Researchers map 50,000 of DNA's mysterious 'knots' in the human genome

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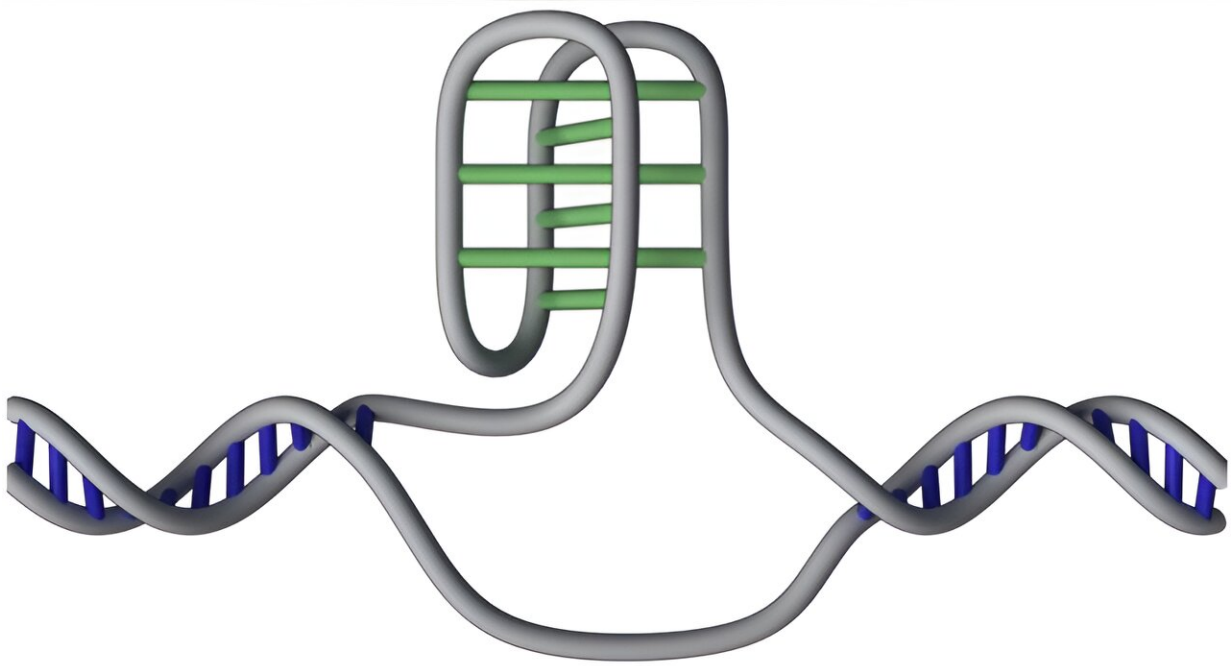

The knot-like i-motif structure protruding from DNA's double helix has been mapped in 50,000 locations in the human genome, concentrated in key functional areas including regions that control gene activity. Credit: Garvan Institute

Researchers have mapped 50,000 of DNA's mysterious "knots" in the human genome. The innovative study of DNA's hidden structures may open up new approaches for treatment and diagnosis of diseases,

including cancer.

DNA is well-known for its double helix shape. But the human genome also contains more than 50,000 unusual knot-like DNA structures called i-motifs, researchers at the Garvan Institute of Medical Research have discovered.

Published today in *The EMBO Journal* is the first comprehensive map of these unique DNA structures, shedding light on their potential roles in gene regulation involved in disease.

In a landmark 2018 study, Garvan scientists were the first to directly visualize i-motifs inside living human cells using a new antibody tool they developed to recognize and attach to i-motifs. The current research builds on those findings by deploying this antibody to identify i-motif locations across the entire genome.

"In this study, we mapped more than 50,000 i-motif sites in the human genome that occur in all three of the cell types we examined," says senior author Professor Daniel Christ, Head of the Antibody Therapeutics Lab and Director of the Centre for Targeted Therapy at Garvan. "That's a remarkably high number for a DNA structure whose existence in cells was once considered controversial. Our findings confirm that i-motifs are not just laboratory curiosities but widespread—and likely to play key roles in genomic function."

Curious DNA i-motifs could play a dynamic role in gene activity

I-motifs are DNA structures that differ from the iconic double helix shape. They form when stretches of cytosine letters on the same DNA strand pair with each other, creating a four-stranded, twisted structure

protruding from the double helix.

The researchers found that i-motifs are not randomly scattered but concentrated in key functional areas of the genome, including regions that control gene activity.

"We discovered that i-motifs are associated with genes that are highly active during specific times in the cell cycle. This suggests they play a dynamic role in regulating gene activity," says Cristian David Peña Martinez, a research officer in the Antibody Therapeutics Lab and first author of the study.

"We also found that i-motifs form in the promoter region of oncogenes, for instance the MYC oncogene, which encodes one of cancer's most notorious 'undruggable' targets. This presents an exciting opportunity to target disease-linked genes through the i-motif structure," he says.

"The widespread presence of i-motifs near these 'holy grail' sequences involved in hard-to-treat cancers opens up new possibilities for new diagnostic and therapeutic approaches. It might be possible to design drugs that target i-motifs to influence gene expression, which could expand current treatment options," says Associate Professor Sarah Kummerfeld, Chief Scientific Officer at Garvan and co-author of the study.

More information: Human genomic DNA is widely interspersed with i-motif structures, *The EMBO Journal* (2024). DOI: 10.1038/s44318-024-00210-5

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