Medical Xpress

Suspicions confirmed: Brain tumors in children have a common cause

July 9 2013

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.

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 "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."

More information: Recurrent alterations in FGFR1 and NTRK2 represent novel therapeutic targets in childhood astrocytoma. *Nature Genetics* (2013) DOI:10.1038/ng.2682

Provided by Helmholtz Association of German Research Centres