Study finds mutations tied to aggressive childhood brain tumors

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Researchers studying a rare, lethal childhood tumor of the brainstem discovered that nearly 80 percent of the tumors have mutations in genes not previously tied to cancer. Early evidence suggests the alterations play a unique role in other aggressive pediatric brain tumors as well.

The findings from the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project (PCGP) offer important insight into a poorly understood tumor that kills more than 90 percent of patients within two years. The tumor, diffuse intrinsic pontine glioma (DIPG), is found almost exclusively in children and accounts for 10 to 15 percent of pediatric tumors of the brain and central nervous system.

"We are hopeful that identifying these mutations will lead us to new selective therapeutic targets, which are particularly important since this tumor cannot be treated surgically and still lacks effective therapies," said Suzanne Baker, Ph.D., co-leader of the St. Jude Neurobiology and Brain Tumor Program and a member of the St. Jude Department of Developmental Neurobiology. She is a corresponding author of the study published in the January 29 online edition of the scientific journal Nature Genetics.

DIPG is an extremely invasive tumor that occurs in the brainstem, which is at the base of the skull and controls such vital functions as breathing and heart rate. DIPG cannot be cured by surgery and is accurately diagnosed by non-invasive imaging. As a result, DIPG is rarely biopsied

in the U.S. and little is known about it.

Cancer occurs when normal gene activity is disrupted, allowing for the unchecked cell growth and spread that makes cancer so lethal. In this study, investigators found 78 percent of the DIPG tumors had alterations in one of two genes that carry instructions for making proteins that play similar roles in packaging DNA inside cells. Both belong to the histone H3 family of proteins. DNA must be wrapped around histones so that it is compact enough to fit into the nucleus. The packaging of DNA by histones influences which genes are switched on or off, as well as the repair of mutations in DNA and the stability of DNA. Disruption of any of these processes can contribute to cancer.

Researchers said that the mutations seem unique to aggressive childhood brain tumors.

"It is amazing to see that this particular tumor type appears to be characterized by a molecular 'smoking gun' and that these mutations are unique to fast-growing pediatric cancers in the brain," said Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis and one of the study's corresponding authors. "This is exactly the type of result one hopes to find when studying the genomes of cancer patients."

The results are the latest from the PCGP, an ambitious three-year effort to sequence the complete normal and cancer genomes of 600 children with some of the most poorly understood and aggressive pediatric cancers. The human genome includes the complete set of instructions needed to assemble and sustain human life. The goal is to identify differences that explain why cancer develops, spreads and kills. Researchers believe the findings will provide the foundation for new tools to diagnose, treat or prevent the disease.

For this study, researchers sequenced the complete normal and cancer genomes of seven patients with DIPG. "The mutations were found at such high frequency in the cancer genomes of those seven patients that we immediately checked for the same alterations in a larger group of DIPGs," Baker said. When researchers sequenced all 16 of the related genes that make closely related variants of histone H3 proteins in an additional 43 DIPGs, they found many of the tumors contained the same mistakes in only two of these genes.

Of the 50 DIPG tumors included in this study, 60 percent had a single alteration in the makeup of the H3F3A gene. When the mutated gene was translated into a protein, the point mutation led to the substitution of methionine for lysine as the 27th amino acid in this variant of histone H3 protein. Another 18 percent of the DIPG patients carried the same mistake in a different gene, HIST1H3B.

Researchers are now working to understand how mutations in H3F3A and HIST1H3B impact cell function and contribute to cancer. Earlier research provides some clues. The lysine that is mutated is normally targeted by enzymes that attach other molecules to histone H3, influencing how it interacts with other proteins that regulate gene expression, Baker said. Mutations in the enzymes that target histone H3 have been identified in other cancers, but this is the first report showing a specific alteration of histones in cancer.

H3F3A and HIST1H3B were also mutated in other aggressive childhood brain tumors, glioblastoma, that develop outside the brain stem. Of 36 such tumors included in this study, 36 percent carried one of three distinct point mutations in the genes. The alterations included another single change in the makeup of H3F3A not found in DIPGs.

The histone H3 genes, however, were not mutated in any of the 252 other childhood tumors researchers checked for this study. The list

included the brain tumors known as low-grade gliomas, medulloblastomas and ependymomas plus other cancers outside the brain and nervous system. The H3 changes have not been reported in any other cancers, including adult glioblastoma. "This suggests these particular mutations give a very important selective advantage, particularly in the developing brainstem and to a lesser degree in the developing brain, which leads to a terribly aggressive brain tumor in children, but not in adults," Baker said.

"This discovery would not have been possible without the unbiased approach taken by the Pediatric Cancer Genome Project," Baker said. "The mutations had not been reported in any other tumor, so we would not have searched for them in DIPGs. Yet the alterations clearly play an important role in generating this particular tumor."

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