New tumor markers determine therapy intensity

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Characteristic changes in the DNA of medulloblastoma, the most frequent malignant brain tumor in childhood, indicate precisely how aggressively the tumor will continue to spread and what the chances of disease relapse are. Researchers at the Center for Pediatric and Adolescent Medicine at the Heidelberg University Hospital and the German Cancer Research Center have discovered this correlation. With this new set of tumor markers, the intensity of treatment can be adjusted individually and the potentially damaging effects reduced. The results have now been published online in the prestigious *Journal of Clinical Oncology*.

Medulloblastoma is the most frequent childhood brain tumor

The most common malignant brain tumor in childhood is the medulloblastoma - every year, more than 100 children in Germany develop this tumor of the cerebellum and some 30-40 children die from it. The first symptoms generally appear at primary school age, but the tumor, which can already arise during embryonal development, can also occur in babies and toddlers. Aggressive radiation and chemotherapy regimens after surgery can permanently damage the brain of the growing child, for example, leading to coordination disorders and limited growth.

"Using the characteristic changes in the genetic makeup of medulloblastoma, we can predict more accurately than with conventional methods how a patient will respond to therapy and how great the risk is

that the tumor will return after surgery and subsequent radiation and chemotherapy," explained Dr. Stefan Pfister, who works with his team in the department of pediatric oncology at the Center for Pediatric and Adolescent Medicine (Medical Director: Professor Dr. Dr. Andreas Kulozik) and in the department of molecular genetics at the German Cancer Research Center (Director: Professor Dr. Peter Lichter). Thus far, oncologists could estimate this risk only on the basis of histology findings, age at diagnosis, residual tumor after surgery, and existence of metastases at diagnosis.

Patients with a poor prognosis can be treated more intensively

Stefan Pfister and his research group "Molecular Genetics of Pediatric Brain Tumors" first described the new tumor markers in the medulloblastoma in 2007. For the current study, he examined tumor samples from 340 patients and compared the documented course of disease with genetic aberrations in the tumor DNA. Aberrations were seen at the chromosome level, the units in which the entire genetic information is distributed and contained. Each chromosome contains large amounts of genetic information; the entire genetic material of humans is distributed in 23 such portions, each of which is usually present in two copies (2 x 23 chromosomes). Stefan Pfister discovered that if entire segments of chromosomes number 6 and 17 are present in three copies (instead of the usual 2 copies) in the genetic material of the brain tumors, the patient's prognosis is poor. If however, one copy of chromosome 6 is missing in the tumor, the patients in the collective observed always survived. The combination of these and other characteristics led to a classification of the patients in a total of five groups requiring varying levels of intensity in treatment.

"With these markers, we can reliably identify patients with a poor prognosis and treat them more intensely from the start," said Dr. Stefan

Pfister. "At the same time, we can reduce the treatment intensity for patients who will presumably respond especially well to radiation and chemotherapy. We can thus reduce consequential damage and the risk of secondary malignancies."

Another advantage of the new markers - the test is very robust and can be carried out within 48 hours in any neuropathology laboratory on tissue samples conventionally preserved in paraffin.

BMBF promotes the search for other tumor markers

The prospective validation of these markers in an independent patient cohort and the search for the simplest and most reliable methods of analysis is now the goal of a project promoted by the Federal Ministry for Education and Research (BMBF) entitled "Molecular Diagnostics," in which the university hospitals of Bonn, Mainz, Düsseldorf, Würzburg, and Heidelberg as well as the German Cancer Research Center in Heidelberg are participating under the coordination of Dr. Stefan Pfister.

More information: Outcome prediction in pediatric medulloblastoma based on DNA copy-number aberrations of chromosomes 6q, 17q, and the MYC/MYCN loci. Stefan Pfister, Marc Remke, Axel Benner, Frank Mendrzyk, Grischa Toedt, Jörg Felsberg, Andrea Wittmann, Frauke Devens, Nicolas U. Gerber, Stefan Joos, Andreas Kulozik, Guido Reifenberger, Stefan Rutkowski, Otmar D. Wiestler, Bernhard Radlwimmer, Wolfram Scheurlen, Peter Lichter and Andrey Korshunov. *J. Clin. Oncol*. 2009, March 2nd online ahead of print.

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