Gene sequencing project discovers mutations tied to deadly brain tumors in young children

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The St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project has identified new mutations in pediatric brain tumors known as high-grade gliomas (HGGs), which most often occur in the youngest patients. The research appears today as an advance online publication in the scientific journal *Nature Genetics*.

The discoveries stem from the most comprehensive effort yet to identify the genetic missteps driving these deadly tumors. The results provide desperately needed drug development leads, particularly for agents that target the underlying mutations. This and other studies show these mutations often differ based on patient age. HGGs represent 15 to 20 percent of brain and spinal tumors in children. Despite aggressive therapy with surgery, radiation and chemotherapy, long-term survival for HGG patients remains less than 20 percent.

The study is one of four being published simultaneously in the same issue of *Nature Genetics* that link recurring mutations in ACVR1 to cancer for the first time. Pediatric Cancer Genome Project researchers found that ACVR1 was mutated in 32 percent of 57 patients diagnosed with a subtype of HGG called diffuse intrinsic pontine glioma (DIPG). While DIPGs are usually found in children ages 5 to 10, ACVR1 mutations occurred most frequently in younger-than-average patients. DIPG occurs in the brainstem, which controls vital functions and cannot be surgically removed.

The investigators also identified alteration in NTRK genes that drove

tumor development in young HGG patients whose tumors developed outside the brainstem. This study included 10 patients who were age 3 or younger when they were diagnosed with such non-brainstem HGGs. Of those, 40 percent had tumors with alterations in one of three NTRK genes and few other changes. The alterations occurred when a segment of the NTRK genes involved in regulating cell division fused with part of another gene.

"These results indicate the NTRK fusion genes might be very potent drivers of cancer development that have the ability to generate tumors with few other mutations," said co-corresponding author Suzanne Baker, Ph.D., a member of the St. Jude Department of Developmental Neurobiology. The other corresponding author is Jinghui Zhang, Ph.D., a member of the St. Jude Department of Computational Biology. "We want to see if these tumors might be selectively sensitive to therapies that target the pathways that are disrupted as a result of these fusion genes," Baker said.

Added co-author Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis: "We've made some very exciting discoveries that likely will result in more effective diagnosis and treatment of these particularly nasty tumors."

In this study, researchers analyzed 127 HGGs from 118 pediatric patients, including whole genome sequencing of the complete tumor and normal DNA from 42 patients. More targeted sequencing of additional tumors was conducted to track how instructions encoded in DNA were translated into the proteins that do the work of cells.

The recurring presence of ACVR1 mutations in a subset of DIPG patients was one of the biggest surprises, Baker said. ACVR1 carries instructions for making a protein receptor on the cell membrane. The

receptor functions as an on-off switch for a biochemical pathway named bone morphogenetic protein, or BMP. The pathway helps regulate growth and development of bone and other tissue. Working in zebra fish and mouse brain cells, researchers found evidence that ACVR1 mutations from DIPG resulted in the BMP pathway being inappropriately and permanently switched on.

In individuals with an inherited disorder called fibrodysplasia ossificans progressiva (FOP), the same ACVR1 mutations lead not to cancer, but to a different mechanism resulting in abnormal growth of bone in other tissues. Patients with FOP carry the ACVR1 mutation in every cell, while the gene is mutated only in the tumor cells of DIPG patients. "The same mutations are doing something very different in these two terrible and rare diseases. We are working to understand not only how the mutations contribute to cancer, but also whether blocking the BMP pathway offers a new way to treat the tumor," Baker said.

The ACVR1 mutations often occurred with mutations in a gene that carries instructions for making the histone H3.1 protein. That protein influences gene activity through its role in packaging DNA in the nucleus. Mutations in the histone H3 family of proteins were first reported in an earlier Pediatric Cancer Genome Project study. Baker said the new findings suggest the two mutations work together to give tumor cells a selective advantage in the developing brainstem.

While the ACVR1 mutations occurred only in tumors in the brainstem, the NTRK fusion genes were found in HGGs that developed throughout the brain. By combining pieces of different genes, fusion genes can lead to production of abnormal proteins that disrupt cell function. Fusion genes were identified in almost half of all pediatric HGGs in this study, but the NTRK fusions were the most common. The NTRK fusions involved a gene segment encoding a tyrosine kinase domain. This domain functions as an on-off switch for several important regulatory

mechanisms in cells that often malfunction in cancer cells.

NTRK fusion genes have been identified in other pediatric and adult brain tumors. This study marks the first report of the genes in pediatric HGGs. The NTRK fusion genes were identified in part through targeted sequencing of RNA. RNA molecules help translate the instructions carried in DNA into the proteins that do the work of cells. This study was the first to include RNA sequencing in an analysis of HGGs.

The study was part of the Pediatric Cancer Genome Project, which has sequenced the complete normal and tumor genomes of 700 young cancer patients. The project was launched in 2010 to harness advances in genome sequencing technology to improve understanding and treatment of some of the most aggressive and least understood childhood cancers.

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