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Suspicions confirmed: brain tumors in children have a common cause

An overactive signaling pathway is a common cause in cases of pilocytic astrocytoma, the most frequent type of brain cancer in children. This was discovered by a network of scientists coordinated by the German Cancer Research Center (as part of the International Cancer Genome Consortium, ICGC). In all 96 cases studied, the researchers found defects in genes involved in a particular pathway. Hence, drugs can be used to help affected children by blocking components of the signaling cascade. The project is funded by the German Cancer Aid (Deutsche Krebshilfe) and the Federal Ministry of Education and Research (BMBF). The findings are published in the latest issue of the journal "Nature Genetics".

Brain cancer is the primary cause of cancer mortality in children. Even in cases when the cancer is cured, young patients suffer from the stress of a treatment that can be harmful to the developing brain. In a search for new target structures that would create more gentle treatments, cancer researchers are systematically analyzing all alterations in the genetic material of these tumors. This is the mission of the PedBrain consortium, which was launched in 2010. Led by Professor Stefan Pfister from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), the PedBrain researchers have now published the results of the first 96 genome analyses of pilocytic astrocytomas.

Pilocytic astrocytomas are the most common childhood brain tumors. These tumors usually grow very slowly. However, they are often difficult to access by surgery and cannot be completely removed, which means that they can recur. The disease may thus become chronic and have debilitating effects for affected children.

In previous work, teams of researchers led by Professor Dr. Stefan Pfister and Dr. David Jones had already discovered characteristic mutations in a major proportion of pilocytic astrocytomas. All of the changes involved a key cellular signaling pathway known as the MAPK signaling cascade. MAPK is an abbreviation for for "mitogen-activated protein kinase." This signaling pathway comprises a cascade of phosphate group additions (phosphorylation) from one protein to the next – a universal method used by cells to transfer messages to the nucleus. MAPK signaling regulates numerous basic biological processes such as embryonic development and differentiation and the growth and death of cells.

"A couple of years ago, we had already hypothesized that pilocytic astrocytomas generally arise from a defective activation of MAPK signaling," says David Jones, first author of the publication. "However, in about one fifth of the cases we had not initially discovered these mutations. In a whole-genome analysis of 96 tumors we have now discovered activating defects in three other genes involved in the MAPK signaling pathway that have not previously been described in astrocytoma."

"Aside from MAPK mutations, we do not find any other frequent mutations that could promote cancer growth in the tumors. This is a very clear indication that overactive MAPK signals are necessary for a pilocytic astrocytoma to develop," says study director Stefan Pfister. The disease thus is a prototype for rare cancers that are based on defects in a single biological signaling process.

In total, the genomes of pilocytic astrocytomas contain far fewer mutations than are found, for example, in medulloblastomas, a much more malignant pediatric brain tumor. This finding

is in accordance with the more benign growth behavior of astrocytomas. The number of mutations increases with the age of the affected individuals.

About one half of pilocytic astrocytomas develop in the cerebellum, the other 50 percent in various other brain regions. Cerebellar astrocytomas are genetically even more homogenous than other cases of the disease: In 48 out of 49 cases that were studied, the researchers found fusions between the BRAF gene, a central component of the MAPK signaling pathway, and various other fusion partners.

“The most important conclusion from our results,” says study director Stefan Pfister, “is that targeted agents for all pilocytic astrocytomas are potentially available to block an overactive MAPK signaling cascade at various points. We might thus in the future be able to also help children whose tumors are difficult to access by surgery.”

International collaboration in tumor genome analysis

The International Cancer Genome Consortium (ICGC), a network of scientists from currently 15 countries, aims to obtain a comprehensive description of genomic and epigenomic changes in all significant types of cancer. Germany takes part with the PedBrain Tumor Project to analyze pediatric brain tumors (medulloblastoma, which in Germany affects approximately 100 children each year; and pilocytic astrocytoma, which is diagnosed in approximately 200 children each year). Within the PedBrain Tumor Project, 300 samples of each tumor type will be analyzed, along with the same number of samples of healthy tissue from the same patients, to identify changes that are cancer-specific.

The PedBrain Tumor network consists of researchers from seven institutes led by project coordinator Peter Lichter of DKFZ. Alongside the DKFZ, participating project partners in Heidelberg are: the National Center for Tumor Diseases (NCT), Heidelberg University and the University Hospital, and the European Molecular Biology Laboratory (EMBL). In addition, scientists from Düsseldorf University Hospital and the Max Planck Institute for Molecular Genetics in Berlin have taken on tasks in the network project.

The German Cancer Aid (Deutsche Krebshilfe) provided funds of eight million Euros for PedBrain Tumor. Since July 1, 2012, the project has received another seven million Euros from the Federal Ministry of Education and Research (BMBF).

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of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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