N E W O P T I O N S N E W H O P E

WALL CENTER UPDATE

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VERA MOULTON WALL CENTER FOR PULMONARY VASCULAR DISEASE AT STANFORD

The Third Annual Dunlevie Family Lecture in Pulmonary Medicine:

Richard C. Trembath, M.D., F.R.C.P.

BMPR2: Genetic Key to PPH

Geneticists are the locksmiths of the medical world, using genes as keys to unveil the mysteries behind disease. Richard C. Trembath, M.D., F.R.C.P., Professor of Medical Genetics at the University of Leicester in the United Kingdom, discussed his discovery of the genetic key to primary pulmonary hypertension (PPH) at the third annual Dunlevie Family Lecture at Stanford University Medical Center.

Trembath's interest in the pathogenesis of human disease was firmly established during his undergraduate days at Guy's Hospital Medical School. His general medical training was followed by clinical training in diabetes and endocrinology at St. Bartholomew's Hospital, as well as genetic research in diabetes at the Institute of Child Health. Today, he is an internationally renowned leader in the field of medical genetics who has published more than 100 papers and abstracts. In addition to his research in pulmonary vascular disease, Trembath and his team are also concerned with conditions such as partial lipodystrophy, a disease in which abnormal fat deposits develop under the skin.

In his opening remarks, Trembath stated that a patient named Nicola first piqued his interest in the genetic causes of PPH in 1992. The newly married Nicola asked Trembath if he believed she was likely to develop PPH, since three of her sisters had already died from the disease. She was also concerned about the possibility of transmitting the gene for PPH to the children she planned to have. When Trembath attempted to research the answers to Nicola's questions, he noted his efforts took only a "second" because there was "virtually nothing known" about the genetic causes of PPH.

After assembling Nicola's extended family history, Trembath found what he now maintains is a classic case of familial, or inherited, PPH: more than 40 members within her family appeared to be at 50-percent risk of inheriting the gene to develop the disease. By referring to the family histories of other PPH patients, Trembath and his colleagues identified a region on chromosome 2 that cosegregated with PPH in the majority of the families they investigated. However, the team was still left with a fairly large area in which the gene could reside, since more than 100 different locations within that region were potential candidates to carry the gene.

A fortuitous clinical observation freed Trembath from the painstaking work of sifting through all 100 locations. He discovered that in the mid-1980s, one New Zealand family contained two girls who had been diagnosed with PPH and passed away; an extended family member had died from the condition as well. When Trembath visited New Zealand to research the case, he learned many members of the same family had suffered from another inherited vascular disorder: hereditary hemorrhagic telangiectasia, or HHT. Trembath then realized a direct connection exists between PPH and HHT, since the same two genes on one chromosome 2 interval can be identified in both diseases.

Upon further study of the same chromosome 2 interval, Trembath identified the presence of a third gene-bone morphogenetic protein receptor type 2, (BMPR2), a gene that is known to aid in lung development. Thanks to the human genome project, Trembath and his team were able to isolate the gene in 24 hours, gather their initial patient data, and confirm that the BMPR2 gene had undergone a mutation in one of their patients. Additional research by both Trembath and scientists at Vanderbilt University further substantiated these initial results.

Trembath observed that while the discovery of BMPR2 created an opportunity to better understand familial PPH, the breakthrough also had implications for

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The Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford

Lucile Packard Children's Hospital and Stanford Hospital and Clinics are one of the few combined centers in the United States currently offering diagnostic and advanced therapeutic services to both adults and children with pulmonary hypertension. In the fall of 2000, through the generous gift of an anonymous donor, the Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford was established.

The Wall Center seeks to serve as a leader in both the clinical treatment and research of pulmonary vascular disease, while also providing advanced training opportunities for researchers and clinicians. The *Wall Center Update* is published biannually in the spring and fall.

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sporadic PH, or the disease as associated with other circumstances including AIDS and the use of appetite-suppressant drugs. In one instance, Trembath related, a researcher revealed males with sporadic PH have a 50-percent chance of carrying the BMPR2 mutation.

Although Trembath and his associates have identified BMPR2 as the genetic key to pulmonary hypertension, he cautioned that many questions remain about the specific role the gene plays in the evolution of the disease. He is currently using mice and other animal models to ascertain the answers to these questions.

In the meantime, Trembath concluded, his research has had immediate consequences for patients like Nicola, who chose to undergo genetic testing nearly ten years following her first visit to Trembath. After learning she hadn't inherited the BMPR2 mutation, Nicola gave birth to her first child in February 2002.