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Researchers identify definitive genetic defect in angiocentric gliomas

Published on February 2, 2016 at 12:18 AM

Genetic cause identified in rare pediatric brain tumor

•A definitive genetic defect was identified for the first time in angiocentric gliomas, a rare type of childhood brain tumor.
•Researchers found an accidental joining of two genes triggered excessive cell growth through three different mechanisms simultaneously.
•The unique genetic 'signature' will aid diagnosis of angiocentric gliomas and help patients avoid unnecessary treatment.

Diagnosis and treatment decisions for a recently recognized type of children's brain tumor should be improved by the discovery of the genetic mechanism that causes it, say researchers who identified the unusual DNA abnormality in angiocentric gliomas.

Currently there is no definitive pathological test to help identify this rare type of low-grade glioma. Named for their curious behavior of "hugging" blood vessels in the brain, angiocentric gliomas are usually cured with surgery and don't need further treatment with radiation or chemotherapy. But given their recent description and difficulties in identifying them confidently, some patients receive the additional therapy, which often is damaging to the growing brain, in an effort to prevent a recurrence.

"Now we know these angiocentric gliomas have a different biology, and we have an exact way of identifying them so that patients can avoid this additional therapy that has life-long consequences," said Rameen Beroukhim, MD, PhD, of Dana-Farber Cancer Institute, a senior author of the report in Nature Genetics along with Keith Ligon, MD, PhD, and Adam Resnick, PhD. Ligon is a pathologist at Dana-Farber/Boston Children's Hospital Cancer and Blood Disorders Center and Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC). Resnick is an investigator at Children's Hospital of Philadelphia.

Angiocentric gliomas were recognized as distinct entities less than 10 years ago. Their name reflects the tumor cells' tendency to line up around blood vessels. Fewer than 30 cases have been described in medical literature. Seizures are typically the first symptom leading to diagnosis. Although they are classified as a tumor, they are not malignant and don't spread to other parts of the body.

These rare tumors fall under the umbrella of pediatric low-grade gliomas (PLGG), which collectively are the most common pediatric brain tumor. Until now, no specific genetic abnormality had been identified as a "driver" of angiocentric gliomas.

In the current study, the researchers analyzed data from 249 PLGG tumors, including 19 angiocentric gliomas, and discovered an unusual genetic accident as the fundamental cause of the angiocentric gliomas. The culprit event is a shuffling of DNA segments that brings together two separate genes, MYB and QKI, which become joined, or fused. MYB is a "proto-oncogene" - a normal gene that can become a cancer-causing oncogene. QKI is a tumor-suppressor gene that normally functions to prevent cells from becoming malignant.

When these two genes are abnormally joined, the researchers found, it triggers not one but three different mechanisms that converge to produce a tumor:

•Epigenetic control elements called enhancers are "hijacked" and brought closer to the MYB gene, which increases MYB activity.
•The MYB-QKI fusion gene causes cells to make a protein that binds to another control element - a promoter - that also revs up MYB activity, prodding the cells into runaway growth.
•The rearrangement also knocks out one of the two copies of the QPI tumor suppressor gene, enabling cancer-related genes to escape control and contribute to tumor formation.

"This represents the first example of a single driver rearrangement simultaneously transforming cells via three genetic and epigenetic mechanisms in a cancer," the authors wrote. They identified this specific abnormality as "a

defining event" found only in the angiocentric gliomas - it was not present in any of the other pediatric low-grade gliomas examined in the study.

Because of these findings, the researchers said, angiocentric glioma should be classified as a separate biologic entity, with the presence of the gene fusion confirming the diagnosis. "This could aid in distinguishing angiocentric glioma from tumors with higher potential for recurrence that could require further treatment," they said. The authors have developed the first genetic test now available for these patients through collaboration with cytogeneticist Azra H. Ligon, PhD, of DF/BWCC.

Source:
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

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