GENETICS MOVES TO CENTER STAGE

Our understanding of pulmonary hypertension (PH) has advanced steadily. Almost 100 years ago, light microscopy provided the earliest insights into a rare progressive and fatal disease, primary pulmonary hypertension ("PPH"). Pathologists described the histopathology of PPH, with terms like "plexogenic" and "microthromboembolic" PPH. Pathologists, who specialized in pulmonary vascular disease, identified two rare disorders, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH), that mimicked PPH clinically, but were distinctly different under the microscope.

By the middle of the 20th century, the introduction of pulmonary artery catheterization to the study of cardiovascular diseases produced a new level of understanding of PH based upon physiologic observations of intravascular pressures and flows, with an emphasis on mechanisms that caused constriction and relaxation of pulmonary arterioles. This era supported early efforts to treat sporadic PPH and familial PPH, now known as idiopathic and heritable pulmonary arterial hypertension (PAH) with vasodilators, eventually leading to treatments which targeted three pathways integral to vasoconstriction and vasodilation of pulmonary arterioles.

Even as pathologic, physiologic, and treatment studies proceeded during the second half of the 20th century, the genetic era began. Investigators took advantage of scientific advances in genetics to discover heritable causes of PH. The first breakthrough occurred in 2000, when two research teams independently reported that mutations in the gene (*BMPR2*), encoding the bone morphogenetic protein type 2 receptor, caused familial PPH. Over the next two decades investigators linked DNA sequence variations in 16 additional genes to heritable forms of PAH, including PVOD and PCH. These discoveries shaped a new understanding of PAH.

Investigators quickly determined that *BMPR2* regulated the proliferation of vascular cells, not vasoconstriction. Recognition of the pivotal role of cellular proliferation and transforming growth factor β (TGF-β) signaling paved the way for a new approach to the treatment of PAH. In the Study of Sotatercept for the Treatment of Pulmonary Arterial Hypertension (PULSAR), sotatercept, a fusion protein that impairs activation of a TGFβ pro-proliferative pathway, produced a greater reduction in pulmonary vascular resistance than placebo. Now studies are underway to assess the efficacy and safety of sotatercept across a broad spectrum of PAH disease severity.

We have entered a new era of understanding and treating PAH, as genetics moves to center stage. This issue of *Advances in Pulmonary Hypertension* was organized to serve as a valuable resource for the PH community. The first article, authored by Drs. Carrie Welch and Wendy Chung of Columbia University, provides a comprehensive overview of the genomics of pulmonary hypertension. With this foundation in place, the second article, authored by Rachel Sullivan, MD (Stanford University) and Eric Austin, MD (Vanderbilt University) reviews the relationships between specific gene sequence variations and PAH phenotypes that clinicians are likely to encounter.

In recent years genetic counseling and genetic testing have become important affordable services for patients with PAH and their families. Sumathi Rachamadugu, MSc, MS and Melanie Emmerson, MS (Intermountain Healthcare) collaborated with Barbara Girerd, PhD (Université Paris-Saclay) and Hunter Best, PhD (University of Utah) to provide an in depth introduction pretest genetic counseling, genetic testing, and posttest genetic counseling for PAH patients and their families. The PH Professional network contribution by Athena Angelopoulos, MS and Rachel Farrell, MS (University of California San Francisco) complements the preceding article by providing additional details related to genetic counseling and testing for PAH patients and their families.

Finally, Drs. Austin, Chung, and Yu, joined us for a roundtable discussion on the genetics of pulmonary hypertension. Participants shared their personal knowledge of the history of genetic research and discovery related to PH, their advice on discussing genetic aspects of PH with patients and families, their thoughts about involving genetic counselors and ordering genetic tests, as well as how genetic test results influence treatment decisions and how knowledge of molecular pathways informs the development of new medications to treat PAH.

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