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DEUTSCHES
KREBSFORSCHUNGSZENTRUM
IN DER HELMHOLTZ-GEMEINSCHAFT

50 Jahre – Forschen für
ein Leben ohne Krebs

joint press release of the German Cancer Research Center (DKFZ) and Heidelberg University Hospital

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New brain cancer types emerge based on molecular characteristics

An international team headed by scientists from the German Cancer Research Center (DKFZ), Heidelberg University Hospital and St. Jude Children's Research Hospital has conducted a comprehensive molecular analysis of a subgroup of so-called primitive brain tumors in children. They found that the majority of cases with this pathologic diagnosis have molecular features that correspond to those of other types of brain cancer and must therefore be treated in the same way. Based on molecular characteristics, the researchers classified another part of the tumors into four new types, which also vary in their clinical features. In the future, this classification may help assign patients to appropriate clinical trials. The researchers have now published their results in the journal CELL.

Many childhood brain tumors arise from extremely immature and undifferentiated cells of the central nervous system (CNS) and are therefore referred to as embryonal tumors. These include, for example, medulloblastomas, which always occur in the cerebellum. A large part of embryonal brain tumors that are located above the cerebellum are grouped as primitive neuroectodermal tumors of the central nervous system (CNS PNET). About 10 children and 40 adults are diagnosed with this type of cancer in Germany every year. These brain tumors grow extremely rapidly and aggressively and are difficult to treat.

"More recent studies have revealed that PNET are a group of heterogeneous cancers," says Andrey Korshunov, a neuropathologist who works at the DKFZ and Heidelberg University Hospital. "However, precise diagnosis is difficult because there are no molecular markers and in histologic differentiation of tumor tissue under the microscope there are overlaps with many other types of brain cancer."

In order to facilitate better classification of these dangerous tumors and, thus, more precise and eventually more successful treatment for each individual patient, an international research group led by Marcel Kool from the DKFZ and David Ellison from St. Jude, (Memphis, Tenn., USA) launched a large-scale study in which researchers conducted a comprehensive molecular and histologic analysis of tissue samples from over 300 CNS PNET cases.

In the first step, the investigators mapped the distribution of methyl labels in the tumor genomes. By comparing these methylation profiles with reference tumors, they recognized that approximately two thirds of the presumed CNS PNET could be grouped with other known CNS tumor types. In many cases, this observation was additionally supported by histologic re evaluation of the tumor tissue.

"This result shows how important molecular analysis of these primitive tumors is. In many cases, our new classification suggests completely different treatment options," says

pediatrician and molecular geneticist Dominik Sturm, who is one of the first authors of the article. At St. Jude, the study was directed by first author and neuropathologist Brent Orr.

The researchers were able to classify the bulk of the remaining tumors in four new, previously unknown tumor types, which exhibit significant differences as to patients' age and gender as well as clinical course. Further analyses such as gene activity profiles, determining the copy number of chromosomes as well as DNA sequencing revealed a characteristic genetic alteration for each of the four new tumor types in addition to their specific DNA methylation profiles. In contrast, it was difficult to distinguish these groups based solely on their histologic features.

“Based on the molecular tumor profiles, we can assign affected patients to future clinical trials that make sense for them,” Sturm explains. “The tumors in the four newly described groups differ from all previously known brain tumors markedly enough to speak of new tumor types. We expect that they also vary in their response to chemotherapy and targeted drugs.” The molecular analysis has already yielded first clues about potential targets in the individual tumor groups.

This research shows the importance of international collaborations in the study of rare types of cancer. This comprehensive study would not have been possible without the linkage of two of the world's largest research centers with a focus on pediatric oncology, the DKFZ in cooperation with Heidelberg University Hospital and St. Jude.

The project was supported, among other sources, by German Cancer Aid (Deutschen Krebshilfe), the German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung), the Federal Ministry of Education and Research (BMBF) and ALSAC (Memphis, USA).

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The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment 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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**Heidelberg University Hospital and Medical Faculty:
Internationally recognized patient care, research, and teaching**

Heidelberg University Hospital is one of the largest and most prestigious medical centers in Germany. The Medical Faculty of Heidelberg University belongs to the internationally most renowned biomedical research institutions in Europe. Both institutions have the common goal of developing new therapies and implementing them rapidly for patients. With about 12,600 employees, training and qualification is an important issue. Every year, around 66,000 patients are treated on a fully or partially inpatient basis and over 1,000,000 patients have been treated on an outpatient basis in more than 50 clinics and departments with 1,900 beds. Currently, about 3,500 future physicians are studying in Heidelberg; the reform Heidelberg Curriculum Medicinale (HeiCuMed) is one of the top medical training programs in Germany.

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