Gene sequencing project identifies potential drug targets in common childhood brain tumor

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Researchers studying the genetic roots of the most common malignant childhood brain tumor have discovered missteps in three of the four subtypes of the cancer that involve genes already targeted for drug development.

The most significant gene alterations are linked to subtypes of medulloblastoma that currently have the best and worst prognosis. They were among 41 genes associated for the first time to medulloblastoma by the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project.

"This study provides new direction for understanding what drives these tumors and uncovers totally unexpected new drug targets. There are drugs already in development against these targets aimed at treating adult cancers and other diseases," said Richard Gilbertson, M.D., Ph.D., St. Jude Comprehensive Cancer Center director. Gilbertson and Jinghui Zhang, Ph.D., an associate member of the St. Jude Department of Computational Biology, are the study's corresponding authors. The work appears in the June 20 advance online issue of the scientific journal *Nature*.

The results mark progress toward more targeted therapies against medulloblastoma and other cancers. While better use of existing drugs and improved supportive care have helped push long-term survival rates

for childhood cancer to about 80 percent, drug development efforts have largely stalled for more than two decades, particularly against pediatric brain tumors.

"This study is a great example of the way whole-genome sequencing of cancer patients allows us to dig deep into the biology of certain tumors and catch a glimpse of their Achilles heel," said co-author Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis. "These results help us better understand the disease and, as a result, we will be able to more effectively diagnose and treat these kids."

This study involved sequencing the complete normal and cancer genomes of 37 young patients with medulloblastoma, making it the largest such effort to date involving the cancer. Researchers then checked tumors from an additional 56 patients for the same alterations. The genome is the complete set of instructions needed for human life. It is carried in the DNA found in nearly every cell.

The findings are part of the Pediatric Cancer Genome Project, which launched in 2010 as a three-year effort to decipher the complete normal and tumor genomes of 600 young cancer patients with some of the most challenging tumors. The endeavor has already yielded important clues into the origin, spread and treatment response in childhood cancers of the blood, brain, eye and nervous system.

Medulloblastoma is diagnosed in about 400 U.S. children and adolescents annually. Their outcome varies widely based on the subtype they have. While nearly all patients with the wingless (WNT) subtype survive, just 60 percent of those with subtype 3 medulloblastoma are alive three years after diagnosis. WNT medulloblastoma is named for the pathway disrupted in the tumor subtype.

This study found a high percentage of patients with WNT-subtype medulloblastoma had mutations in the DDX3X gene. The investigators found evidence that mutated DDX3X is required to sustain the brain cells where WNT subtype tumors develop. The research also found evidence linking alterations in other genes, including CDH1 and PIK3CA, to the development and spread of the WNT subtype. "It is particularly exciting that these genes, or the pathways in which they work, are already the focus of drug development efforts. This opens up the possibility of using these drugs to treat medulloblastoma in new ways," said Giles Robinson, M.D., St. Jude Department of Oncology research associate and one of the study's first authors.

Investigators demonstrated that subtype three and four medulloblastoma often had alterations in genes that impact cell maturation. The genes carry instructions for proteins that add or remove the chemical group methyl to the H3K27 protein. H3K27 is part of the chromatin structure that packages DNA to fit inside cells. That packaging helps determine if genes are switched on or off. The addition of methyl to H3K27 permits less specialized cells to keep dividing and blocks activity of genes that would prompt cells to stop dividing, differentiate and take on more specialized roles.

Some subgroup 3 and 4 tumors were characterized by a gain in EZH2, which adds methyl to H3K27. EZH2 is also associated with adult cancers and the focus of ongoing drug development. St. Jude has begun screening those and other compounds for evidence of effectiveness against medulloblastoma.

In other subtype 3 and 4 tumors a different gene, KDM6A, was inactivated by mutations. KDM6A works to remove methyl groups from H3K27, thus eliminating this gene's function could keep cells in an immature dividing state. The results suggest the genes possibly work together to promote medulloblastoma development.

The EZH2 and KDM6A alterations were found only in the subgroup three and four tumors, which also had higher levels of H3K27 methylation than other medulloblastoma subtypes. "With this research we have 'lifted the lid' on the most aggressive and challenging form of medulloblastoma, subtype 3, which was really a black box in terms of our understanding, and revealed a major driver of the disease," Gilbertson said.

The findings add to mounting evidence from the Pediatric Cancer Genome Project that epigenetic changes play a pivotal role in fueling childhood cancer. Epigenetic mechanisms can serve as on-off switches, altering gene activity without changing the makeup of the gene. Such changes can lead to the unlimited cell growth of cancer.

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