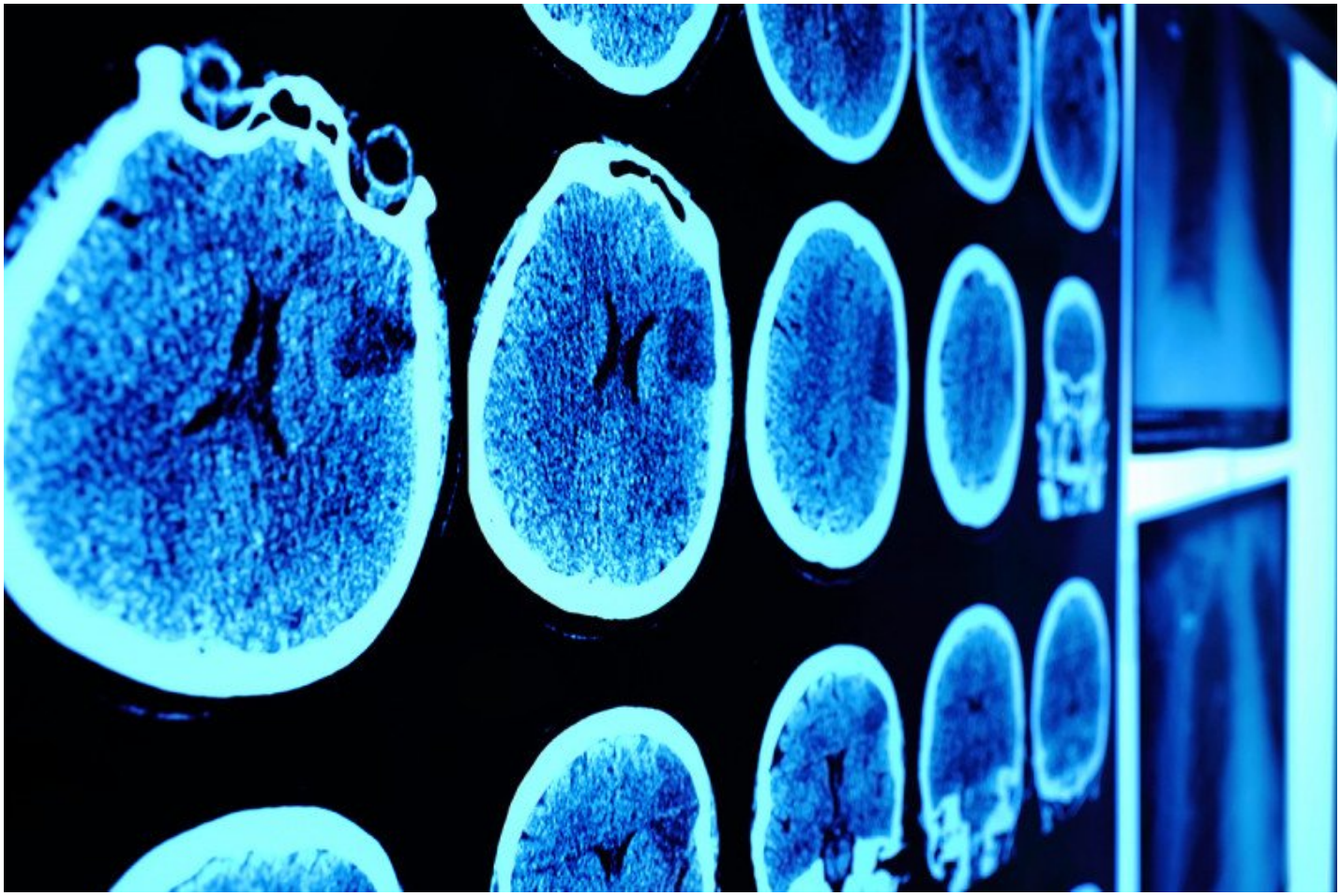
Research Advances the Genetic Understanding of Pineoblastoma, a Rare Brain Cancer

By Julie Grisham, **Friday, July 20, 2018**



A new analysis has revealed molecular differences between certain brain tumors in adults and children.

Summary

> Experts say the findings about this type of tumor will lead to more accurate diagnoses and, potentially, to better treatments.

In recent years, there have been many advances in treating children with cancer, but brain tumors remain a major challenge. For many **pediatric brain tumors**, the current treatments often are not very effective or are very toxic. Experts at Memorial Sloan Kettering are focused on learning more about the genetic and molecular underpinnings of these cancers.

Pediatric Neuro-Oncology Service Chief **Matthias Karajannis** is leading many of these efforts. Dr. Karajannis, along with a team from MSK and several other hospitals in the United States and Germany, published **a paper in *Nature Communications*** that focuses on a rare brain tumor called pineoblastoma. This type of tumor accounts for less than 1% of all primary brain tumors. The study reports that pineoblastomas in adults and children are distinct from each other — something that was not previously known. The findings also point the way toward developing better therapies for the disease.

"Over the past decade, we've made major progress in understanding the distinct biological differences in various pediatric brain tumors," Dr. Karajannis says. "Now this research in the lab is starting to bear fruit and help us better diagnose and treat patients, especially those with rare tumors like pineoblastoma."

Decoding the Alterations in a Rare Cancer

Pineoblastoma is a member of the class of tumors called primitive neuroectodermal tumors (PNETs). It usually occurs in children and young adults, but the tumors can sometimes appear in older adults. One of the findings from the new study is that the adult form of the disease more closely resembles other, less-aggressive PNETs, while the pediatric form is driven by a different set of molecular changes. These distinct changes make pineoblastoma in children more aggressive.

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Pineoblastoma arises in the pineal gland. This pea-size organ in the brain produces and controls certain hormones, including melatonin, which affects sleep. The symptoms of pineoblastoma are similar to those of other brain tumors, including headaches, nausea and vomiting, and problems with eye movement and vision. It can also cause a buildup of fluid in the brain.

Sometimes pineoblastoma runs in families that have a certain inherited mutation. These inherited mutations lead to errors in one of the proteins that control small molecules called microRNAs. MicroRNAs monitor which genes get turned on and off. When errors aren't property controlled, they can drive the formation of tumors. The new study found that in nonfamilial pineoblastoma, dysregulation of microRNAs occurs because of a different mutated gene, called *DROSHA*.

A Breakthrough in Understanding Brain Tumors

In the paper, the investigators report the latest discoveries based on the genetic and molecular analysis of 16 pineoblastoma tumors removed from patients, including 13 children. They looked at more than the changes in DNA that were connected with the disease, however. They also considered what is called the methylation profile. Methylation is one way that DNA gets modified without changing the DNA sequence. Earlier this year, **another study** from Dr. Karajannis and his collaborators reported a new system for distinguishing 100-plus types of brain tumors based on their methylation profiles.

"We were surprised to find these different molecular fingerprints between the adult and pediatric forms of the disease," Dr. Karajannis says. "Another surprising finding was that, similar to what is seen in familial pineoblastoma, dysregulation of microRNAs appears to play a major role in the development of pineoblastoma that comes up sporadically. We also found that one of

the genes involved in the formation of pineoblastoma is connected to brain development in embryos as well. This provides an intriguing link between the formation of this tumor and normal brain development."

The investigators also identified repeated mutations in a gene called *ARRB2*. This gene has previously been linked to kidney and liver cancers. Very little is currently known about how *ARRB2* functions, however.

"Further studies will be needed to assess the role of *ARRB2* and the other genes we found to be recurrently mutated in pineoblastoma," Dr. Karajannis concludes. "But our findings open up new avenues of research toward novel therapies that exploit the abnormal processing of microRNA that we've observed."

This research was funded by the Friedberg Charitable Foundation; the Sohn Conference Foundation; the Making Headway Foundation; the Alice and Thomas J. Tisch Brain Tumor Research Fund; a New York University Perlmutter Cancer Center Support Grant; and National Institutes of Health and National Cancer Institute grants P30 CA016087, S10 OD01058, S10 OD018338, and P30 CA008748.

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