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First cancer-promoting oncogenes discovered in rare brain tumor of children and adults

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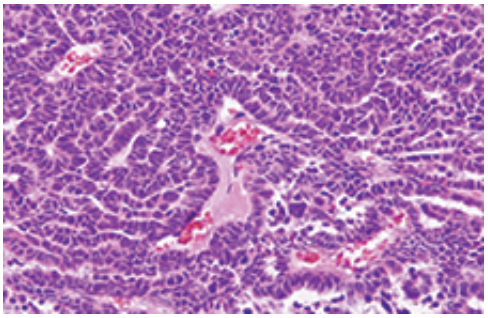

Choroid plexus carcinomas are poorly understood and frequently lethal brain tumors with few treatment options.

Researchers have identified three genes that play a pivotal role in the brain tumor choroid plexus carcinoma (CPC), a discovery that lays the groundwork for more effective treatment of this rare, often fatal cancer. St. Jude Children's Research Hospital scientists led the study, which appears today in the journal *Cancer Cell*.

The genes - TAF12, NFYC and RAD54L - are involved in DNA repair and regulation. Researchers showed that CPC often has at least one extra copy of each gene and demonstrated that the genes work cooperatively to launch and sustain the tumor.

Investigators also found evidence that investigational drugs called ATR inhibitors that are already in development for cancer treatment may be

effective against CPC. The drugs work by blocking certain DNA repair enzymes, increasing the susceptibility of tumor cells to chemotherapy or radiation. Planning has begun for a possible international clinical trial featuring an ATR inhibitor.

The findings suggest that disruption of normal DNA maintenance and repair plays a central role in CPC, a tumor with few treatment options. Of the estimated 50 pediatric CPC patients identified each year in the U.S., about two-thirds will die of their disease. While CPC occurs in both children and adults, most CPC patients are ages 2 or younger.

"This work provides hope for this rare, neglected disease by identifying some significant drivers of the tumor and providing the first real direction for treatment," said corresponding author Richard Gilbertson, M.D., Ph.D., St. Jude scientific and Comprehensive Cancer Center director. The study's first author is Yiai Tong, Ph.D., a St. Jude associate scientist.

The strategy used to discover the CPC oncogenes should also help researchers identify oncogenes that play important roles in other adult and pediatric cancers that include genetic changes called copy number alterations (CNAs). These alterations occur frequently in childhood cancer and involve the duplication or deletion of large pieces of DNA.

Of the 23 human CPCs in this study, 61 percent had at least one extra copy of chromosome 1, which carries more than 2,000 genes. "Large copy-number alterations are a common feature of childhood cancer, but until now there was no good way to answer the question of which of those genes was important to initiating or sustaining the cancer," Gilbertson said.

For CPC, the answer began by chance. Gilbertson and his colleagues developed a mouse model of CPC while working to create an animal

model to advance understanding of another pediatric brain tumor.

In this study, investigators used the CPC model to look for blocks of genes that are carried on human chromosome 1 and also duplicated in the mouse tumor. A search of 47 mouse CPCs turned up a chromosome fragment with 671 genes from human chromosome 1 that was duplicated in half of the mouse tumors. Researchers found evidence that 21 of the 671 duplicated genes were "switched on" or overexpressed in the mouse tumors.

CPC develops in cells that line the fluid-filled ventricles in the brain and produce cerebrospinal fluid. When researchers introduced each of the 21 genes into mouse choroid plexus cells in the laboratory, only Taf12, Nfyc and Rad54l led to changes associated with CPC, including cell proliferation. Researchers also showed that all three genes were required to initiate and sustain the tumors in mice.

"This same cross-species mapping approach holds promise for identifying oncogenes located in large regions of chromosomal gain that are a feature of other adult and pediatric cancers," Gilbertson said.

For CPC patients, the results provide much needed direction for designing tumor-specific therapy. "These oncogenes may function like a mechanic who is always on the spot to keep a junk car running," Gilbertson said. "Just like the car will break down if you get rid of the mechanic, preclinical trials are underway using different drug combinations to block the hyperactive DNA repair mechanism so the tumors eventually succumb to the accumulated DNA damage."

Provided by St. Jude Children's Research Hospital

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