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Gene change identifies brain cancer patients that respond better to treatment

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New research proves that a change in a particular gene can identify which patients with a specific kind of brain cancer will respond better to treatment. Testing for the gene can distinguish patients with a more- or less-aggressive form of glioblastoma, the most common and an often-fatal type of primary brain cancer, and help guide therapy, the researchers say.

The prospective study looked at a gene called MGMT in tumors removed from 833 glioblastoma patients. It showed that when the gene promoter is altered by a chemical change called methylation, patients respond better to treatment.

"We show that MGMT methylation represents a new genetic test that can predict clinical outcomes in glioblastoma patients who have been treated with radiation combined with the chemotherapeutic drug temozolomide," says coauthor Dr. Arnab Chakravarti, chair and professor of Radiation Oncology and co-director of the brain tumor program at the Ohio State University Comprehensive Cancer Center – Arthur G. James Comprehensive Cancer Center and Richard J. Solove Research Institute (OSUCCC – James).

"Clearly, all glioblastomas are not the same. Rather, they are a collection of different molecular and genetic entities that behave uniquely and require personalized treatment," says Chakravarti, who is the translational-research study chair for the study.

Principal investigator Dr. Mark Gilbert, professor of neuro-oncology at M.D. Anderson Cancer Center, will present the research June 5, 2011, at the 2011 American Society of Clinical Oncology annual meeting in Chicago. It comes from a prospective international phase III clinical trial sponsored by the Radiation Therapy Oncology Group (RTOG).

"Our study confirms the prognostic significance of MGMT gene methylation and demonstrates the feasibility of prospective tumor-tissue collection, molecular stratification and collection of patient outcomes in a large transatlantic intergroup trial," Gilbert says.

A tentative indication that MGMT methylation status might have prognostic importance emerged from an earlier retrospective study sponsored by the European Organisation for Research and Treatment of Cancer (EORTC).

The current study (RTOG 0525) validates that finding. Patients with tumors carrying the methylated gene had an overall survival of 21 months versus 14 months for those with the unmethylated gene. The difference in progression-free survival – the period after treatment during which cancer does not worsen – was 8.7 months and 5.7 months for methylated versus unmethylated tumors respectively. The narrow difference, Chakravarti says, indicates that patients with the methylated gene had slower growing tumors.

About 18,500 new cases of glioblastoma multiforme are expected annually in the U.S., and 12,760 Americans are expected to die of the disease. Symptoms often include headache, seizures and motor or sensory changes. A brain scan detects the tumor. After a surgeon removes the tumor, it can be tested for MGMT methylation.

"Patients with the methylated gene could receive the standard treatment, radiation therapy plus the chemotherapeutic drug temozolomide,"

Chakravarti says. "Those with an unmethylated gene might receive an experimental treatment through a clinical trial."

Research is now needed, he says, to learn whether MGMT contributes directly to tumor aggressiveness, or whether it is just an indicator of other changes that cause tumor aggressiveness. "If the gene itself helps cause aggressive disease, MGMT or related DNA repair pathways might be an important targets for a novel therapies," Chakravarti says.

Provided by Ohio State University Medical Center