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Variations in 5 genes raise risk for most common brain tumors

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Common genetic variations spread across five genes raise a person's risk of developing the most frequent type of brain tumor, an international research team reports online in *Nature Genetics*.

Genetic risk factors identified by the research team, led by scientists at The University of Texas M. D. Anderson Cancer Center and the Institute of Cancer Research in the United Kingdom, also are the first glioma risk factors of any type identified in a large study.

"This is a ground-breaking study because it's the first time we've had a large enough sample to understand the genetic risk factors related to glioma, which opens the door to understanding a possible cause of these brain tumors," said co-senior author Melissa Bondy, Ph.D., professor in M. D. Anderson's Department of Epidemiology.

Bondy and colleagues expect their findings eventually to help identify people most at risk for the disease and to provide potential targets for treatment or prevention.

Gliomas, deadly tumors that form in the supportive tissue of the brain and spine, account for about 80 percent of all primary malignant brain tumors, with about 22,000 new cases annually in the United States and 13,000 deaths. They include astrocytomas, oligodendrogliomas and glioblastoma multiforme, the most aggressive, deadly and common glioma in adults.

Risk rises with each variation

The top variations in each of the five genes individually raise a person's glioma risk by 18, 24, 27, 28 and 36 percent over someone without the variations. The team found the effects are independent of one another, so risk escalates with the number of genes involved. People with eight or more of the 14 risk variations discovered on the five genes have a three-fold risk of developing glioma.

Even though this is the largest genetic study of a rare cancer, and thus provides a high degree of statistical confidence in the findings, co-first author Sanjay Shete, Ph.D., associate professor of epidemiology at M. D. Anderson, cautions that it's too early to screen people for risk using these variations alone.

Additional research is needed on the genes involved and how variation affects their function and contributes to development of gliomas. And the disease is not solely genetic. A more comprehensive model that includes demographic and behavioral factors and environmental exposures will be needed to identify those at risk.

Bondy will be principal investigator on a multi-center research project that will examine the complex interplay of all of those factors in 6,000 glioma patients and 6,000 controls beginning next year. "We will be able to look at all of the potential risk and protective factors we've identified in much smaller studies over the years, such as exposure to ionizing radiation, allergies, infections, and use of non-steroidal anti-inflammatory drugs, in a much larger study that will include the genes involved," Bondy said.

Combing through 521,571 variations to find 14

Researchers from M. D. Anderson and the Institute of Cancer Research analyzed 521,571 single nucleotide polymorphisms (SNPS) - points in the genome known to commonly vary from person to person - in 1,878 glioma patients and 3,670 controls. They discovered 34 SNPS with evidence of association with glioma.

These 34 were then analyzed in independent case-control studies in Germany, France and Sweden that examined 2,545 cases of glioma and 2,973 controls. The combined analysis winnowed the candidates down to 14 SNPS that mapped to five addresses in the genome.

The five genes identified, listed in descending order by their strongest effect, are:

- CCDC26, located on chromosome 8, modulates retinoic acid, which in turn increases programmed cell death in glioblastoma cells and reduces telomerase activity (see next).

- TERT, found on chromosome 5, is essential for telomerase activity that preserves telomeres, which are found on the ends of chromosomes and prevent them from unraveling. TERT expression in tumors has been associated with tumor grade and prognosis.

- CDKN2A, located on chromosome 9, regulates p14, which activates the tumor-suppressor p53. It also regulates cyclin-dependent kinases vital to the cell cycle. At least one copy of the gene is deleted in half of brain tumors, and loss of CDKN2A expression is associated with poor prognosis.

- RTEL1, found on chromosome 20, maintains genomic stability. Its chromosomal address is amplified in 30 percent of gliomas.

- PHLDB1, on chromosome 11, is commonly deleted in neuroblastoma but there is no evidence to date of a role for the gene in glioma.

The fact that four of the genetic variations found in a person's genome point to a gene that has been associated in some way with the genome of the tumors is an encouraging sign, Shete said.

"I've been collecting families and case studies since the early 90s," Bondy said. "We have only just begun to understand the causes of brain tumors. Our findings give reasons for hope for those who might be affected and an incentive for a more comprehensive investigation of what has been a mysterious disorder."

Source: University of Texas M. D. Anderson Cancer Center