

Newly discovered gene could be a prime target in the most lethal brain cancer

18 February 2009

Scientists at Duke University Medical Center and Johns Hopkins University have discovered mutations in two genes that could become therapeutic targets in malignant glioma, a dangerous class of brain tumors.

"The fact that the defective genes code for metabolic enzymes found only in malignant glioma, and not in normal tissue, could make the gene products therapeutic targets," says Hai Yan, M.D., Ph.D., lead author, an assistant professor in the Duke Department of Pathology. The findings are published in the Feb. 19 issue of the *New England Journal of Medicine*.

These genetic flaws might also help distinguish between primary and secondary glioblastoma multiforme (GBM), two subtypes of especially deadly malignant gliomas, with survival of only months after their diagnosis. Patients that have mutation of the genes, isocitrate dehydrogenase 1, gene 1 and 2 (IDH1 and IDH2), also had a longer survival time.

Because the researchers found this genetic mutation in several different stages of glioma development, "the results suggested that the IDH mutations are the earliest genetic changes that start glioma progression," said Darell Bigner, M.D., Ph.D., a co-author and director of the Preston Robert Tisch Brain Tumor Center at Duke University. Yet, patients with GBM or anaplastic astrocytoma who had the IDH mutations also were found to live longer than patients with those two cancers who lacked the mutations.

Malignant glioma appears to be two diseases, one that involves IDH mutations and one that doesn't, Yan explained. "As a cancer culprit gene, IDH mutations do contribute to cancer," he said. "Meanwhile, patients with the IDH mutation live longer with their cancer. The IDH mutation could serve as a biomarker that would help single out individuals who are likely to have better outcomes

and receive different treatment."

He said that IDH mutations appear to define a specific subtype of GBMs, which is important so that physicians can plan specific treatment strategies to target this specific subtype of GBMs. "All GBMs are basically considered the same and are treated in the same way," Yan said. "Our studies clearly demonstrate that we need to start thinking about them as different. It is entirely possible that treatments that work for the IDH-mutation subtype would not work for the rest of GBMs, or vice versa." Knowing the tumor subtype has significant implications for how we plan future clinical trials for patients with GBMs, he added.

"I can say this is potentially one of the most important discoveries in genetic studies on malignant gliomas, in the low-grade to high-grade forms of the tumor," Yan said. "The results are so clear cut. I have been doing intensive genetic studies in brain cancers for six years, and I have never seen gene mutations as striking as in this study."

The researchers found IDH1 mutations in more than 70 percent of astrocytomas and oligodendrogliomas (WHO grade II and III), as well as in secondary GBMs (WHO grade IV). Those without the IDH1 mutation had similar mutations in the closely related IDH2 gene. The mutations decreased IDH enzymatic activity. This signaled that IDH mutations are likely important in initiating malignant gliomas, but it is not known yet how they contribute to glioma development.

The findings are important in many ways. IDH can be used to distinguish primary GBMs, which do not arise from an existing tumor, from secondary GBMs, which arise from low-grade glioma tumors. The IDH1 mutation is missing in pilocytic astrocytomas, which means these particular brain tumors arise through a different mechanism.

Source: Duke University Medical Center

APA citation: Newly discovered gene could be a prime target in the most lethal brain cancer (2009, February 18) retrieved 9 June 2022 from <https://medicalxpress.com/news/2009-02-newly-gene-prime-lethal-brain.html>

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