Key regulatory genes often amplified in aggressive childhood tumor of the brainstem

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The largest study ever of a rare childhood brain tumor found more than half the tumors carried extra copies of specific genes linked to cancer growth, according to research led by St. Jude Children's Research Hospital investigators.

The findings identify possible new targets for treatment of a tumor in the brainstem known as diffuse intrinsic pontine glioma (DIPG). Current survival rates for children with this cancer are low. Fewer than 10 percent of DIPG patients are alive two years after diagnosis. DIPGs account for 10 to 15 percent of pediatric tumors of the brain and central nervous system.

This study analyzed 43 tumors. Forty-seven percent carried extra copies of genes that transmit signals for cell growth and survival. In 30 percent of tumors, the amplification involved different genes that help control cell division. Twenty-one percent of tumors included genes involved in both mechanisms. The research appears in the September 19 online edition of the Journal of Clinical Oncology.

"Our findings have potential therapeutic relevance and suggest it may be useful to combine drugs that target the pathways disrupted in these tumors both broadly and selectively," said Suzanne Baker, Ph.D., the paper's senior author and member of the St. Jude Department of Developmental Neurobiology.

The work also provided insight into DIPG's origins and added evidence

that DIPG is a distinct tumor subtype within a category of brain and spinal tumors known as gliomas. The findings offer the most detailed picture yet of the molecular missteps, including chromosomal changes and altered gene activity, that characterize this tumor.

Efforts to improve patient survival have been hampered in part by limited DIPG samples. "These tumors are one of the most understudied types of cancer because the tumor infiltrates the brainstem, which controls vital functions. It cannot be surgically removed," Baker said. Safety concerns and the accuracy of diagnosis by non-invasive imaging mean that in the U.S. DIPG patients are rarely biopsied.

Baker said these and other research results have prompted renewed discussion about biopsies. "While there may be a rationale for biopsy at diagnosis to determine if specific therapy targets are amplified, our study showed that such amplifications are not always uniformly found within the tumor sample. This suggests that a small biopsy could fail to detect amplification of specific targets, and also that cells within the same tumor may show different responses to selective therapy," she said.

Of the 43 tumors in this study, 37 were donated after autopsy for use in research. Samples of normal tissue were collected as well. Researchers also analyzed other gliomas, including brainstem low-grade gliomas (LGG) and non-brainstem LGG, which occur in the brain outside the brainstem.

Scientists checked for deletions or additions of genetic material at more than 1 million locations across the genome of each tumor. A genome is the complete set of instructions needed to create and sustain a human or other organism. The information is encoded in the DNA molecule, which is packaged into the chromosomes found in nearly every cell.

The screening showed that although DIPGs included extra copies of a variety of genes, two key regulatory mechanisms harbored the most.

Forty-seven percent of DIPGs included extra genes in the receptor tyrosine kinase signaling pathway. This regulatory pathway is disrupted in many tumors and is associated with the unchecked tumor growth and survival that makes cancer deadly. In 30 percent of tumors, the pathway included extra copies of the PDGFRA gene, making it the most commonly amplified gene. Other amplified genes, included MET, IGF1R, ERBB4 and EGFR. In some DIPGs, the pathway included extra copies of more than one of these genes.

Genes that help regulate the cell cycle and cell division were also affected. About 30 percent of DIPGs contained extra copies of the genes that carry instructions for making the Cyclin D family of proteins or the cylin-dependent kinases CDK4 and CDK6.

Chemotherapy agents targeting both pathways are already used to treat other cancers. At St. Jude, a Phase I study is underway using the experimental drug crenolanib to block activity of the PDGFRA protein in DIPGs and related tumors.

When researchers compared gene activity in 27 DIPGs with results from other gliomas found outside the brainstem in both children and adults, they identified significant differences. Baker said those differences offer clues about where DIPGs begin and suggest the HOX family of genes might be involved. "We saw much higher expression of particular HOX gene family members in DIPGs compared to non-brainstem gliomas," she said. This gene family plays an important developmental role in a range of organisms.

Provided by St. Jude Children's Research Hospital