Genetic variation linked to cognitive differences after radiation for pediatric medulloblastoma

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Long-term cognitive problems are a frequent side effect in children undergoing life-saving radiation therapy for medulloblastoma—the most common malignant pediatric brain tumor. Medulloblastoma affects between 250 and 500 U.S. children annually, but not all children experience cognitive difficulties.

An Atlanta research team using whole-genome sequencing has found that variations in patients' DNA profiles result in significantly different cognitive outcomes among surviving medulloblastoma patients. Using genomics to identify those patients most at risk for long-term cognitive difficulties could ultimately lead to changes in clinical practice.

The study was published online in the journal *Translational Oncology* and will be in the July print edition.

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"It is crucial for health care teams to understand what drives this different response to radiation," says first author Benjamin I. Siegel, MD, a neurology resident at Emory University School of Medicine. "Doing so will help clinicians provide patients with more information about their prognosis at the time of diagnosis and will also help researchers develop personalized interventions for high-risk patients."

In addition to whole-genome sequencing on the peripheral blood of 22 long-term survivors of medulloblastoma, a research team led by Tricia Z. King, Ph.D., at Georgia State University conducted neurocognitive testing on 18 of those patients who were exposed to similar doses of radiation at similar ages. The analysis identified different DNA profiles in survivors with cognitive impairment compared to those with better outcomes. Using a whole genome approach allowed them to discover unique DNA variants in non-coding DNA regions that would have been missed by targeting specific genes or gene groups—the approach used in earlier studies.

Non-coding DNA comprises about 99 percent of the human genome, but historically was dismissed as "junk DNA" with no function. Recently, researchers have recognized that non-coding DNA is integrally involved in gene regulation.

"Most of the significant variants in our sample were in non-coding DNA regions," says Siegel. "The

implication of our study is that differences in non-coding DNA regions are important in determining which medulloblastoma patients are vulnerable to treatment-related neurocognitive problems and which are resistant to those difficulties. Our next step in this line of precision medicine research is to validate the study's findings in a larger cohort, with the ultimate goal of translating them to clinical practice."

Provided by Emory University