Team identifies mutations associated with development of congenital heart disease

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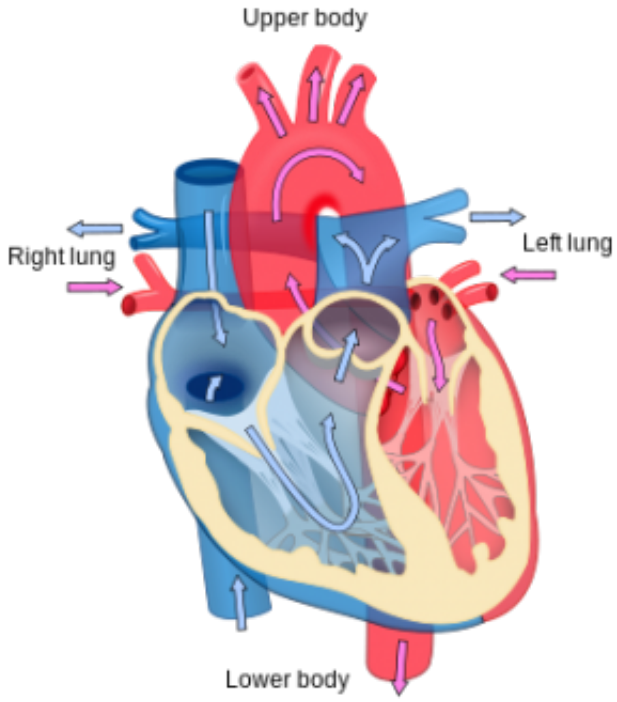

Heart diagram. Credit: Wikipedia

Fetal ultrasound exams on more than 87,000 mice that were exposed to chemicals that can induce random gene mutations enabled developmental biologists at the University of Pittsburgh School of Medicine to identify mutations associated with congenital heart disease in 61 genes, many not previously known to cause the disease. The study, published online today in *Nature*, indicates that the antenna-like cellular

structures called cilia play a critical role in the development of these heart defects.

The findings are the culmination of an effort to find the genetic determinants of structural heart disease in the "Bench to Bassinet" program, launched six years ago by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, led at Pitt by principal investigator Cecilia Lo, Ph.D., professor and chair of the Department of Developmental Biology, Pitt School of Medicine.

"This project has given us new insights into the biological pathways involved in development of the heart," Dr. Lo said. "The genes and pathways identified in our study will have clinical importance for interrogating the genetic causes of congenital heart disease in patients."

For the study, Dr. Lo's team mated mice exposed to chemicals that could create random genetic mutations, resulting in 87,355 pregnancies. They scanned each fetus using noninvasive ultrasound and recovered over 3,000 independent cases of congenital heart defects, all incompatible with life. They sequenced the genes of mutant animals and compared them to those of unaffected offspring to identify 91 recessive mutations in 61 genes.

"We were surprised to learn many of these genes were related to the cilia, or cilia-transduced cell signaling," Dr. Lo said. "These findings suggest cilia play a central role in the regulation of heart development, including patterning left-right asymmetry in the cardiovascular system critical for efficient oxygenation of blood."

She added that pathways recovered in the mouse study show overlap with those associated with de novo, or spontaneous, mutations identified in congenital heart disease patients. Co-investigators of the project include other researchers from the University of Pittsburgh; the

University of Massachusetts Medical School; the Jackson Laboratory; and Children's National Medical Center.

More information: Global genetic analysis in mice unveils central role for cilia in congenital heart disease, *Nature*, DOI: 10.1038/nature14269

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