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

REFERENCE


Patterns of Gene Expression in Human Airway Epithelial Cells*

James C. Willey, MD; Mark W. Frampton, MD; Mark J. Utell, MD; Michael J. Apostolakos, MD; Erin L. Coy, BS; Dan E. Olson, MD; PhD; Jeffrey R. Hammersley, MD; Dawn Matteson, BS; and William G. Thilly, PhD

(CHEST 1997; 111:83S)

It is becoming clear that the information obtained from measurement of gene expression is much more mechanistic when the relative level of gene expression is determined in tissue as opposed to absolute quantification of individual genes. Considering this, we have developed methods for simultaneous measurement of multiple genes by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) amplification. Our initial efforts have been directed at characterizing patterns of expression of xenobiotic metabolism enzyme genes. We first determined which of 16 phase 1 and phase 2 metabolism genes are expressed in airway epithelial or alveolar macrophage cells.1 We then used quantitative RT-PCR to determine patterns of gene expression in human airway epithelial cells from smokers and nonsmokers.

We have determined that the expression of cytochrome p450 1A1 relative to microsomal epoxide hydrolase varies considerably among individual smokers. Variation in the relative expression of these genes may affect the risk of airway cells from inhaled carcinogens by determining whether predominantly carcinogenic or noncarcinogenic metabolites are generated. We are correlating the patterns of expression observed with the relative level of DNA and protein adducts and mutations present. We have expanded the capability of our methods to measure the expression of 60 genes simultaneously, including 15 xenobiotic genes expressed in airway epithelial cells and 4 cytokine genes expressed in airway epithelial cells with interleukin-1β, interleukin-8, lymphocyte chemotactic factor, and tumor necrosis factor-α. Reagents for quantitative measurement of additional cytokine, DNA repair, apoptosis, and differentiation genes are being incorporated into the system. This system is very sensitive (required RNA from as few as 10 cells) and is reproducible. In addition, the internal controls may be distributed to multiple laboratories for interlaboratory comparison of results.

REFERENCE


Transcriptional Control in the Developing Lung*

The Parker B. Francis Lectureship

Thomas R. Korfhagen, MD; PhD; and Jeffrey A. Whitsett, MD

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Formation of the vertebrate lung requires an orderly array of complex cell to cell and cell to matrix interactions to produce the conducting airways and alveolar

*From the Division of Pulmonary Biology, Children’s Hospital Research Foundation, Cincinnati. Reprint requests: Jeffrey A. Whitsett, MD, Children’s Hospital Medical Center, Division of Neornatology and Pulmonary Biology, 3333 Burnet Ave, Cincinnati OH 45229-3039; email: WHITJT@CHMCC.ORG

*From the Medical College of Ohio, Departments of Medicine and Physiology and Molecular Medicine, Toledo (Drs. Willey, Olson, and Hammersley, Ms. Coy, and Ms. Matteson); Rochester School of Medicine, New York (Drs. Frampton, Utell, and Apostolakos); and the Massachusetts Institute of Technology, Cambridge (Dr. Thilly).

Reprint requests: James C. Willey, MD, Dept of Medicine, Medical College of Ohio, 3000 Arlington Ave, Toledo OH 43699