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Whole genome sequencing finds new mutations to blame for a majority of brain tumor subtype

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Washington University Pediatric Cancer Genome Project has identified mutations responsible for more than half of a subtype of childhood brain tumor that takes a high toll on patients. Researchers also found evidence the tumors are susceptible to drugs already in development.

The study focused on a family of brain tumors known as low-grade gliomas (LGGs). These slow-growing cancers are found in about 700 children annually in the U.S., making them the most common childhood tumors of the brain and spinal cord. For patients whose tumors cannot be surgically removed, the long-term outlook remains bleak due to complications from the disease and its ongoing treatment. Nationwide, surgery alone cures only about one-third of patients.

Using whole genome sequencing, researchers identified genetic alterations in two genes that occurred almost exclusively in a subtype of LGG termed diffuse LGG. This subtype cannot be cured surgically because the tumor cells invade the healthy brain. Together, the mutations accounted for 53 percent of the diffuse LGG in this study. Researchers also demonstrated that one of the mutations, which had not previously been linked to brain tumors, caused tumors when introduced into the glial brain cells of mice.

The findings appear in the April 14 advance online edition of the scientific journal *Nature Genetics*.

"This subtype of low-grade glioma can be a nasty chronic disease, yet prior to this study we knew almost nothing about its genetic alterations," said David Ellison, M.D., Ph.D., chair of the St. Jude Department of Pathology and the study's corresponding author. The first author is Jinghui Zhang, Ph.D., an associate member of the St. Jude Department of Computational Biology.

The Pediatric Cancer Genome Project is using next-generation whole genome sequencing to determine the complete normal and cancer genomes of children and adolescents with some of the least understood and most difficult to treat cancers. Scientists believe that studying differences in the 3 billion chemical bases that make up the human genome will provide the scientific foundation for the next generation of cancer care.

"We were surprised to find that many of these tumors could be traced to a single genetic alteration," said co-author Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis. "This is a major pathway through which low-grade gliomas develop and it provides new clues to explore as we search for better treatments."

The study involved whole genome sequencing of 39 paired tumor and normal tissue samples from 38 children and adolescents with different subtypes of LGG and related tumors called low-grade glioneuronal tumors (LGGNTs). Although many cancers develop following multiple genetic abnormalities, 62 percent of the 39 tumors in this study stemmed from a single genetic alteration.

Previous studies have linked LGGs to abnormal activation of the MAPK/ERK pathway. The pathway is involved in regulating cell division and other processes that are often disrupted in cancer. Until now, however, the genetic alterations involved in driving this pathway

were unknown for some types of LGG and LGGNT.

This study linked activation in the pathway to duplication of a key segment of the FGFR1 gene, which investigators discovered in brain tumors for the first time. The segment is called a tyrosine kinase domain. It functions like an on-off switch for several cell signaling pathways, including the MAPK/ERK pathway. Investigators also demonstrated that experimental drugs designed to block activity along two altered pathways worked in cells with the FGFR1 tyrosine kinase domain duplication. "The finding suggests a potential opportunity for using targeted therapies in patients whose tumors cannot be surgically removed," Ellison said.

Researchers also showed that the FGFR1 abnormality triggered an aggressive brain tumor in glial cells from mice that lacked the tumor suppressor gene Trp53.

Whole-genome sequencing found previously undiscovered rearrangements in the MYB and MYBL1 genes in diffuse LGGs. These newly identified abnormalities were also implicated in switching on the MAPK/ERK pathway.

Researchers checked an additional 100 LGGs and LGGNTs for the same FGFR1, MYB and MYBL1 mutations. Overall, MYB was altered in 25 percent of the diffuse LGGs, and 24 percent had alterations in FGFR1. Researchers also turned up numerous other mutations that occurred in just a few tumors. The affected genes included BRAF, RAF1, H3F3A, ATRX, EP300, WHSC1 and CHD2.

"The Pediatric Cancer Genome Project has provided a remarkable opportunity to look at the genomic landscape of this disease and really put the alterations responsible on the map. We can now account for the genetic errors responsible for more than 90 percent of low-grade gliomas," Ellison said. "The discovery that FGFR1 and MYB play a

central role in childhood diffuse LGG also serves to distinguish the pediatric and adult forms of the disease."

More information: Whole genome sequencing identifies genetic alterations in pediatric low-grade gliomas, DOI: 10.1038/ng.2611

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