

A divide and conquer strategy for childhood brain cancer

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Medulloblastomas are the most common malignant brain tumors of childhood, with 40 to 50 percent overall mortality. One of the greatest challenges in treating them is that they vary substantially from patient to patient. In the largest genomic study of human medulloblastomas to date, researchers from Children's Hospital Boston, together with collaborators, have identified six subtypes with distinct molecular "fingerprints" that will improve doctors' ability to direct and individualize treatment.

The study, reported online November 22nd in the [Journal of Clinical Oncology](#), is expected to lead to the first use of [biomarkers](#) for medulloblastoma in the clinic. The Children's Oncology Group, an international cooperative for childhood cancer research, already plans to apply some of the new data to subtype patients in upcoming clinical trials. Recognition of tumor subtypes will allow patients who need the most aggressive interventions to get them and patients with better prognoses to avoid treatments with potential long-term neurological and cognitive side effects.

"We're basically redefining the disease," says Scott Pomeroy, MD, PhD, Neurologist-in-Chief at Children's and the study's senior author. "This tumor breaks down into subtypes that really act like different diseases, and they will be treated differently looking forward."

The team examined 194 [medulloblastomas](#), accrued through the collaboration of many institutions. "We have far more samples than what was studied before, which gives us much better resolution in determining

the number of molecular subtypes represented in medulloblastomas," says first author Yoon-Jae Cho, MD, a neurologist at Children's. "Over the past two decades, Scott has worked very hard to accrue samples here at Children's Hospital and has also created national tumor banks that allow for this type of work to be done."

The study identifies a subtype of medulloblastoma—never before characterized—that has the worst prognosis. "We determined the survival rates associated with each molecular subtype," says Cho. "One in particular accounts for a large percentage of tumors that do not respond to current treatments . . . we need to develop more effective strategies to treat this subtype".

Medulloblastomas originate in the cerebellum, a part of the brain that controls motor coordination and other essential functions. The current standard of care is surgery to remove the tumor, followed by a blend of radiation and chemotherapy.

Earlier studies by Pomeroy and others showed that different gene activity patterns in tumor samples correlate with different outcomes—a better or worse prognosis. The new study went further by examining the DNA of tumors in each category, to see if the differences in gene activity were accompanied by differences in the actual genetic makeup of the subtypes. The researchers examined changes in the number of DNA copies (known as copy number variation) throughout the entire genome of each tumor subtype, and found distinctly different patterns.

"The basic genetic makeup is fundamentally different from one tumor subtype to the next," says Pomeroy.

For example, copies of MYC, a well-known oncogene, are markedly increased in the tumor subtype with the worst prognosis, but not in the other subtypes. In upcoming clinical trials coordinated by the Children's

Oncology Group, DNA samples from medulloblastomas will be accessed for the number of MYC copies, and this information will be incorporated into treatment decisions. This will mark the first use of biomarkers for medulloblastoma in the clinic.

The team also looked at about 500 microRNAs, regulatory molecules that usually dampen the activity of their target genes. Again, the results revealed distinctly different patterns of microRNA activity across the different medulloblastoma subtypes.

The biomarkers identified in the new findings could potentially be used to personalize treatment by determining the disease subtype and providing information about prognosis within a subtype. A companion study, not yet published, details a model for predicting medulloblastoma relapse that significantly outperforms existing models by integrating disease subtype, other clues gleaned from the genomic analysis and clinical presentation. The model was a collaborative project with the Broad Institute of MIT and Harvard.

"Certain markers portend good outcome in one subtype, but that same marker would be a bad marker in a different subtype . . . this emphasizes the advantage of knowing the molecular subtype of medulloblastoma that you are dealing with," explains Cho.

"Until recently, all we could do is look at [brain tumors](#) under the microscope and say what they look like. And knowing what part of the brain they come from, we could say, that looks like medulloblastoma," Pomeroy says. "Now we actually have precise molecular signatures and we know what subtype of medulloblastoma it is. And we can say something about that subtype . . . and what seems to be driving their growth and what the prognosis might be."

Provided by Children's Hospital Boston

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