Coancestry in Apparently Sporadic Primary Pulmonary Hypertension*

Greg Elliott, MD; Gary Alexander, MD; Mark Leppert, PhD; Sandy Yeates, RN; and Richard Kerber, PhD

Objective: To examine sporadic cases of primary pulmonary hypertension for coancestry.

Design: An epidemiologic study of families of patients with primary pulmonary hypertension.

Setting: A university-affiliated referral population.

Participants: Family members of 13 patients with primary pulmonary hypertension.

Measurements: Family pedigrees involving grandparents, parents, siblings, and children were supplemented by genealogic records. Coefficients of kinship (Ck) were calculated for the patients with primary pulmonary hypertension who demonstrated coancestry and compared with 500 sets of controls drawn at random from genealogic records.

Results: Two patients with sporadic primary pulmonary hypertension demonstrated coancestry. The great-great grandfather and great-great grandmother of one patient were the great-grandfather and great-grandmother of the other patient. No other cases of primary pulmonary hypertension were identified in these two families. The Ck of the affected individuals (Ck=10.02×10⁻⁵) suggests strongly that the observed relationship did not occur by chance alone. Among 500 random sets of matched controls, only two sets yielded Ck of 10.02×10⁻⁵ or greater (p=0.004). Coancestry could not be identified for the other five families of patients with sporadic primary pulmonary hypertension for whom genealogic records were available.

Conclusions: The finding of coancestry in patients with sporadic primary pulmonary hypertension suggests that a genetic basis exists for some patients with apparently sporadic primary pulmonary hypertension. Familial primary pulmonary hypertension may be more common than previously recognized.

(CHEST 1995; 108:973-77)

Ck = coefficient of kinship; NIH = National Institutes of Health

Key words: coancestry; genetics; inheritance; primary pulmonary hypertension

Primary pulmonary hypertension is a disorder characterized by severe pulmonary arterial hypertension that does not result from other conditions such as venous thromboembolism. Pathologic alterations of small muscular pulmonary arterioles and veins contribute to the severe pulmonary hypertension. When uniform diagnostic criteria are applied, the disease is rare. In an unselected series of 17,901 patients at autopsy, the prevalence of primary pulmonary hypertension was 0.13%. A national registry conducted at 32 US referral centers identified only 187 patients with primary pulmonary hypertension between 1981 and 1985. Nevertheless, the disease has attracted considerable interest because it commonly affects young individuals and follows a progressive, intractable, and usually fatal course.

Familial primary pulmonary hypertension has been described. The clinical features and mortality of familial primary pulmonary hypertension do not differ from sporadic cases of primary pulmonary hypertension. The inheritance pattern of familial primary pulmonary hypertension is thought to be autosomal dominance with incomplete penetrance. This inheritance pattern of skipped generations and a high proportion of unaffected family members interferes with the recognition of familial primary pulmonary hypertension.

Current evidence suggests that familial primary pulmonary hypertension occurs uncommonly, affecting only about 6% of patients with primary pulmonary hypertension. However, apparently sporadic cases of primary pulmonary hypertension actually may represent familial primary pulmonary hypertension. Identification of coancestry in apparently unrelated patients with primary pulmonary hypertension would support the hypothesis that more cases of sporadic primary pulmonary hypertension have a genetic basis. Previous investigators have searched unsuccessfully for coancestry among patients with primary pulmonary hypertension residing in Tennessee. In the present report, we test the hypothesis that patients with apparently spo-
radic primary pulmonary hypertension actually have familial primary pulmonary hypertension.

**Materials and Methods**

From July 1, 1981 through July, 1993, 32 patients were seen at the LDS Hospital and were diagnosed as having primary pulmonary hypertension using the criteria of the National Institutes of Health (NIH) registry for primary pulmonary hypertension.\(^6\) Family histories from each of these patients were taken to determine if parents, siblings, or children had evidence for primary pulmonary hypertension. One patient’s mother had primary pulmonary hypertension, diagnosed according to NIH registry criteria; she was considered to have familial primary pulmonary hypertension, although other primary pulmonary hypertension cases could not be identified in this family pedigree. The remaining 21 patients were considered to have sporadic primary pulmonary hypertension, insofar as none had parents, siblings, or children with a history of primary pulmonary hypertension.

Questionnaires were sent to these 21 patients or their surviving family members. The questionnaires sought the names and health status, ie, alive or dead, and cause of death when known of grandparents, parents, siblings, and children. The names included maiden names.

We then began an ancestry search with the names of grandparents. We used the resources of the family history files at the Resource for Genetic and Epidemiology Research at the University of Utah to search for pedigree information for each grandparent. When records were available, we performed two different kinds of computer searches to complete as much of their pedigree as possible. First, we performed a family search that yields the individual grandparent name and birth year, and their parents’, brothers’, and sisters’ names and birth years. Second, we performed a pedigree search, that yields the direct ancestors of the individual grandparent (eg, parents, grandparents, great-grandparents—up to five generations). When the same last name appeared in more than one pedigree, we performed a descendant search to identify family members in the generations after the identified individual (eg, children, grandchildren, cousins). All names, birth dates, and ancestral file numbers (a unique number that avoids two individuals with the same name and birthday being identified to be the same person) were listed in a database that was then searched for common individuals (based on match of name, birthday, and ancestral file number).

To assess the possibility that common ancestors would be found by chance, we calculated the coefficient of kinship (Ck) using a standard method.\(^9\) Ck represents the probability that randomly selected homologous genes from two individuals in a pedigree are identical by descent from a common ancestor. To determine if the kinship among these patients with primary pulmonary hypertension was greater than would be expected by chance, the average Ck across all possible pairs of primary pulmonary hypertension cases with genealogic data was calculated, and compared with the average Ck among each of 500 sets of controls drawn at random from the Utah Population Database.\(^10\) The Utah Population Database contains pedigree data on more than 1 million individuals from Utah, drawn from the records of the Family History Library of the LDS Church. Controls were individually matched to primary pulmonary hypertension cases on year of birth and sex.

**Results**

Thirteen patients or their family members completed questionnaires that provided at least partial pedigrees. Six of the 13 patients had grandparents without ancestral data registered with the Family History Centers of the LDS Church. Seven patients had grandparents whose lineage could be traced. Three had records for all four grandparents for five preceding generations; two had records for three of four grandparents for five preceding generations; and two had records for two of four grandparents for five preceding generations. A review of genealogic records confirmed that two of these seven patients with apparently sporadic primary pulmonary hypertension actually had common ancestors (Fig 1). The great-grandfather and great-great grandmother of a 29-year-old man were the great-grandmother and great-grandfather of a 48-year-old woman.

**Case Reports**

**Patient 1**

A 29-year-old white man was referred for evaluation of progressive exertional dyspnea and hemoptysis. He had “always been a little short of breath.” More recently he had noted dyspnea when climbing one flight of steps. There was no history of other cardiorespiratory disease, eg, thromboembolic disease, collagen vascular disease, or Raynaud’s phenomenon. The family history was considered unremarkable. His father had asthma and his maternal and paternal grandfather had coronary artery disease. His mother, his brother, and his two children were healthy.

Physical examination revealed a well-developed, well-nourished white man. A right ventricular impulse and closure of the pulmonic valve were easily palpable and the intensity of P2 was increased.

Laboratory studies included a perfusion lung scan that showed diffuse nonhomogeneous uptake of radionuclide. A chest radiograph showed enlarged main pulmonary arteries without parenchymal infiltrates. An echocardiogram disclosed right atrial and right ven-

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**Figure 1.** The family pedigree of two patients with apparently sporadic primary pulmonary hypertension. Squares represent men; circles, women. The Roman numerals identify the generation. Crosses indicate deaths and ages at death are identified. Dark symbols identify patients with confirmed primary pulmonary hypertension. No evidence of pulmonary hypertension was found when living members of generations IV, V, and VI were screened (physical examination and echocardiogram).
tricular enlargement without shunt by contrast or color Doppler display. Cardiac catheterization revealed severe pulmonary arterial hypertension (Table 1)[11,12] without evidence of intracardiac shunt and without improvement when nifedipine was titrated to a cumulative dose of 180 mg.

On September 16, 1989, the patient underwent right single lung transplantation. His native lung was used for investigative purposes and discarded without pathologic examination. His posttransplant course was complicated by rejection and recurrent Aspergillus pneumonia that proved fatal. An autopsy was not performed.

**Patient 2**

A 48-year-old white woman was referred for evaluation of exertional dyspnea and light-headedness that had progressed over 5 years. Raynaud’s phenomenon appeared 32 years earlier. Two years prior to hospital admission she had exertional syncope. There was no history to suggest other cardiorespiratory illness or collagen vascular disease. The family history was considered unremarkable. Her mother had coronary artery disease without any evidence of pulmonary hypertension by physical examination, chest radiograph, or electrocardiogram.

Physical examination revealed an increase in the pulmonic component of the second heart sound, a right sided S3 gallop, and the murmur of tricuspid regurgitation.

A perfusion lung scan revealed diffuse nonhomogeneous uptake of radionuclide. A chest radiograph revealed cardiomegaly and enlarged main pulmonary arteries. An ECG showed right ventricular hypertrophy. Pulmonary function tests showed a mild restrictive defect and reduction of single-breath carbon monoxide diffusing capacity. An antinuclear antibody test was positive in a titer of 1:40. Cardiac catheterization revealed severe pulmonary arterial hypertension with no evidence for intracardiac shunting and without a response to vasodilators.

The patient died consequent to right ventricular failure. Autopsy demonstrated thrombotic arteriopathy consistent with primary pulmonary hypertension (G. Pietra, MD, personal communication, September 19, 1989). Pathologic lesions were limited to the pulmonary arterial tree and consisted of moderate medial hypertrophy, eccentric intimal fibrosis, and occasional recanalized thrombi.

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**Table 1—Clinical, Laboratory, and Pathologic Findings**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td><strong>Clinical findings</strong></td>
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<td>Age at presentation, yr</td>
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<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
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<td>Hemoptysis</td>
<td>Exertional syncope</td>
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<td>Signs</td>
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<tr>
<td>Right ventricular lift</td>
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<td>–</td>
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<tr>
<td>Increased P₂</td>
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<td><strong>Hemodynamics</strong></td>
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<td>RAP, mm Hg</td>
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<tr>
<td>PAPmean, mm Hg</td>
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<td>PcwP, mm Hg</td>
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<td>RVH</td>
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<td>FVC, L (% pred)</td>
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<td>3.16 (79)</td>
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<td>FEV₁, L (% pred)</td>
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<td>TLC, L (% pred)</td>
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<td><strong>Pathologic findings</strong></td>
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<td>Eccentric intimal fibrosis and medial hypertrophy of muscular arterioles</td>
</tr>
</tbody>
</table>

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1RAC=right atrial pressure; PAPmean=mean pulmonary artery pressure; PcwP=pulmonary capillary wedge pressure; CO=cardiac output; RAD=right axis deviation; RVH=right ventricular hypertrophy; Dco=single-breath carbon monoxide diffusing capacity; TLC=total lung capacity.

1Predicted from Crapo and associates.[11,12]

14,500-ft altitude.
Kinship Coefficient

The calculated mean Ck of the 13 individuals who responded to the questionnaire was 10.02 × 10⁻⁵. Among the 500 random sets of controls drawn from the Utah Population Database, only two sets yielded mean Cks greater than or equal to the observed value. The estimated p value is 0.004 (95% confidence interval, 0.004 to 0.011).

Discussion

This study describes coancestry for 2 of 13 patients with apparently sporadic primary pulmonary hypertension. It is unlikely that chance explains the discovery of two patients with common ancestry. Rather a common genetic predisposition to the development of pulmonary hypertension is more likely. Such genetic predispositions have been recognized for a small subset of patients with primary pulmonary hypertension and for patients with the clinical picture of primary pulmonary hypertension who have pulmonary capillary hemangiomatosis. The latter diagnosis was excluded by autopsy in one of the two cases presented herein.

The results of this study suggest that familial primary pulmonary hypertension may be more common than previously recognized. The NIH registry identified 187 patients with primary pulmonary hypertension. Six percent of these patients had familial primary pulmonary hypertension based on family histories that ascertained the health of patient’s parents, siblings, and children. Using this method, the relatedness of the two patients we describe would not have been recognized. More detailed family histories may identify coancestry for more patients with apparently sporadic primary pulmonary hypertension. Family histories that detail several generations are warranted because familial primary pulmonary hypertension has an inheritance pattern characterized by incomplete penetrance. Thus, this disease may skip one or more generations before reappearing.

The present study collected genealogic records for four generations of ancestors to one patient and three generations preceding the other patient in order to establish coancestry. Such information cannot be acquired easily. In the present study, we were unable to find genealogic information for the grandparents of 6 of 13 patients with sporadic primary pulmonary hypertension. Furthermore, the genealogic records were incomplete for four of the remaining seven patients’ grandparents. Thus, it is possible that additional examples of coancestry may have been identified with more complete records.

In addition to the problems posed by limited genealogic records, diagnostic terminology can interfere with the search for ancestors who had primary pulmonary hypertension. Primary pulmonary hypertension was first described as a clinical entity in 1951. Thus, recognition of ancestors with primary pulmonary hypertension before 1951 is speculative or depends on recognition of older terms used to describe disease of the pulmonary circulation (“Ayerza’s syndrome,” “cardiacos negros,” or “syphilitic disease of the pulmonary arteries”). Indeed most reports of familial primary pulmonary hypertension provide no information for generations preceding the parents of affected individuals.

Nevertheless, the results of the present study suggest that a larger cohort of patients with apparently sporadic primary pulmonary hypertension should be examined for the presence of common ancestry. Identification of coancestry in a number of patients with sporadic primary pulmonary hypertension could provide evidence that many cases of primary pulmonary hypertension are inherited.

Given that apparently sporadic cases of primary pulmonary hypertension may represent familial primary pulmonary hypertension, it is interesting to note the different clinical presentations of the two patients in this report. One patient was a woman who had Raynaud’s phenomenon, whereas the other patient was a young man who had no history of Raynaud’s phenomenon. This clinical heterogeneity parallels the pathologic heterogeneity reported previously for familial primary pulmonary hypertension.

Acknowledgment: The authors thank Beth Jarman for manuscript preparation and Louisa Holt and Violet Loertscher for assistance with genealogic records. We also thank Theodore E. Woodward, MD, for insight into the history of pulmonary hypertension, and we thank Robert Crapo, MD, for critically reviewing the manuscript.

References