Acronyms

ALK1 = activin-like kinase type 1
BMPR2 = bone morphogenetic protein receptor type 2
ENG = endoglin
GRR = genotypic relative risk
GWA = genome-wide association
HHT = hereditary hemorrhagic telangiectasia
HPAH = heritable pulmonary arterial hypertension
IPAH = idiopathic pulmonary arterial hypertension
PAH = pulmonary arterial hypertension
TGF = transforming growth factor

The TGF-β Family and PAH

The TGF-β superfamily comprises a large series of cytokine growth factors that control a host of cellular functions, among them proliferation, migration, differentiation, apoptosis, and extracellular matrix secretion and deposition. Displaying high evolutionary conservation across species, TGF-β members are segregated into several subfamilies, notably the prototypic TGF-β ligands, receptors, and accessory molecules, activins, and the largest of these groups, the bone morphogenetic proteins (26). The implication of *BMPR2*, *ALK-1*, and *ENG* as causal factors in hereditary and associated forms of PAH has emphasized the critical importance of this pathway to the integrity of the pulmonary vasculature (27).

BMPR-II Structure and Signal Transduction

The 4 functional domains of TGF-β type II receptors are typically highly conserved across the family. They consist of an N-terminal ligand binding domain, a single transmembrane region, a serine/threonine kinase, and a cytoplasmic tail domain. Particular to BMPR-II, however, is the presence of an exceptionally long postkinase cytoplasmic domain, primarily encoded by exon 12 of the gene. A second isoform, generated by alternative splicing of exon 12, is expressed ubiquitously at the mRNA level, although the in vivo function of the mature polypeptide remains enigmatic (28).

Signal transduction routed through the TGF-β pathway has been extensively interrogated over the last 2 decades; in contrast, BMP signaling remains less well described. The paradigmatic BMP pathway is a phosphorylation relay of signaling intermediaries initiated at the cell surface and culminating in the nucleus (Fig. 1) (29). A heterotetrameric complex consisting of type I receptors, for example ALK1, BMPR1A or BMPR1B, and BMPR-II, amalgamate to bind extracellular dimeric ligand. These interactions promote close receptor species proximity and activation of the type I receptor by the constitutive kinase BMPR-II. The type I receptors, in turn, bind and phosphorylate members of the receptor R Smad family, namely SMAD1/5 or 8. When activated, the affinity of the R-Smads for a nuclear chaperone, Smad-4, common across the TGF-β system, is