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CHOP experts collaborate in gene survey of childhood brain cancer; intriguing clues found

Comprehensive study of medulloblastoma suggests targeted drugs may be especially effective in children

Pediatric cancer researchers at The Children's Hospital of Philadelphia contributed important expertise to a new landmark study of medulloblastoma, a type of brain tumor typically found in children. The large multicenter study defines the genetic landscape of this cancer, and holds intriguing clues to gene changes on signaling pathways that may become fruitful targets for future therapies.

The most common cancerous brain tumor in children, medulloblastoma is, fortunately, rare. However, it causes significant mortality, and survivors may suffer serious long-term side effects from treatment, so less toxic, more effective therapies are sorely needed.

The study appears online today in the journal *Science*. Collaborators from three countries and more than a dozen institutions co-authored the research, which was led by three scientists from Johns Hopkins University and the Howard Hughes Medical Institute: Bert Vogelstein, M.D., Kenneth Kinzler, Ph.D., and Victor Velculescu, M.D., Ph.D.

The researchers used recent innovations in gene-sequencing and informatics technology to analyze the whole exome (all the genes known to code for proteins) of medulloblastoma tumors. "This is the first application of whole-exome DNA sequencing analysis to a solid pediatric tumor, and there were encouraging results," said co-author Tom Curran, Ph.D., whose laboratory at The Children's Hospital of Philadelphia focuses on finding new treatments for medulloblastoma.

Curran added, "The study team found that the number of mutations in pediatric medulloblastoma tumors is five to ten times fewer than in adult medulloblastoma tumors. This suggests that, compared to adult tumors, pediatric tumors may respond better to drugs that target the genes and pathways altered by mutations that drive cancer progression. This is a hopeful finding."

In addition to detecting gene alterations previously found in medulloblastoma, such as mutations in the Hedgehog and Wnt signaling pathways, the current study also identified new and unexpected mutations in the MLL2 and MLL3 genes, genes not previously implicated in medulloblastoma. Both are tumor suppressor genes, genes that normally act as a brake on the development of cancer. If a mutation perturbs such a gene, cancer may then develop.

"Like other genes found in medulloblastoma, the MLL2 and MLL3 genes disrupt normal brain development during childhood," said co-author Peter C. Phillips, M.D., director of the Pediatric Neuro-oncology Program at The Children's Hospital of Philadelphia. "These genes interfere with biological signals during development, specifically with a process called histone methylation." In histone methylation, chemical tags that bind to DNA regulate how specific genes become active.

Both Curran and Phillips stressed the importance of collaboration among many institutions to the success of this study. "Even the largest oncology programs may see small numbers of medulloblastoma patients, so sharing data and materials is crucial to producing stronger statistical results," said Phillips. Children's Hospital and other centers have contributed resources and data to the Children's Brain Tumor Tissue Consortium, which provided tumor samples to the current study.

Direct clinical applications from this study are not immediate, but both researchers noted that clinical trials are already in progress to test whether inhibiting the Hedgehog pathway benefits medulloblastoma patients. Phillips added that the current study may lay a foundation for developing drugs that target the gene pathways associated with the MLL2 and MLL3 genes.

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Among the funders of the study was the National Cancer Institute, part of the National Institutes of Health. The Children's Hospital of Philadelphia's portion of the study was supported by the Children's Brain Tumor Tissue Consortium, which received a grant from the Children's Brain Tumor Foundation.

In addition to Curran and Phillips, other co-authors from The Children's Hospital of Philadelphia were Jane E. Minturn, M.D., Ph.D.; Jaclyn A. Biegel, Ph.D.; Adam C. Resnick, Ph.D.; Alexander R. Judkins, M.D.; and Phillip B. Storm, M.D.

"The Genetic Landscape of the Childhood Cancer Medulloblastoma," *Science*, published online Dec. 16, 2010.

About The Children's Hospital of Philadelphia: The Children's Hospital of Philadelphia was founded in 1855 as the nation's first pediatric hospital. Through its long-standing commitment to providing exceptional patient care, training new generations of pediatric healthcare professionals and pioneering major research initiatives, Children's Hospital has fostered many discoveries that have benefited children worldwide. Its pediatric research program is among the largest in the country, ranking third in National Institutes of Health funding. In addition, its unique family-centered care and public service programs have brought the 460-bed hospital recognition as a leading advocate for children and adolescents. For more information, visit <http://www.chop.edu>.

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