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Biomarker may help predict aggressive cancers

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For children with central nervous system cancers, the presence of a specific genetic modification—hypermethylation of the TERT promoter—may help predict tumor progression and patient survival, according to results presented here at the American Association for Cancer Research (AACR) special conference on "Pediatric Cancer at the Crossroads: Translating Discovery Into Improved Outcomes," held Nov. 3-6.

The protein TERT is a component of the enzyme telomerase, which is found at elevated levels in the majority of cancers. Although this makes telomerase and its components potential biomarkers for cancer, there are currently no sensitive and specific methods for measuring levels of these candidates.

"DNA methylation controls gene usage," said Uri Tabori, M.D., a staff oncologist at The Hospital for Sick Children in Toronto. "We decided to examine whether there were different patterns of DNA methylation in an area of the genome that controls TERT expression in cancer cells and normal cells."

"We found that a region of DNA near the TERT gene was hypermethylated in 100 percent of the malignant pediatric cancer tissues expressing TERT that we examined and unmethylated in normal tissues and in low-grade tumors lacking TERT. Although these results are restricted to pediatric cancers, we believe that this hypermethylation signature could be a pancancer biomarker because TERT levels are

elevated in almost every cancer cell."

Tabori and colleagues began by conducting whole-genome methylation arrays on 280 pediatric brain tumor tissue samples (from pediatric gliomas, ependymomas, choroid plexus tumors, medulloblastomas, and atypical teratoid-rhabdoid tumors) and six normal brain tissue samples. To validate their findings, they used 219 tissue samples from multiple types of pediatric central nervous system cancer.

The data revealed that a specific region of the TERT gene was hypermethylated in 100 percent of the malignant tumor tissue samples expressing TERT. In addition, hypermethylation of this region of DNA, which the researchers termed the TERT hypermethylated oncological region, or the THOR, was able to distinguish malignant tumor tissue samples from normal tissue and low-grade tumor tissue samples 95 percent of the time, meaning the candidate biomarker was 95 percent sensitive.

In further analysis, the researchers demonstrated that the THOR was hypermethylated in tumors that went on to progress from low to high grade and that went on to become metastatic. According to Tabori, this suggests that preventing THOR hypermethylation might prevent cancer from progressing and that THOR hypermethylation may be a biomarker to predict which low-grade pediatric central nervous system cancers will become malignant.

Consistent with the latter idea, for the 45 samples from children with ependymomas, THOR hypermethylation predicted worse outcome. Patients with ependymomas with THOR hypermethylation had a five-year overall survival of 51 percent compared with 95 percent for patients with ependymomas without this hypermethylation.

"This is a DNA-based assay, which is simple to do in every lab in the

world," Tabori said. "The tool is so sensitive and specific that you can actually detect cancer before you can see it."

In the future, Tabori and colleagues hope to expand this research to common adult cancers such as gliomas and prostate and colon cancers, where the ability to predict which cancers will be more aggressive could have a large effect on patient care.

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More information: www.aacr.org/page34138.aspx

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