



## New Gene Implicated in Childhood Brain Tumors

November 1, 2009  
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*Neurology Today*

Researchers in the Washington University Neurofibromatosis Center have traced the molecular lineage of pilocytic astrocytomas from young people with these benign tumors, and identified a molecular pathway that could serve as a target for blocking tumor growth.

David H. Gutmann, MD, PhD, director of the Neurofibromatosis Center and the Donald O. Schnuck Family endowed professor in the department of neurology, has spent decades unraveling the connection between these benign tumors and mutations in the *NF1* gene. These tumors are a common feature in patients with neurofibromatosis type 1. But does an alteration in *NF1* expression have anything to do with sporadic cases of pilocytic astrocytoma, the most common pediatric brain tumor?

To answer that question, they performed a detailed genetic and genomic analysis of pilocytic astrocytomas from 70 children without NF1 and nine others with a diagnosis of NF1. They extracted RNA and DNA from the tissue to better understand the genetic alterations at play in the development of these benign brain tumors. A year ago, they identified a small region on chromosome 7 and narrowed their search to a gene called *HIPK2*. But Dr. Gutmann said that *HIPK2* did not seem to be the significant genetic alteration sufficient to generate benign brain tumors.

Knowing that a number of cancers have been linked to a subtle alteration in another gene called *BRAF* and that this gene resided on the same region of chromosome 7 as the *HIPK2* gene, the Washington University group and others have recently tested the hypothesis that *BRAF* alterations may be the trigger for pilocytic astrocytoma. What made the genetic target even more enticing is that it controls a signaling pathway that overlaps with that controlled by the *NF1* protein, neurofibromin. What's more, a number of inhibitors of this signaling pathway have been developed and are being tested experimentally for their ability to block the growth of tumors. Clinical trials are now underway for the treatment of melanoma.

In the current study, published in the journal *Neurology*, Dr. Gutmann and their colleagues found that two-thirds of the children with sporadic pilocytic astrocytoma had alterations in the *BRAF* gene. However, none of the children with NF1 had alterations in this gene. After further exploration, they showed that the business end of the *BRAF* molecule (second half) gets fused to another gene in the region and the result is overactive *BRAF* protein function. *BRAF* normally regulates cell growth. In cells with overactive *BRAF* signaling, there is increased growth, culminating in astrocytoma development.

“Now that we understand the signature mutation in these common pediatric tumors, we can now think about designing treatments that alter this pathway,” said Dr. Gutmann. “Knowing that BRAF is involved allows us to find clever ways to treat pilocytic astrocytoma.”

Currently, besides standard chemotherapy, there are no treatments that specifically target the molecular alterations seen in pilocytic astrocytoma. While surgery is often curative, these tumors frequently arise in regions of the brain that are not surgically accessible, like the optic nerve and brainstem. Moreover, radiation can lead to long-term cognitive deficits.

The Washington University study is the largest and most comprehensive study to date, said Scott Pomeroy, MD, PhD, chief of neurology at Children’s Hospital in Boston. That *BRAF* alterations did not pop up in the patients with NF1 provides even more support that BRAF is the driving force behind these tumors in patients without NF1.

“*BRAF* rearrangement represents the most common genetic alteration in sporadic, but not NF1-associated, pilocytic astrocytoma,” the scientists concluded in their *Neurology* study.

The Washington University scientists are now working on a mouse model using *BRAF* alterations to see whether the animals develop these benign tumors. They want to understand exactly how BRAF is involved in cell growth. Previously, Dr. Gutmann’s group developed a mouse model of NF1-associated optic glioma - the most common location for pilocytic astrocytoma in children with NF1.

“Low-grade pilocytic astrocytomas are very slow growing, insidious and most often can be difficult to reach (surgically),” said Dr. Pomeroy of Children’s Hospital in Boston. “For a long time we didn’t have a good feel about the molecular problems. Now, we have a good target for possible new treatments.”

The recent findings from Dr. Gutmann and others all point to the same molecular pathway. Once this pathway is over-active, it can drive cells to become tumors. Thus, finding ways to shut down this over-active pathway may inhibit further tumor growth. With such a targeted treatment “we can be much more specific than we can with radiation or chemotherapy,” said Dr. Pomeroy. He thinks that the findings will generate clinical trials for young patients with these tumors in the coming months. “Everyone agrees that these pathways are critical to tumor growth,” said Dr. Pomeroy.

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Yu J, Deshmukh H, Gutmann RJ, Emmett RJ, Rodriguez FJ, Watson MA, Nagarajan R, Gutmann DH: Alterations of *BRAF* and *HIPK2* loci predominate in sporadic pilocytic astrocytoma. *Neurology* Epub Sept 30, 2009