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Scientists find link between congenital cardiac malformation and adult adrenal cancer

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An international team led by Dr. Patricia Dahia, M.D., Ph.D., of UT Health San Antonio, discovered a genetic mutation that explains why adults with severe congenital heart defects—who live with low oxygen in their blood—are at dramatically high risk for adrenal gland cancer.

The finding is being made public March 29 in the *New England Journal of Medicine.*

The study focused on patients who were born with cyanotic congenital heart disease and went on to develop adrenal gland or related tumors called pheochromocytomas or paragangliomas. Detailed genetic analysis of these cases revealed mutations in a gene that regulates a hypoxia (low oxygen)-related pathway called EPAS1, also known as HIF2A. Cyanotic refers to a bluish or purplish discoloration that occurs when blood levels of oxygen are low. Patients with cyanotic heart disease have a sixfold higher risk of developing the adrenal gland tumors than patients without this severe type of heart disease, but the genetic basis for this heightened incidence was unknown.

An amplified response

"It was suspected that in patients with cyanotic heart disease, the low oxygen levels might lead directly to the growth of pheochromocytomas," said Dr. Dahia, professor of medicine in the Joe R. & Teresa Lozano

Long School of Medicine at UT Health San Antonio. "We found instead that a genetic mutation is the main reason why the tumor can appear in these patients. Most remarkably, the mutation turns on the main gene that causes the body to respond to low oxygen, further amplifying this response."

"This finding provides important insights into our understanding of how the body adapts to conditions of low oxygen and how this can lead to tumors," said Dr. Dahia, who also is a member of the Mays Cancer Center, the newly named center home to UT Health San Antonio MD Anderson Cancer Center.

A perfect storm

"We found that this mutation is not inherited but is acquired later," Dr. Dahia said. "The patient's heart disease may create conditions that make it more likely for the mutation to appear. Understanding this mechanism requires further studies."

Importantly, clinical-grade inhibitors of HIF2A exist and are in early clinical trials for a variety of conditions, including pheochromocytomas. "Thus, this discovery can potentially have an impact on patients' lives," she said.

Provided by University of Texas Health Science Center at San Antonio