Crystallized alternative DNA structure sheds light on insulin and diabetes

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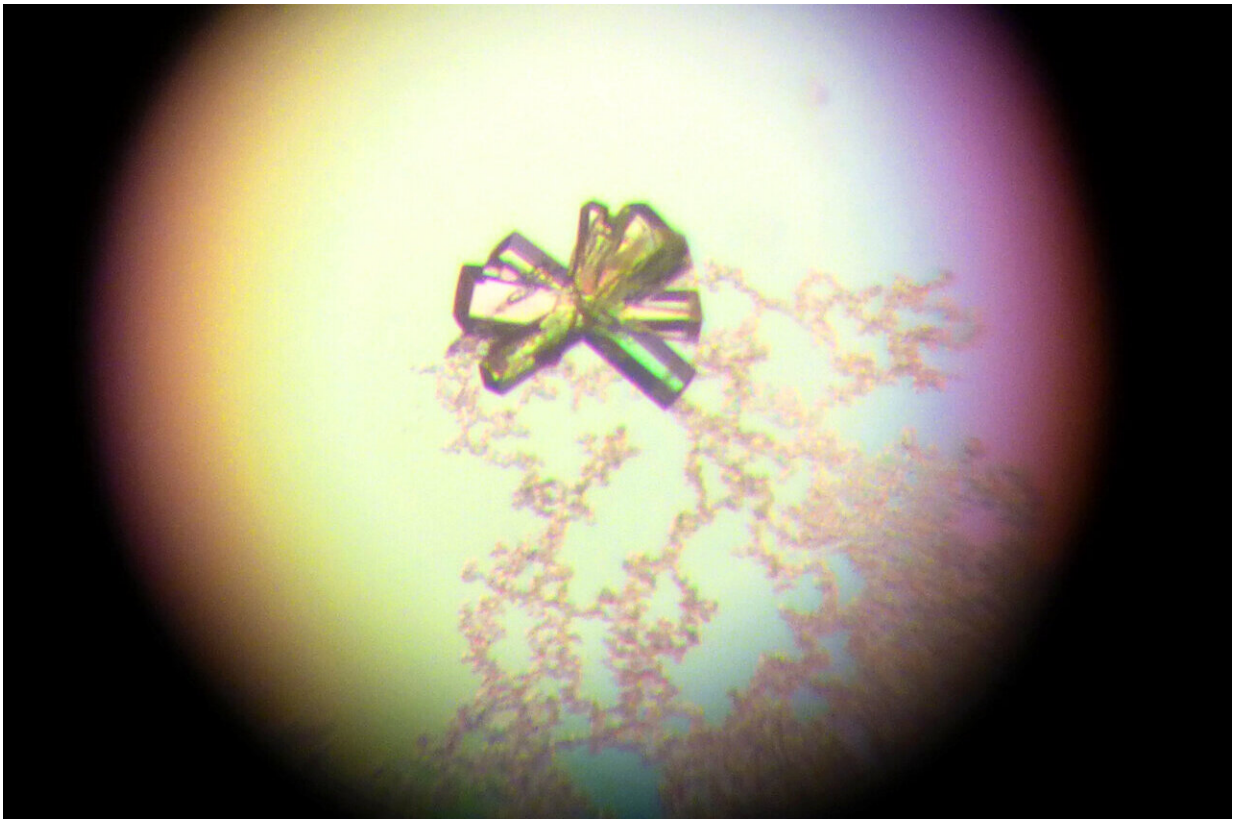

Crystal of the 4C i-motif, used in X-ray experiments. Credit: Dilek Guneri et al, UCL School of Pharmacy

The first crystal structure of an alternative DNA shape from the insulin gene has been revealed by a UCL-led research team.

DNA is widely accepted to be formed of two strands that wind around one another, known as a double helix, but it is possible for DNA to change shape and structure. The new study, published in *Nature Communications*, reveals the detail in the structure of a type of DNA called i-motif by crystallizing it for the first time.

Co-lead author Dr. Zoë Waller (UCL School of Pharmacy) said, "DNA is our genetic material, and its structure usually looks a bit like a twisted ladder called a double helix. This shape is iconic, but alternative DNA structures exist and are thought to potentially play a role in the development of genetic diseases, such as diabetes or cancer."

The researchers were focusing on i-motif DNA, which has an interlocking structure resembling a knot, and was only confirmed to be found in living human cells in 2018.

Dr. Waller said, "It was previously known that there was a region of DNA in the insulin gene that can fold into alternative DNA structures and shapes. It was also known that this region of DNA varies between people. Our work shows that these different variants in sequence fold into different DNA shapes."

The scientists employed a crystallography technique that concentrates a solution containing the DNA, enabling crystals to form, which is an important method for researchers to see the structure of DNA using X-ray crystallography.

Dr. Waller explained, "We were able to crystallize a four-stranded DNA structure, called an 'i-motif.' Our crystals allowed us to determine exactly what the structure of this DNA looks like using X-rays. This has revealed that certain DNA sequences have special, additional interactions which help them form alternative DNA structures more easily."

The research team demonstrated that different sequence variants in the insulin gene form different DNA structures, which in turn could affect whether insulin is switched on or off.

By demonstrating how the shape of DNA can affect insulin gene function, already known to be critical in diabetes, they hope their findings could guide future research into diabetes treatment.

The crystal structure the scientists developed can enable computational-based drug discovery to be used to target the i-motifs from the insulin gene, because when scientists know the specific 3D shape, they can design molecules digitally and model them to see whether they will fit.

Scientists can then develop new drugs using particular chemicals when they know which ones will fit the drug target best—a process called rational design.

As the first crystal structure of this type, the researchers say it will also be useful as a model for other targets in the genome, besides the insulin gene, which form this shape of DNA.

Dr. Waller added, "This research means that now we can use the shape of DNA to design molecules to bind these structures, which could be developed into drugs and potentially medicines."

More information: Dilek Guneri et al, Structural insights into i-motif DNA structures in sequences from the insulin-linked polymorphic region, *Nature Communications* (2024). DOI: 10.1038/s41467-024-50553-0

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