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Severe heart defect likely caused by genetic factors

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Hypoplastic Left Heart Syndrome (HLHS), a severe cardiovascular malformation that is difficult to treat and often lethal, is caused primarily by genetic factors, according to a new study by researchers at Cincinnati Children's Hospital Medical Center. The study – to be published in the Oct. 16 edition of the *Journal of the American College of Cardiology* – is the first to show the high heritability and likely genetic underpinnings of HLHS and recommend a direction for future research into its cause, development and possible therapeutic strategies.

"Our study demonstrates that HLHS has high heritability, suggesting it is caused almost entirely by genetic effects instead of environmental factors, and that families with a child with HLHS carry a significant recurrence risk of HLHS or related heart defects. This should be considered by physicians when counseling parents to ensure they are aware of potential risks," said Robert B. Hinton, Jr., M.D., a physician and researcher at Cincinnati Children's and the study's lead author.

HLHS is rare, occurring in about two of every 10,000 children born, Dr. Hinton said. Of those children born with HLHS approximately 20 percent die during the first months of life, he added. Children with HLHS suffer from restricted blood and oxygen flow because their hearts are abnormally shaped with an underdeveloped left side. This can include an undersized and/or malformed left ventricle (the heart's primary pumping chamber), aorta, aortic valve or mitral valve. Despite significant advances in diagnosis and therapy, the condition remains challenging to treat and the specific causes remain unknown, Dr. Hinton

said. Babies can survive HLHS by undergoing a series of three complex operations after birth or receiving a heart transplant.

The study at Cincinnati Children's included 38 family-based test groups with a history of HLHS. Researchers found that 55 percent of those families had one or more blood relative with HLHS or an associated heart defect. Of 193 blood relatives evaluated between the ages of 3 days and 74 years, 21.4 percent had HLHS or associated heart defects. In families where one child already had HLHS, the risk of HLHS recurring in a sibling was 8 percent while the risk of a sibling having an HLHS-associated cardiovascular defect was 22 percent. In families where a child and one parent had HLHS, the recurrence risk increased dramatically to 21 percent for recurring HLHS and 25 percent for an associated defect. All participants were evaluated using echocardiography to determine specific phenotype, or the visible heart characteristics and defects found among the different family test groups. During those examinations researchers diagnosed 12 new cases of associated defects among relatives of HLHS patients.

Researchers recommend further studies to pinpoint specific genes responsible for the condition. Finding the genetic basis of HLHS could have significant implications for treating children with the disease, said D. Woodrow Benson, M.D., Ph.D., director of Cardiovascular Genetics at Cincinnati Children's and the study's senior author. This includes identifying possible interventions during fetal life (such as catheter-based procedures), the most appropriate postoperative drug therapies for individual children and determining the potential risks for failure of the right ventricle.

"By using family based linkage analysis, where specific genetic traits are mapped, it should be possible to identify the genes that cause the disease," Dr. Benson said. "Once we know what genes are involved we can study how the disease developments, which may lead to new

treatment approaches."

Earlier studies in animals indicate HLHS may develop because of embryonic alterations in blood flow, such as a premature narrowing of the aortic valve and foramen ovale (which in the fetal heart allows blood to enter the left atrium from the right). Other studies have pointed to the role of certain genes (TBX5 and IRX1) in the formation of defective heart chambers with distinct shapes, functionality and molecular structure. Based on analysis of how these genes function, scientists hypothesize that HLHS may result from a primary defect in the growth of muscle tissue during the heart's development.

"Currently there are no experimental models to clarify the relative contributions of these two hypotheses to the development of HLHS," Dr. Hinton said. "An important step forward in this research will be to understand the degree to which these hypothetical causes actually contribute to the condition."

Source: Cincinnati Children's Hospital Medical Center