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Hidden origins of pulmonary hypertension revealed by network modeling

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In a groundbreaking study, researchers from Brigham and Women's Hospital (BWH) have identified a related family of molecules believed to be a major root cause of pulmonary hypertension, a deadly vascular disease with undefined origins. This is one of the first studies to leverage advanced computational network modeling to decipher the molecular secrets of this complex human disease.

The study is published online June 24, 2014 in *The Journal of Clinical Investigation*.

Despite the rising number of people diagnosed with the disease worldwide, pulmonary hypertension has been a historically neglected disease. It occurs when there is increased pressure in the blood vessels of the lung, thus compromising the delivery of blood and oxygen to the body. Symptoms are debilitating and include shortness of breath and fatigue, but can progress to heart failure and death.

"Pulmonary hypertension is an example of a cardiovascular disease so complex that traditional methods of research have failed to provide adequate treatments to prevent or halt its progression," said Stephen Y. Chan, MD, PhD, BWH Divisions of Cardiovascular Medicine and Network Medicine, senior corresponding author. "We have been advancing the idea that mathematical models of this disease can be generated to perform high-volume, systematic analyses that are not feasible with standard experimentation. In doing so, we can make predictions regarding critical molecular networks that underlie the

molecular origins of pulmonary hypertension that have not been possible to this point."

Chan and colleagues have focused on the study of microRNAs, which are small, non-coding nucleic acid molecules that can block production of numerous proteins in human cells with implications in health and disease. With the help of sophisticated computational analyses, the researchers developed a unique molecular model tracing the architecture interconnecting the network of genes and microRNAs associated with pulmonary hypertension.

"Historically, most computational approaches in the study of human disease gene networks go no further than theoretical predictions," said Thomas Bertero, PhD, BWH Division of Cardiovascular Medicine, lead study author. "We wanted to be sure that our predictions were truly valid in real instances of pulmonary hypertension."

Consequently, the researchers confirmed their mathematical predictions with experiments using a wide range of pre-clinical and human models. In doing so, the researchers identified the microRNA family, miR-130/301, as a master regulator of diverse target genes and additional microRNAs, ultimately orchestrating a global proliferative response in diseased blood vessels leading to pulmonary hypertension.

"This is the first microRNA family found to regulate such a diverse number of pathways specific for pulmonary hypertension, and these molecules could be very effective therapeutic targets for treating this deadly disease," said Chan. "Since all of these findings were previously missed by conventional experiments, our efforts also provide great support for using network modeling to discover the molecular origins of other complex human diseases."

Provided by Brigham and Women's Hospital