

Diabetes switch in DNA: Non-coding region in the genome influences ONECUT1 gene

They are underestimated genetic control elements: it is known that changes in the genome can trigger diabetes. But now researchers at the University Hospital Ulm and the INSERM Cochin Institute in Paris have shown that a previously under-researched region of the genome also plays a crucial role in the development of this disease. The German-French collaboration has revealed that a region of "non-coding DNA" has a significant influence on the activity of the diabetes gene ONECUT1. The results of the project have been published in the renowned journal Cell Reports – and open up new avenues for personalised therapies.

"Our research focused on a young patient of our French partners who had been diagnosed with a rare form of diabetes in infancy due to a mutation in the ONECUT1 gene," explains Professor Alexander Kleger, Director of the Institute of Molecular Oncology and Stem Cell Biology (IMOS) at Ulm University and head of the Interdisciplinary Pancreatology Section at the Department of Internal Medicine I. "At birth, he was significantly smaller and lighter than other newborns, had malformations of the toes, a severely reduced pancreas and no gallbladder." In his teens, his condition deteriorated dramatically, with severe gastrointestinal bleeding and progressive liver cirrhosis. He eventually died of a complication of the disease as a young adult. "Although it was known that ONECUT1 plays an important role in the development of the pancreas and liver, as well as in the development of this rare form of diabetes," said Kleger, "this could not explain the extraordinary severity of the disease."

The research team at IMOS genetically modified human stem cells to reflect the specific mutations of this patient. They then used these cells to generate pancreatic progenitor cells and examined them using modern molecular biological methods. In collaboration with other Ulm research institutes (Human Genetics, Transfusion Medicine), a special form of nanopore sequencing was used to analyse the human genome. In addition, the spatial structure of chromatin was examined to understand how different parts of DNA interact in the cell nucleus. Finally, the researchers used CRISPR-Cas9 technology, also known as gene scissors, to specifically remove a non-coding region of the genome and examine its influence on the development of the pancreas.

This non-coding part contains elements that can control gene activity – while the coding region provides the blueprint for proteins. For a long time, the non-coding region was considered to be functionless "junk DNA", but the researchers in Ulm made an important discovery precisely there. "We found that the patient lacked a piece of the DNA strand at this point. This turned out to be an 'enhancer' – an element that promotes the transcription of DNA into RNA and thus enhances gene activity," explains Dr Sandra Heller, a biologist at Ulm University. Although this element is located further away from the ONECUT1 gene, it still influences its activity. ONECUT1 is crucial for the development of beta cells and thus for insulin production in the pancreas.

While the researchers from Ulm and Paris identified this enhancer element through genetic analyses in the DNA of the diabetes patient, it was discovered by a research group in the USA using CRISPR screening. "In subsequent experiments in human pluripotent stem cells," explains IMOS doctoral student Sarah Merz, "both teams obtained consistent and complementary results." The US study was also recently published in Cell Reports.

Promising approach for personalised diabetes therapy

The researchers' discovery opens up new possibilities for targeted diabetes treatment. For example, they tested various drugs already used to treat type 2 diabetes on cells that replicated the genetic changes of the patient. Some of these drugs improved the impaired insulin secretion – a promising approach for personalised therapies. "Our goal is to adapt the therapy individually to the genetic characteristics of the patients in order to achieve better treatment results. To implement such a project, we need unique partnerships on equal terms, which is why I am particularly grateful to my colleague Cécile Julier from the INSERM Cochin Institute in Paris," explains Professor Alexander Kleger.

The findings of the German-French team are not only important for the treatment of patients with rare genetic mutations, but also for those with the more common type 2 diabetes. This is because the researchers also found a genetic variation in the

newly identified region that is associated with a higher risk of common forms of diabetes. By specifically analysing these regions, it may be possible in the future to develop genetically tailored treatment options for these individuals. "Our work shows that the non-coding genome can play a much greater role in disease development than previously thought," emphasises Alexander Kleger. It is now important to rethink genetic diagnostics and to examine such regulatory elements more closely – in order to uncover the mechanisms of complex diseases such as diabetes.

The project was funded by the German Research Foundation (DFG) and the Medical Scientist Programme of Ulm University and carried out in cooperation with partners such as the Institute of Human Genetics at Ulm University, the Clinic for Internal Medicine I, the Institute for Computational Genomics at RWTH Aachen and the Institute for Clinical Transfusion Medicine and Immunogenetics Ulm.

Background: The ONECUT1 gene is located on human chromosome 15 and plays a central role in the development of liver and pancreas as well as in metabolic processes. As early as 2021, the Ulm researchers were able to show that mutations in ONECUT1 strongly influence the development of certain forms of diabetes. These findings are important for personalised medicine, as some cases of supposed type 2 diabetes may be due to a change in just one gene and could be treated specifically.

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