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The Presence of Genetic Anticipation Suggests That the Molecular Basis of Familial Primary Pulmonary Hypertension May Be Trinucleotide Repeat Expansion*

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Primary pulmonary hypertension (PPH) is a progressive disease that usually leads to death from right ventricular failure, due to occlusion of small pulmonary arteries. PPH usually occurs sporadically without a positive family history, but the disease is familial in 5% to 6% of patients. Sporadic and familial PPH appear to be identical processes since there are no differences in clinical findings and outcomes or in pathologic features. Women are affected more than men (2:1) in both sporadic and familial disease. The genetics basis of familial PPH is unproven and many unusual features occur. Ongoing analysis of more than 50 families in a national registry of families with PPH continues to add new information regarding the mode of transmission. As many as 10 individuals have been affected in one US family. Vertical transmission of familial PPH, which has been observed in 5 generations in one family, 4 generations in another, and 3 generations in several families, suggests that the disease is due to a single dominant gene. Father-to-son transmission, which excludes X linkage, has been observed in seven families. Transmission of disease by unaffected members (incomplete penetrance) was observed in 25 individuals. The characteristics of familial PPH are compatible with autosomal dominant transmission with incomplete penetrance, but formal confirmation awaits successful segregation analysis. Genetic anticipation, a phenomenon in which a disease is worse in successive generations, may be shown by greater penetrance, greater severity, or earlier age of onset. Our analysis of age at death from PPH demonstrated genetic anticipation is present, manifested as earlier age of death in successive generations; the oldest generation died at age 45, the next generation died at age 36, and the most recent generation died at age 24. Genetic anticipation and incomplete penetrance in seven neurologic diseases are now known to be caused by trinucleotide repeat expansion, a molecular mechanism of human disease first described in 1991 in the fragile X syndrome. The results of a method to identify trinucleotide repeat expansion in genomic DNA, the repeat expansion detection (RED) assay, demonstrated many expanded triplets in both familial PPH patients and in control subjects. A genome-wide microsatellite marker study is in progress in specimens from five PPH families. The subsequent mapping of this familial PPH gene has been recently reported.[1]

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