Key mutations discovered for medulloblastoma -- most common childhood brain cancer

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Researchers at Dana-Farber/Children's Hospital Cancer Center (DF/CHCC) and several collaborating institutions have linked mutations in specific genes to each of the four recognized subtypes of medulloblastoma, the most common malignant brain tumor of children. The discovery, reported July in the journal *Nature*, provides doctors with potential biomarkers for guiding and individualizing treatment and reveals prospective therapeutic opportunities for countering this devastating malignancy.

The study was conducted by a research team led by Scott Pomeroy, MD, PhD, Neurologist-in-Chief at Boston Children's Hospital and a neuro-oncologist at DF/CHCC; Yoon-Jae Cho, MD, formerly of Boston Children's and now at Stanford University School of Medicine; and Matthew Meyerson, MD, PhD, of Dana-Farber Cancer Institute and the Broad Institute.

Medulloblastomas occur in the cerebellum (the part of the brain that controls balance and other complex motor functions) and are treated with a combination of surgery, radiation and chemotherapy. Though overall survival hovers around 70 percent, most survivors are unable to live independently due to the lasting effects of both tumor and treatment.

Doctors have historically classified medulloblastoma patients as either standard or high risk based on biopsy results, but have long suspected

that what we call medulloblastoma could actually be several different diseases. Over the last two years, studies by researchers including Pomeroy and his colleagues have bolstered this view by dividing medulloblastoma into four molecular subtypes based on gene expression profiles and copy number variations. Each subtype has a distinct survival rate, ranging from 20 to 90 percent.

"Not only do we now know how to stratify medulloblastomas genomically, we have a firm grasp of what gene mutations drive each molecular subtype," said Pomeroy, who has spent 20 years trying to understand the biological basis of the tumor's variability. "For the first time, we'll be able to classify and treat medulloblastoma based on molecular typing, providing the best therapy with the fewest long-term consequences."

In this new study, Pomeroy and his team used next generation sequencing technologies to read the full complement of protein-coding genes (also called the exome) of tumors from 92 patients. Within these tumors the team discovered that somatic (that is, non-heritable) mutations occur at very low frequency, one-tenth to one-hundredth of that seen in cancers of adults. Specific gene mutations clustered neatly into the four molecular subtypes, although the majority of genes (88%) were mutated only once in the entire tumor collection. Only 12 genes were mutated in more than one tumor, illustrating medulloblastoma's genetic heterogeneity.

Functionally, the mutated genes fell into two broad categories: genes like Shh and Wnt that play direct roles in molecular pathways controlling cell growth, and genes like DDX3X and GPS2 that play more of a coaching role, modulating the activity of other genes.

Taken as a whole, the study's results confirm the view of medulloblastoma as a family of tumors driven by disruptions in just a

few common mechanisms. However, the form those disruptions take—the actual mutations or genomic changes—can vary from tumor to tumor.

"The results reflect two emerging genetic themes seen throughout childhood tumors," Pomeroy noted. "First, very low mutation rates, much lower than those seen in adult tumors, and second, the importance of mutations in genes that regulate the function of the cell's growth pathways but which aren't direct components of those pathways."

Some of the study's findings could be translated to patients relatively quickly. For instance, with the main mutations of each subtype in hand, it should soon be possible to rapidly classify individual medulloblastoma patients' tumors and tailor treatment appropriately based on each subtype's known prognosis. In addition, clinical trials of Shh-blocking drugs already under investigation for other cancers could begin within the next couple of years in patients with the medulloblastoma subtype driven by Shh mutations.

Pomeroy credits the high level of cooperation between groups at different institutions studying medulloblastoma as a significant factor in the progress made over the last few years. "Because of our collective efforts, medulloblastoma has gone from an important but obscure tumor to one that we understand better than many other cancers at the molecular level."

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