From the clinic to the lab, understanding medulloblastoma relies on molecular profiling

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Left to right: Giles Robinson, M.D., Paul Northcott, Ph.D., and Amar Gajjar, M.D., all of St. Jude Children's Research Hospital. Credit: St. Jude Children's Research Hospital

Scientists at St. Jude Children's Research Hospital and their colleagues have published a detailed account of SJMB03, a clinical trial for pediatric patients with medulloblastoma. Additionally, they report results of the largest analysis of matched primary and relapsed medulloblastoma tumors to date. In both the clinic and the lab, results underscore the need for integrated molecular assessment of these tumors. The papers were published recently in the *Journal of Clinical Oncology*.

Clinical trial confirms subgroups, highlights need for additional analysis

Medulloblastoma is among the most common malignant pediatric brain tumors. Previous research by St. Jude scientists and others has classified medulloblastoma into four distinct molecular groups: WNT and SHH (which are driven by their namesake genetic mutations), Group 3 and Group 4. Prognosis for medulloblastoma is different for each molecular group. Retrospective analyses have shown that WNT tumors respond the best, with 95% five-year survival. SHH and Group 4 tumors have approximately 75% five-year survival, and Group 3 has 60%.

"This was a large clinical trial that really incorporated biology into the analysis," said first author Amar Gajjar, M.D., chair of the St. Jude Department of Pediatric Medicine. "This allowed us to interpret the outcomes based on clinical and molecular risk features."

SJMB03 was an international, multicenter phase 3 clinical trial for children with newly diagnosed medulloblastoma. The trial enrolled patients from 2003-12 and provided risk-adapted therapy based on clinical features of the tumor. The study also assessed the frequency and clinical significance of molecular groups and genetic alterations using DNA methylation and next-generation sequencing.

The findings confirm the outcomes previously observed in retrospective analyses. The study also provided detailed genetic annotation by molecular group. This allowed researchers to identify new risk groups within the previously established molecular groups. They found that all WNT, and some SHH and Group 3/4, are low risk. Scientists also found that some SHH and Group 3/4 are high risk.

"This study has given us a more granular understanding of risk that can help us determine when to reduce or escalate therapy," said corresponding author Giles Robinson, M.D., of St. Jude Oncology. "These findings will help inform the design of future clinical trials for medulloblastoma."

Relapsed medulloblastoma is not always as it appears

In a complementary study, researchers analyzed data from SJMB03 alongside another clinical trial, SJYC07 (which enrolled infants). The scientists also assembled a cohort of primary and relapsed medulloblastoma tumor samples from St. Jude and its collaborators around the world. These analyses enabled the researchers to learn more about relapsed medulloblastoma.

Approximately one-third of all patients with medulloblastoma will relapse, but the rate of relapse varies based on factors such as the patients' age and what type of therapy they receive. This study is the most comprehensive effort to look at clinical trial data and matched samples. Results challenge the current understanding of relapsed disease.

In particular, the researchers found that 10% of tumors classified as relapsed medulloblastoma are actually a secondary malignancy. Most often these secondary cancers, which are known to occur as a result of prior treatment, are high-grade gliomas. Newly diagnosed high-grade glioma and relapsed medulloblastoma may receive different treatments.

Additionally, this study found that while most tumors remain in the same molecular group from diagnosis to relapse, this is not always the case. The researchers found evidence of subgroup switching between Group 3 and Group 4 tumors.

This study also provides evidence that tumors are more genetically stable from diagnosis to relapse than previously thought. The researchers used whole exome sequencing to look at genes involved in cancer. They found that these genes are often retained between the primary and relapsed tumors.

"We've been able to provide important context to the patterns of relapse that we see in childhood medulloblastoma," said corresponding author Paul Northcott, Ph.D., of St. Jude Developmental Neurobiology. "These findings underscore the need to include molecular analysis in the diagnosis and treatment of these tumors."

More information: Rahul Kumar et al, Clinical Outcomes and Patient-Matched Molecular Composition of Relapsed Medulloblastoma, *Journal of Clinical Oncology* (2021). DOI: 10.1200/JCO.20.01359

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