The Future of Genetics in Pulmonary Arterial Hypertension

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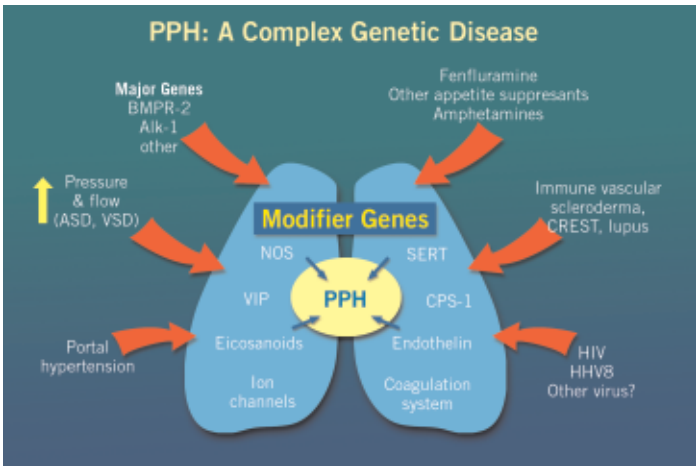
Research into the genetic basis of pulmonary arterial hypertension is going forward with increasing intensity. It appears that mutations in bone morphogenetic protein receptor type II (BMPR2) and activin receptor-like kinase-1 (ALK1) genes will be the most common genetic risk factors for the development of pulmonary arterial hypertension. However, there are more than 10 other genes encoding transforming growth factor-beta receptors, and a systematic search needs to undertaken to determine if mutations in these other receptors are associated with pulmonary arterial hypertension. It is possible that other major genes causing pulmonary arterial hypertension exist, but the evidence to date in familial disease is that BMPR2 causes at least 75% of cases, and ALK1 somewhere fewer than 5% of cases.

It is unclear whether any other specific genetic predisposition is necessary for the development of pulmonary arterial hypertension. Because pulmonary arterial hypertension can occur in response to multiple stimuli, such as appetite suppressants or liver disease, there may be many kinds of genetic predisposition, depending on the stimulus. In each form of pulmonary arterial hypertension associated with another disorder or risk factor, the percentage of patients who develop pulmonary arterial hypertension is quite small, less than 1% to 10%, so that other susceptibilities almost certainly play a role in the development of disease.

One of the mysteries of familial pulmonary arterial hypertension has recently been solved by Cogan et al.[1] We have known for the past 4 years that most family mutations are in the area of chromosome 2 where BMPR2 resides, but have been unable to find mutations in the approximately 50% of families. By studying messenger RNA in lymphocytes from patients with familial pulmonary arterial hypertension, mutations in the noncoding intronic regions that lead to errors in splicing and duplication of messenger RNA, and ultimately to altered protein synthesis, have been discovered. This finding has led to the identification of additional mutations in familial pulmonary arterial hypertension and clears up much of the mystery but also seriously complicates the process of genetic testing.

Another major uncertainty that has not been settled is how many patients with apparently idiopathic pulmonary arterial hypertension have BMPR2 mutations, and whether these mutations are inherited or are spontaneous and new. The implications are large. The presence of a BMPR2 or ALK1 mutation changes the disease from sporadic to heritable and increases the risk of other family members having the mutation and developing disease. A large-scale study is needed to better define and quantitate the prevalence of BMPR2 mutations in the population of patients with apparently idiopathic pulmonary arterial hypertension. Work by several groups is probing the extent of BMPR2 mutations in a variety of pulmonary and cardiovascular diseases. BMPR2 mutations have now been identified in association with congenital heart anomalies, underscoring the developmental importance of the gene. See Dr. Morse's article in this issue for more details.

Beyond looking for major genes of lesser and lesser frequency in pulmonary arterial hypertension, the thrust over the next several years will be to identify genes that modify expression of disease and outcome. These genes include those known to encode products important in pulmonary arterial hyperten-



Primary pulmonary hypertension can be induced in susceptible individuals by a number of conditions or stimuli, shown in circumference around the cartoon of the lungs. These conditions elicit a response which is modulated by genetic susceptibility, in the form of functional polymorphisms of an unknown number of genes. Listed are some genes with functional polymorphisms known to influence vascular function, including NOS (nitric oxide synthases), SERT (serotonin transporter), VIP (vasoactive intestinal peptide), AII (angiotensin II), CPS (carbomyl phosphate synthetase), E-receptors (endothelin). The state of knowledge with regard to modifying genes is in its infancy.

sion, such as serotonin receptors and the serotonin transporter, endothelin receptors, prostacyclin, inflammatory mediators, potassium channels, immune genes, and others to be identified. Additional genes that determine cardiac function and response to stress need evaluation, and genes involved in vasoconstriction and vasodilation need elucidation. This kind of genetic work will enhance our understanding of the different ways patients respond to vascular changes of pulmonary arterial hypertension and to treatment. Ultimately, this should allow for more targeted therapies. Coupling genomic studies with proteomics will allow more rapid advancement in the field.

Genetic testing will become a more important part of pulmonary arterial hypertension evaluation when the technology of scanning the very large BMPR2 gene is improved. Currently, only half of presumptive BMPR2 mutations can be identified by standard exonic analysis, because a large minority of cases have intronic mutations that are revealed as abnormalities only in receptor protein product. Newer RNA-based techniques are improving this yield so that we can now probably identify 75% of inherited cases. Still, this leaves an unsettling percentage of inherited risk that cannot currently be identified, a problem of sensitivity of the test. Over the next several years, genetic testing will likely have a sensitivity closer to 90% for determining BMPR2 mutations in familial pulmonary arterial hypertension.

Genetic counseling remains absolutely essential to help sporadic and familial patients understand the limitations and implications of testing. This is a complex problem because of the low penetrance of disease in patients with known mutations, and because of the lack of sensitivity of testing in patients without an already known family mutation. We have found that most persons who have expressed extreme interest in testing have not taken advantage of it now that it is available, a finding similar to that of many other serious inherited diseases. Nonetheless, genetic testing should be made available when possible after counseling with an expert and after a period of reflection and consideration by the applicant. All persons need counseling; only some will choose testing.

As to the future, there should be a sense of optimism. The real payoff from all this work will be when sufficient understanding of the aberrant actions of the mutated BMPR2 points to either preventive treatments or specific therapies to reverse pulmonary arterial hypertension and restore health. Ongoing work by many talented investigators almost assures this ultimate outcome.

Reference

1. Cogan JD, Vnencak-Jones CL, Pratap S, et al. Gross *BMPR2* gene rearrangements constitute a new cause for primary pulmonary hypertension. *Genet Med*. 2005. In press.