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Push to understand basis of childhood brain tumors leads to a new treatment target

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The most comprehensive analysis yet of the genetic imbalances at the heart of childhood brain tumors known as high-grade gliomas (HGGs) identified a cancer gene that is unusually active in some tumors and is now the focus of a St. Jude Children's Research Hospital clinical trial.

The research, published in the May 17 online edition of the Journal of Clinical Oncology, also details important differences between the defects underlying these tumors in children and adults, said Suzanne Baker, Ph.D., senior author of the study. She is an associate member of the St. Jude Department of Developmental Neurobiology.

"The results tell us that if we want to effectively design innovative new therapies, we need to understand the genetics in childhood tumors in the same depth that we are learning about the adult tumors," Baker said.

Investigators checked tumor samples from 78 young patients at 500,000 different spots in the genome for additions or deletions of genetic material. Researchers also tracked gene activity in 53 of the tumor samples and compared the results with data from adult tumors.

Patients were battling HGGs, which are aggressive tumors that arise from cells called glial cells in the brain and spine. In the U.S., HGGs are diagnosed in 400 to 550 children and adolescents each year and account for 15 to 20 percent of all childhood brain tumors. Long-term survival for these patients remains no better than 30 percent. Technological advances mean it is now possible to study in detail the genetic missteps

driving this disease, Baker said.

Twelve percent of tumors in this study had extra copies of the gene PDGFRA. Researchers reported similar gene-expression patterns associated with high levels of PDGFRA were also found in childhood tumors without extra copies of the gene. Extra copies of PDGFRA were even more common in tumors from children who had received brain irradiation for treatment of earlier cancers. The study included 10 such patients, half of whom carried extra copies of PDGFRA. Baker said these findings suggest the PDGFR pathway plays a key role in childhood HGG. The PDGFRA gene carries instructions for making a protein found on the cell surface that is part of a pathway that helps control cell growth, proliferation and survival. Those processes are improperly regulated in cancer.

A different gene, EGFR, takes center stage in adult tumors, Baker said.

Baker said this broad survey was necessary to obtain a complete and unbiased comparison of the genetic imbalances in childhood and adult HGG. The study found that although childhood and adult HGG are clearly related diseases, showing some strong similarities in the overall pattern of activity of all genes, significant differences exist in the specific genetic changes driving the disease. This has important implications for targeted therapies that aim to directly counteract the effects of specific mutations in tumors.

St. Jude opened a Phase I safety study in October 2009 that combines radiation therapy with drugs targeting both PDGFRA and EGFR. The focus is patients with a type of HGG called diffuse intrinsic pontine glioma (DIPG). With current treatment, 50 to 75 percent of patients die within one year of diagnosis. Dasatinib, which targets PDGFRA, is one of the drugs being studied. Dasatinib is already approved for treating chronic myelogenous leukemia in adults.

Tumor samples for this study were collected before treatment began at St. Jude and at medical centers through the United Kingdom Childhood Cancer and Leukemia Group.

The study was the work of investigators at St. Jude and researchers led by Chris Jones, Ph.D., at the Institute for Cancer Research and the Royal Marsden NHS Foundation Trust, both in Surrey, and by Richard Grundy, M.D., Ph.D., at The Children's Brain Tumour Research Centre at the University of Nottingham. The first authors were Jones and Barbara Paugh, Ph.D., and Chunxu Qu, Ph.D., both of St. Jude.

Along with excess amounts of PDGFRA, researchers reported tumors from young HGG patients were also more likely than adult tumors to carry an extra copy of the long arm of chromosome 1. Genes are organized into 23 pairs of chromosomes, which are found in nearly every cell in the body.

Nearly 30 percent of pediatric HGGs carried the addition, compared with 9 percent of adult tumors. The extra piece of chromosome 1 was found in seven of the 10 patients who had received prior radiation therapy. "This is a mutation that might be important in starting tumor formation in children," Baker said.

Provided by St. Jude Children's Research Hospital