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Genome analysis of brain tumors showing the way to new treatment strategies

As part of the International Cancer Genome Consortium (ICGC), scientists in a project coordinated by the German Cancer Research Center (DKFZ) are systematically investigating the genomes of pediatric brain tumors (medulloblastoma and pylocytic astrocytoma). In their first data evaluation, researchers have now discovered genomic changes which not only reveal targets for new treatment approaches but also provide information about how to use already available drugs more specifically.
The project is supported by the German Cancer Aid (Deutsche Krebshilfe e.V.) and the Federal Ministry of Education and Research (BMBF). The research results are published in the latest issue of *Nature*.

Brain tumors are the primary cause of cancer mortality in children. Even if a cure is possible, young patients often suffer from the stressful treatment which can be harmful to the developing brain. The most common childhood brain tumors are medulloblastoma and pylocytic astrocytoma.

In order to find new target structures for more gentle treatment methods, cancer researchers are systematically analyzing all changes in the genetic material of such tumors. This is the mission of the PedBrain consortium, which was launched in 2010 as the first German part in the International Cancer Genome Consortium (ICGC). The PedBrain Tumor network, which is coordinated by Professor Peter Lichter of DKFZ and Professor Roland Eils (DKFZ and Heidelberg University), has now published, jointly with numerous collaboration partners, an evaluation of the first 125 genome analyses of medulloblastomas.

“We can already see great differences in the genomes of medulloblastomas from one patient to the next,” says Peter Lichter. “But we have also identified a number of frequent and characteristic genomic alterations that may lead the way to developing new methods of diagnosis and treatment.”

Brain tumors with four sets of chromosomes are particularly aggressive

A high percentage of medulloblastomas – particularly among those with very malignant progression – has four sets of chromosomes instead of two as normal. Medulloblastomas are classified into four groups according to aggressiveness. In the study, about half of tumors belonging to groups 3 and 4, which are very difficult to treat, were found to have this aberration. “It is not proven that the extra chromosomes cause cancer. But it is certain that they occur at a very early stage of the cancerous process,” Lichter explains.

Cells with four sets of chromosomes have been found in several types of cancer. However, this genomic aberration also offers a chance of specifically attacking tumors. At the German Cancer Research Center (DKFZ), researchers collaborating with Bayer Healthcare are currently working to develop an agent which specifically inhibits the growth of cells with more than two sets of chromosomes.

About one third of individual mutations in medulloblastoma are found in genes that play a part in what are called epigenetic modifications. “This finding shows once more that drugs influencing such modifications will become increasingly important in cancer treatment,” says Professor Dr. Stefan Pfister, a pediatrician and molecular biologist. DKFZ and Heidelberg University Hospital are already testing such promising substances to treat specific pediatric tumors.

The total number of genomic alterations in medulloblastoma increases with the age of patients. “Although many scientists have supposed that there is such a correlation, it has never been documented before,” Stefan Pfister explains. “We suspect, however, that the foundation for medulloblastoma is laid already during embryonic development.”

For the first time, the PedBrain researchers have also found what are called fusion genes in medulloblastoma. Such genes are formed when, due to genetic accidents, cancer-promoting genes are fused together and new proteins occur as a result. Such fusion genes cause a number of cancers such as chronic myelogenous leukemia (CML). For this cancer, researchers have succeeded in developing a very effective drug against the BCR-ABL fusion gene, which is highly specific for leukemia cells.

“Along with a multitude of individually occurring mutations, we were able to define a number of typical groups of mutations, which will show us the way to new strategies of fighting medulloblastoma”, says Peter Lichter to sum up. “Given the genetic complexity and heterogeneity of this tumor type, a useful future approach would be to analyze the tumor genome in each affected child in order to identify the most promising treatment.”

International collaboration to analyze tumor genomes

The International Cancer Genome Consortium (ICGC), a network of scientists from currently 14 countries, aims to obtain a comprehensive description of genomic and epigenomic changes in all relevant cancers. Germany participates 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 about 200 children each year). As part of the PedBrain Tumor project, 300 tumor samples of each tumor type will be analyzed, along with the same number of healthy samples from the same patients in order 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 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 within the network project.

PedBrain Tumor was supported by the German Cancer Aid (Deutsche Krebshilfe) with funds of eight million euros and has been funded by the Federal Ministy of Education and Research (BMBF) since 1 July 2012 with another seven million euros.

Furthermore, the PedBrain researchers from DKFZ have contributed results of their medulloblastoma analyses to another two publications in the current issue of *Nature*. Besides the PedBrain Tumor network, scientists from DKFZ are collaborating in the genome analysis of early prostate cancer (coordination: DKFZ and University Medical Center Hamburg-Eppendorf) and B cell lymphomas (coordination: University of Kiel).

David TW Jones, Natalie Jäger, ..., Roland Eils, Stefan M Pfister and Peter Lichter, commissioned by the ICGC PedBrain Tumor Project: Dissecting the genomic complexity underlying medulloblastoma. Nature 2012, DOI: 10.1038/nature11284

National Center for Tumor Diseases (NCT) Heidelberg where promising approaches from cancer research are translated into the clinic. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The center is a member of the Helmholtz Association of National Research Centers. Ninety percent of its funding comes from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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