Supposedly "silent" mutation with serious consequences

So-called silent mutations have no effect on the composition of a protein. They are therefore not considered to promote cancer. However, scientists from the German Consortium for Translational Cancer Research (DKTK), partner site Essen, now describe in a case of kidney cancer an overlooked silent mutation with a major impact on prognosis. In the DKTK, the German Cancer Research Center (DKFZ) in Heidelberg, as the core center, joins forces in the long term with university partner sites in Germany that have a special reputation in oncology.

Synonymous or "silent" mutations affect the DNA without causing an amino acid exchange and thus without causing a protein change. Therefore, they are often not taken into account in large genomic studies to search for cancer-causing mutations:

But scientists have now discovered more and more evidence that silent mutations are by no means necessarily without consequences: for example, a silent mutation can affect the stability and structure of the mRNA. Samuel Peña-Llopis from the DKTK partner site at the West German Cancer Center in the University Hospital Essen now describes an example of this.

In the tumor genome database "The Cancer Genome Atlas" (TCGA), the researchers came across the case of a patient with clear-cell renal cancer. A mutation profile was described in the tumor genome that predicted a rather favorable prognosis and a patient survival of 117 months. And yet, this patient had already died 56 months after cancer diagnosis. Upon closer examination, the DKTK researchers found a synonymous mutation in BAP1, a tumor suppressor and an important cancer driver in many tumors.

When a gene is read, only certain regions of the DNA sequence, known as exons, are incorporated into the mature mRNA, which ultimately serves as the building instructions for the protein. The team led by Peña-Llopis has now discovered that the silent BAP1 mutation causes exon no. 11 to be skipped when the individual exons are joined together. This throws the protein blueprint out of sync, resulting in a truncated BAP1 protein that is rapidly degraded. "The complete inactivation of BAP1 as a consequence of this pathogenic synonymous mutation causes higher tumor aggressiveness and decreases almost fourfold the expected patient survival", says Peña-Llopis, who previously classified this tumor type based solely on inactivating mutations in BAP1 and another tumor suppressor. Peña-Llopis thus recommends paying attention to even the supposedly silent mutations in tumor genome analyses, "especially those used for personalized medicine by providing specific treatments to patients depending on the genomic alterations identified".

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Further information

- German Cancer Research Center (DKFZ), Heidelberg