Landmark study on origins of congenital heart disease

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(Medical Xpress)—In a first-of-its-kind study published in the journal *Nature*, scientists identified a group of gene mutations that may be behind up to 10 percent of complex congenital heart defects, the most frequent birth defect and a leading cause of infant death. Up until this point, scientists have understood little about the origin and development of congenital heart disease.

As part of the National Institutes of Health's Pediatric Cardiac Genomics Consortium, the University of Rochester Medical Center is one of 11 major medical centers that contributed to the finding. Under the

leadership of George A. Porter, M.D., Ph.D., a pediatric cardiologist at Golisano Children's Hospital, URMC recruits patients and families from across upstate New York to help scientists investigate relationships between genetic factors, clinical features and outcomes in congenital heart disease.

According to Rae-Ellen Kavey, M.D., M.P.H., professor of Pediatrics at the Medical Center, the size and collaborative nature of the group, which includes URMC, Yale University, Children's Hospital Boston, The Children's Hospital of Philadelphia, Columbia University Medical Center and others, are just as important as the new finding. To date, the group has recruited more than 6,000 congenital heart disease patients to participate in this body of research, called the Congenital Heart Disease Genetic Network Study or the CHD GENES study.

The *Nature* paper is the first published data from the study and focused on children with very serious heart defects. Kavey, a clinician-scientist who served as the coordinator of the Pediatric Cardiology Risk Reduction program at the National *Heart* Lung and *Blood* Institute from 2005 to 2009, says that no single center treats enough of these patients to make meaningful research findings.

"Only through a network like this can you amass the large volume of cases required to conduct such a study," noted Kavey. "This collaboration is very exciting because it will lead to a lot of new knowledge that will one day help patients and families."

Since 2010, Porter's team, including study coordinator Eileen Taillie, has recruited more than 300 patients. Porter says URMC is a valuable contributor to the Consortium because it provides care to a significant number of congenital heart disease patients across upstate New York, from Buffalo to Syracuse and beyond, performing 300 to 350 cases of open heart surgery each year. To participate in the CHD GENES study,

patients and family members give blood and share their medical history.

The goal of the research is to perform complex genetic testing on a large number of patients with congenital heart disease and their parents. Over the last 30 years, animal models have provided clues to genes that control the development of the heart, but the role that these genes play in the developing human heart is not as well understood.

In approximately 360 patients with complex and severe congenital heart defects, researchers found a high frequency of sporadic mutations – those that aren't passed from parent to child – in a group of genes that are highly active in the developing heart and very few mutations in genes that don't play a big role. In contrast, the 260 children without congenital heart defects who served as controls showed few mutations in both the high heart expression genes and the low heart expression genes.

Many of the mutations in the congenital heart disease patients were in a cluster of genes that influence gene expression – whether or not a gene is turned on or off – by controlling the structure of chromosomes. Chromosomes are small bodies in the nucleus of every cell that house our DNA; changes to the layout or organization of these bodies alter gene expression. This cluster of genes is crucial for development because if a gene is not expressed (turned on) or functions abnormally it could alter the normal growth of the heart.

"The study is important because we've found mutations in a critical cell pathway that appear to disrupt cardiac development," said Porter, assistant professor of Pediatrics and a member of the steering committee for the Pediatric Cardiac Genomics Consortium. "With continued research, we hope to learn more about this pathway and others that might contribute to the development of congenital heart disease and use this knowledge to guide treatment."

Congenital heart disease is a malformation of the heart, affecting the heart chambers, valves or major blood vessels: It is present at birth and can require surgery or no treatment at all, depending on the complexity of the case. It affects 0.8 percent of live births, according to a 2008 study in the Journal of Pediatrics.

"The fact that the Medical Center was invited to participate in this network is a reflection of the quality of our pediatric cardiology program," said Kavey. "Our strong record of treatment and research in congenital heart disease allows us to be part of something that we could never do on our own."

Provided by University of Rochester Medical Center