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Analysis of genetic changes in rare cancers enables early detection of hereditary cancer risk

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An international team of researchers in the German Cancer Consortium (DKTK), led by scientists from the University Hospital Carl Gustav

Carus Dresden, the German Cancer Research Center (DKFZ) and the National Center for Tumor Diseases (NCT) in Dresden and Heidelberg, has now shown, in a large-scale study, that patients and their families could benefit from early molecular diagnostics.

Nearly 1,500 patients were included in the trial, of whom about 80% had rare cancers. More than 10% of all participants were found to have a hereditary predisposition to cancer, 75% of these cases were newly detected. Family members can now be included in genetic testing and clinical early-detection programs before developing cancer. The results of the study were published in *Annals of Oncology*.

Experts estimate that about 5 to 10% of all cancers can be traced back to hereditary genetic changes, also called germline mutations. These are present in every cell in the body. Research on this issue is usually conducted on patients with more common forms of cancer, such as breast and colorectal cancer.

In this new study, based on a broad dataset, an international team of researchers was able to demonstrate that hereditary cancer-driving changes play an important role in various rare cancers, but are hardly ever diagnosed. Nearly 1,500 patients were included in the study, of whom about 80% had rare cancers. Using modern high-throughput genome sequencing of blood and tumor samples, researchers looked for germline mutations in 101 clinically relevant cancer risk genes.

More than 10% of all participants were found to have an autosomal dominant, inherited cancer predisposition. This is associated with a much higher lifetime risk of cancer, with a 50% chance of it being passed on from generation to generation, regardless of gender. For 75% of patients and their families, this genetic tumor risk situation was diagnosed for the first time in the MASTER study.

Evelin Schröck, Director of the Institute of Clinical Genetics at University Hospital Carl Gustav Carus Dresden, explains, "In cases where this kind of genetic tumor risk syndrome is suspected, it is particularly important to perform genetic testing on the patients and their family members to determine their individual cancer risk and to be able to detect cancer as early as possible, or even prevent it, through continuous preventive examinations."

Hanno Glimm, a member of the managing directorate of NCT/UCC Dresden and a head of department at the DKFZ, explains, "Our study shows that a surprisingly high proportion of patients with rare cancers have a hereditary predisposition to cancer and that a large proportion of these predispositions are not normally diagnosed. We hope that, in future, many more patients with rare cancers will be able to receive comprehensive molecular analysis."

In the MASTER study, a team of experts in bioinformatics, biology and medicine (human genetics, oncology, internal medicine and pathology) worked together to evaluate the genetic variants in the blood and tumor for all patients. Cases were discussed during the molecular tumor board meeting held twice weekly. They were able to demonstrate that analysis of hereditary cancer risk factors in the blood can support therapy decisions, as well as helping to improve early cancer detection.

The researchers were able to recommend a targeted therapy based on the specific genetic changes for almost half (46%) of patients with a cancer-driving genetic mutation. Around a quarter of these patients were treated in line with the recommendation, resulting in improved disease control for 40% of those affected, in comparison to their previous treatment.

Stefan Fröhling, Managing Director of NCT Heidelberg and a head of department at the DKFZ, says, "Our study combines broad molecular analysis of tumor and control tissue with consistent recommendation and

implementation of targeted therapies. The results show that patients with rare cancers can benefit from this approach, even in late stages of the disease or after several previous therapies." The researchers have since been able to further corroborate the study findings in analyses involving a total of more than 3,500 patients.

Barbara Klink, a research group leader at the Institute of Clinical Genetics and head of the National Center of Genetics of the Laboratoire National de Santé (LNS) in Luxembourg, adds, "In precision oncology research, the focus is often on genetic changes that only affect the tumor cells. We were able to show that in rare cancers, it is also important to analyze hereditary germline mutations in a large number of genes using blood samples. This identifies families with tumor risk syndromes who would not normally meet the current eligibility criteria for genetic testing for hereditary predisposition to cancer. Uncovering a predisposition to cancer in the family increases the chances of early detection and improved treatment for other family members."

The study discovered genetic changes that are associated with an increased cancer risk even more frequently in the blood of patients with certain types of cancer—for instance those with rare tumors of the digestive tract (gastrointestinal stromal tumors: 23%) and malignant tumors of smooth muscle tissue (leiomyosarcoma: 21%). However, in order to further investigate this connection, there is a need for much larger case numbers for individual tumor types, some of which are very rare.

The recent study also offers jumping-off points for numerous other research questions. For instance, Dresden-based researchers plan to investigate how they can make best use of the knowledge about certain rare hereditary cancers for targeted early detection and therapy.

"We are particularly interested in how it can be used to improve life

expectancy and quality of life for patients and their family members," says Arne Jahn, the first author of the study, who is a clinician scientist at the Institute of Clinical Genetics and a research group leader at NCT/UCC Dresden.

"In addition to our involvement in the MASTER study we offer genetic diagnostics and interdisciplinary care to more than 600 individuals with cancers at the University Hospital Dresden yearly. Subsequently patients with genetic tumor risk syndromes and their family members are followed-up. We collaborate with other hospitals and in nationwide German networks to build structures for improved cancer care and early detection in patients and families with tumor risk syndromes. We hope that, in future, we will be able to make similar offers to many more families with suspected hereditary cancer or a genetic tumor risk syndrome," says Schröck.

More information: A. Jahn et al, Comprehensive cancer predisposition testing within the prospective MASTER trial identifies hereditary cancer patients and supports treatment decisions for rare cancers, *Annals of Oncology* (2022). DOI: 10.1016/j.annonc.2022.07.008

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