Familial Primary Pulmonary Hypertension*

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"It is difficult to make predictions, especially about the future."  
Yogi Berra

Often, insights into a disease are gained by studying the exceptional cases, the outliers. For the population with primary pulmonary hypertension (PPH), it is the patients with the familial or hereditary form that are the outliers, representing only 6 percent of the recent NHLBI PPH Registry population. However, with recent advances in molecular biology and genetic analysis, the familial population offers the best hope for identifying and understanding the underlying abnormalities.

HISTORICAL PERSPECTIVE

The first description of the arterial changes in unexplained pulmonary hypertension occurred in 1891. However, the term "primary pulmonary hypertension" was first used only in 1951. Thus, as of 1993, a maximum of three generations have been born who might have been labelled with the diagnosis of PPH on autopsy studies. It is therefore more difficult to identify potential victims who died before 1951 using autopsy records and discharge summaries, although references to "cor pulmonale" or "pulmonary artery thickening and sclerosis" are helpful.

In 1927, two sisters with cor pulmonale were described in a paper which did not include microscopic analysis of lung tissue. They may or may not have had PPH. A larger study by Lange, in 1948, described a family of 156 members, 82 of whom were cyanotic, and many of whom had intimal proliferation in pulmonary arteries. It is unclear whether they had PPH or some other disorder leading to cyanotic cor pulmonale. Dresdale et al. provided the first report of familial PPH, confirmed by catheterization. Subsequently, many case reports have been published with, in some instances, up to three generations being described. The identification of familial cases of PPH has outlasted the initial flurry of searching, and newly affected families are still being reported.

PATTERNS OF INHERITANCE

Classic Mendelian genetic analysis has led to the proposal of several inheritance patterns for familial PPH. Melmon and Braunwald suggested that the pattern of inheritance was autosomal dominant. A subsequent report by Thompson and McRae also suggested autosomal dominance. However, in families in which only a single generation is affected, it has been proposed that the inheritance is autosomal recessive, as opposed to families where multiple generations are affected and the inheritance seems dominant. Although, in many families, transmission occurs from an affected mother to a daughter or son, or from an affected father to daughter, suggesting X-linked inheritance with incomplete penetrance, other studies have demonstrated transmission from a father to a son or from a grandfather to a granddaughter through an unaffected father, thereby excluding the possibility of X-linked inheritance. A detailed analysis of 14 North American families has suggested that the transmission pattern is autosomal dominant, excluding genetic heterogeneity. However, it is only with the tools of molecular genetics that a final answer will be obtained.

PROBLEMS IN THE GENETIC ANALYSIS OF PPH

Problem 1: Is PPH One Disease?

By histologic analysis, PPH has traditionally been divided into three types: plexogenic, veno-occlusive, and thromboembolic. A fourth histologic category, pulmonary capillary hemangiomatosis, has recently been described. All these types can be familial and appear to differ in terms of clinical course and proposed etiologies. Primary pulmonary hypertension has traditionally been diagnosed by measurement of hemodynamics and by exclusion of a variety of other clinical disorders. Using these clinical criteria alone, patients with, for example, underlying plexogenic PPH, might be erroneously pooled with patients with other forms of PPH at the time of genetic analysis, thereby confounding detection of the genetic basis of the disease. Thus, especially when interfamily, as opposed to intrafamily analysis is to be performed, it will be mandatory to confirm similar histologies between families. This
may be more difficult than is initially apparent, since analysis of small biopsy samples may be subject to sampling error. Moreover, in a single cohort, which should have similar histologic findings, heterogeneity of pathologic lesions, in terms of plexogenic changes and intimal fibrosis, has been found.\(^\text{35}\) This observation raises questions as to whether a new histologic classification is required.

As with other vascular beds, the pulmonary vasculature may have a limited structural pattern of response to injury. Thus, plexogenic pulmonary arteriopathy is not specific to PPH and can be seen after aminophylline or HIV-induced injury, congenital heart disease, and even chronic thromboembolic pulmonary hypertension. Conversely, the assumption that all familial plexogenic PPH represents only one disease rather than the end stage of several genetic abnormalities or polymorphisms may hamper genetic analysis if comparisons are to be made between families.

**Problem 3: Associated Diseases**

A variety of hematologic disorders may present with what appears to be familial PPH by the usual clinical criteria. Familial abnormalities in hemoglobin structure,\(^\text{51}\) platelet storage,\(^\text{52}\) and fibrinolysis\(^\text{56}\) have been described. HIV infection can cause PPH, and infection of several family members could thereby lead to the misdiagnosis of familial PPH. It will be important to detect and analyze families with these disorders separately from families with PPH where no associated disorder can be found. A potential clue to an immunologic or autoimmune component in PPH comes from recent studies by Morse et al.\(^\text{42}\) They found an association of histocompatibility complex alleles HLA-DR3, DRW52, and DQW2 with familial PPH. Linkage of PPH to the histocompatibility complex could help localize a culprit gene(s) for PPH.

**ANALYZING THE GENETICS OF FAMILIAL PPH IN THE 1990S**

The advent of molecular biology has provided powerful new tools in the analysis of genetic inheritance. However, in conjunction with these tools, thorough clinical analysis of the pedigree must be performed. Currently, the latter includes construction of a detailed family tree, with the acquisition of autopsy records and clinical summaries on as many deceased members as possible. In addition, all living members, even if asymptomatic, should have serial echocardiograms performed by an operator skilled in estimating pulmonary arterial pressures. In individuals where the echocardiogram results are suggestive but not conclusive, it is the opinion of the author that right heart catheterization, preferably as part of a stage 4 exercise test, be performed. In affected individuals, and in their families, associated hematologic or autoimmune disorders, and HIV infection, must be excluded.

The breakthroughs in understanding the pathophysiology of familial PPH will come through analysis of DNA. It is essential that DNA be collected from all living family members, and that old autopsy or biopsy material be obtained for deceased members. Many hospitals discard tissues obtained at autopsy after a fixed number of years, representing an irreparable loss of genetic information. Physicians caring for PPH patients should ensure safe storage of these tissues until such time as their DNA can be analyzed. Collection of DNA from living individuals requires only a skinpinuncture and subsequent lymphocyte culture. Given the paucity of material, fruitful searches will likely be the result of collaborative efforts of many clinical and genetic centers.

The polymerase chain reaction is a technique which permits massive amplification of DNA sequences, thereby providing sufficient DNA for analysis, even from small tissue samples such as single microscope slide sections.\(^\text{59}\) Restriction endonuclease
analysis, using enzymes which cleave DNA at specific sequence sites, has allowed detection of DNA polymorphisms.\textsuperscript{4,5} Linkage analysis, using a large number of polymorphic markers, can help map an unidentified gene by revealing a linkage between the clinical disorder (PPH) and a polymorphic locus linked closely to the unidentified gene.\textsuperscript{5} The gene itself may then be identified. Mutant and normal alleles, identified through DNA markers, can be used for detection of carriers even before the gene has been finally sequenced.

In 1927, Clarke et al\textsuperscript{4} proposed that PPH resulted from a "familial or at all events, inborn, imperfection of the material of which the pulmonary artery is formed." Advances in understanding of vascular biology have only strengthened the suspicion that a primary vascular abnormality may be the cause of PPH.\textsuperscript{6,5} It would thus be sensible to begin to search for genetic abnormalities resulting in dysfunction of cells of the vessel wall, or disordered autoimmunity (Table 1). The explosive growth in sequencing the human genome has provided a long list of cloned genes and their chromosomal locations,\textsuperscript{56} many of which relate to the vascular functions listed in Table 1. Isolation of a culprit gene(s) would ultimately permit characterization and treatment of a metabolic abnormality, and perhaps more importantly, aid in early detection before the lung has been irreparably ravaged by PPH.

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