Definitive genomic study reveals alterations driving most medulloblastoma brain tumors

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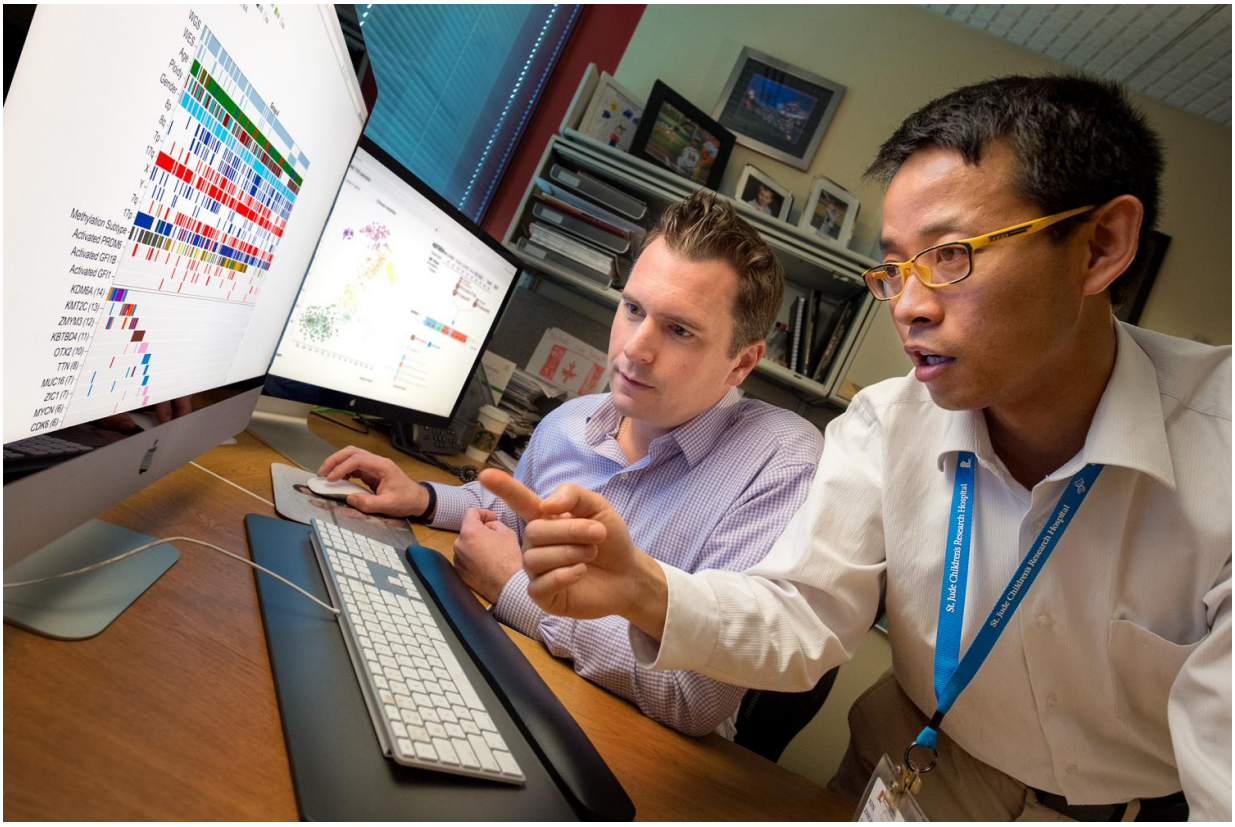

Co-first author Paul Northcott, Ph.D., an assistant member of the St. Jude Department of Developmental Neurobiology and author Xin Zhou, PhD, senior bioinformatics research scientist. Credit: Seth Dixon / St. Jude Children's Research Hospital

The most comprehensive analysis yet of medulloblastoma has identified

genomic changes responsible for more than 75 percent of the brain tumors, including two new suspected cancer genes that were found exclusively in the least understood disease subgroups. The landmark study from an international research consortium was led by St. Jude Children's Research Hospital and investigators in Germany and Canada. The results appear July 20 in the scientific journal *Nature*.

The integrated genomic analysis of tumor and normal tissue from almost 500 patients revealed new mutations and genetic missteps. The discoveries will aid efforts to develop urgently needed precision medicines. Such targeted therapies are designed to increase survival while reducing treatment-related side effects.

"Our goal is to understand each patient's tumor at the molecular level in order to better tailor treatment," said co-first author Paul Northcott, Ph.D., an assistant member of the St. Jude Department of Developmental Neurobiology. "This study provides a rich resource for neuro-oncology researchers and clinicians worldwide to mine in order to better understand and target these tumors."

Medulloblastoma is the most common malignant pediatric brain tumor. It is diagnosed in 250 to 500 individuals annually in the U.S.; most are younger than 16 years old. There are four principal subgroups: WNT, Sonic Hedgehog (SHH), Group 3 and Group 4. The subgroups are driven by different genetic alterations, begin in different cells and often exhibit different clinical outcomes. About 95 percent of patients in the WNT subgroup become long-term survivors compared to about 50 percent for Group 3 patients. There are currently no targeted therapies for Group 3 and Group 4 tumors, which account for 65 to 70 percent of medulloblastoma cases.

The analysis was led by researchers at St. Jude; the German Cancer Research Center, Heidelberg; and the Hospital for Sick Children in

Toronto. The study is among the largest whole genome sequencing studies for any type of cancer. Whole genome sequencing or whole exome sequencing was done on tumor and normal tissue collected from 491 medulloblastoma patients at diagnosis.

Researchers also analyzed DNA methylation and complementary epigenetic data from 1,256 medulloblastoma patients and gene expression data from 392 tumors. The genome is the complete set of genetic information carried inside nearly all cells. The epigenome pertains to chemical modifications to DNA that regulate activity of the genome. The transcriptome is a readout of which genes are being expressed.

"Layering genetic, epigenetic and transcriptional data, combined with better analytic tools, led to discoveries that would have previously been missed in this highly complex and variable cancer," Northcott said. Added co-author Amar Gajjar, M.D., chair of the St. Jude Department of Pediatric Medicine: "Using advanced genomic techniques to gain insight into what genetic abnormalities cause medulloblastoma is essential for developing relevant models to test targeted therapies."

The discoveries include identification of two new suspected oncogenes: KBTBD4 and PRDM6. The genes were found only in Group 3 and Group 4 medulloblastoma and had not previously been associated with any cancer.

KBTBD4 was the most frequently mutated gene in those subgroups. The mutation involved insertion of one or two amino acids in the same small section or "hot spot" of the gene. Research is underway to determine the function of the normal and mutant proteins. The KBTBD4 protein is predicted to function in conjunction with ubiquitin ligase enzymes that tag other proteins for recycling by cells, but Northcott said research is underway to better understand how the normal and mutant proteins

function.

PRDM6 is an epigenetic regulator of gene activity whose own expression was dramatically increased in Group 4 medulloblastoma. Evidence suggested that the increased activity was due to "enhancer hijacking" caused by DNA rearrangements that reconfigured highly active enhancers to activate PRDM6 expression.

PRDM6 activation contributed to 17 percent of Group 4 medulloblastoma tumors. If PRDM6 is confirmed to be an oncogene, researchers hope it will lead to development of the first laboratory model of Group 4 medulloblastoma, which accounts for about 40 percent of medulloblastoma tumors. Such models play a pivotal role in clinical advances.

Overall, the integrated analysis led to identification of altered genes and cellular pathways responsible for more than 75 percent of patients' tumors. Until this study, fewer than one-third of the mutations driving Group 3 and Group 4 medulloblastoma had been identified. The data also revealed additional complexity within different medulloblastoma subgroups, particularly Group 3 and Group 4 tumors. "The more refined classification of medulloblastoma offered in this study opens avenues for improved risk-stratification of patients and more tailored therapies that target the genomic alterations driving their disease," Gajjar said.

Researchers can access processed study data at no cost through the St. Jude PeCan data portal, the R2: Genomics Analysis and Visualization Platform and the PedcBioPortal for Cancer Genomics.

More information: Paul A. Northcott et al, The whole-genome landscape of medulloblastoma subtypes, *Nature* (2017). DOI: 10.1038/nature22973

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