When two rights make a wrong: Combating childhood heart disease

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When the body can't distinguish its right side from its left during development, a child can develop a condition called heterotaxy in which the heart is severely malformed, leading to congenital heart disease. To improve survival in these children, researchers at Yale School of Medicine sought to identify the genes that cause heterotaxy. They have shown in a new study that patients with heterotaxy have considerably more copy number variations (CNVs) on their genomes than do control patients.

The findings are published January 31 in Proceedings of the National Academy of Sciences (*PNAS*) Early Edition. Mustafa Khokha, M.D., assistant professor of pediatrics and genetics at Yale, and co-authors studied over 200 patients with heterotaxy as well as a large number of control subjects. They identified and analyzed genome-wide CNVs in humans and then tested these genes in a frog model called Xenopus tropicalis. Copy number variations are insertions or deletions of regions of the genome, so parts of the genome might be deleted or a region might be duplicated.

Khohka said that the frog is a good model for testing genes identified from patients with heterotaxy because the developmental program to establish the left-right axis is nearly identical in frogs compared to humans.

"Five of the seven genes we identified in heterotaxy patients also cause left-right axis abnormalities in frogs when CNV genes were reduced,"

said Khohka. "Therefore, we have shown that children with heterotaxy have a higher burden of CNVs that also cause abnormalities in frogs."

Khokha explained that while humans may appear symmetric across our right and left sides externally, internally our organs are not symmetric. For example, our heart sits on the left side of our body along with the stomach and spleen. Our liver sits on the right. Also, the left and right side of the heart perform very different functions; the right side pumps blood to lungs while the left pumps blood to the body. In children with heterotaxy, because the body cannot properly place the organs on the left or right sides, the heart in particular is severely malformed and can lead to severe disease. In fact, about 90 percent of these children have complex congenital heart disease, which requires surgery to reconstruct their hearts for the child to survive.

"This study is a big step toward understanding what causes congenital heart disease and hopefully will give us some idea of which genes lead to better or worse outcomes," said Khohka. "We also hope to improve our understanding of the genes that affect left-right development and the mechanisms involved in determining your left side from your right side. We also believe our results show that combining human genetics with rapid model systems such as the frog will allow us to rapidly identify genes that affect embryonic development and better understand the causes of these childhood diseases."

Martin Brueckner, a senior author on this study has been awarded a U01 grant from the NHLBI of the NIH. In this "bench to bassinet" program, they plan to identify many more patients with congenital heart disease and identify the mutations that have caused their disease. A better understanding of the mutations that cause congenital heart disease might allow physicians to tailor surgery and long-term care to improve patient outcomes, he said, adding that congenital heart disease is clearly a broad spectrum of diseases and identifying the causative genes will allow

physicians to better define the specific disease for any one patient.

Provided by Yale University