Discovery of likely subtypes of rare childhood brain tumor signals diagnostic advance

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An international research team has identified four likely new subtypes of a rare brain tumor using molecular techniques that lay the foundation for more accurate diagnosis and tailored therapies for the hard-to-treat cancer. Scientists at St. Jude Children's Research Hospital and the German Cancer Research Center led the study, results of which appear today in the scientific journal *Cell*.

The research involved the most comprehensive analysis yet of the genetic alterations and other molecular characteristics of primitive neuroectodermal tumors of the central nervous system (CNS-PNET). These rare, aggressive tumors occur in children and adults, but are most often diagnosed in young children and account for about 1 percent of pediatric brain tumors.

CNS-PNET tumors arise from extremely immature and undifferentiated tissue in the central nervous system. The tumors are difficult to diagnose using current microscopic techniques, which has hindered development of precision medicine to improve long-term survival. Currently about 40 percent of young patients with CNS-PNET tumors are alive five years after diagnosis.

Researchers in this study used molecular techniques to compare tissue from 323 tumors classified as CNS-PNET to 211 other well-defined brain tumors.

The investigators found that 61 percent of the CNS-PNET tumors could be reclassified as a different type of brain tumor based on the shared molecular features. In many cases, the reclassification suggested a completely different treatment. The analysis of the remaining CNS-PNET tumors found that a majority fell into one of four distinct subgroups, each with unique recurring genetic alterations, including gene rearrangements, deletions and amplifications.

"Important questions about proper classification of these tumors have lingered and stymied efforts to advance treatment by developing and testing targeted therapies," said co-senior author David Ellison, M.D., Ph.D., chair of the St. Jude Department of Pathology. He organized the study with corresponding author Marcel Kool of the German Cancer Research Center in Heidelberg.

Co-first author Brent Orr, M.D., Ph.D., who led the study at St. Jude, said: "In the future, these findings should help us assign patients to the appropriate clinical trial and to improve the design of clinical trials, particularly for precision medicines that target the newly identified genetic alterations that define these tumors." Orr is an assistant member of the St. Jude Department of Pathology. The other first authors include Dominik Sturm, M.D., of the German Cancer Research Center in Heidelberg.

Work has begun to develop clinical tests that incorporate molecular markers into classification and diagnosis of CNS-PNET tumors.

The findings underscore the importance of incorporating molecular information into the World Health Organization system of classifying brain and spinal tumors. "We have supplemented looking down the microscope with cutting-edge molecular techniques to better classify the tumors, which sets the stage for improved diagnosis, treatment and surveillance," Ellison said.

For this study, researchers analyzed the pattern of chemical tags called methyl groups present on DNA from CNS-PNETs and other well characterized brain tumors. Such methylation profiles are considered to reflect a tumor's cell of origin and to provide information on how closely

tumors with similar microscope appearances are related. Based on the methylome profiles, 61 percent of the CNS-PNET tumors could be reclassified as different tumors of the brain or central nervous system, including high-grade gliomas, ependymomas and atypical teratoid/rhabdoid tumors (AT/RTs). Most of the remaining CNS-PNET tumors could be classified into one of four distinct subgroups based on their methylation profile.

Additional analysis demonstrated that the methylation profiles correlated with other genetic characteristics of the four molecularly distinct CNS-PNET tumor subgroups. In contrast, some tumors from the subgroups were difficult to distinguish using microscopic techniques.

DNA and RNA sequencing of the four likely new CNS-PNET subtypes revealed subgroup-specific signature mutations, including gene deletions, amplifications or rearrangements. Analyses of gene expression data identified other subgroup-specific differences in pathways that are disrupted in tumor cells. The disruptions feature alterations in genes that could be targeted for drug development.

The tumor subgroups also differed in regards to the age and gender of patients as well as the treatment outcome. The findings suggest that the tumors would also respond to different targeted therapies.

"The findings on this rare and devastating tumor would not have been possible without international cooperation," Orr said.

The other first authors are Umut Toprak and Volker Hovestadt, both of the German Cancer Research Center. The other St. Jude authors are Sariah Allen and Amar Gajjar as well as Paul Northcott, formerly of the German Cancer Research Center and now of St. Jude. The study included authors from more than 40 institutions in 14 countries in Europe, North America and Australia.

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