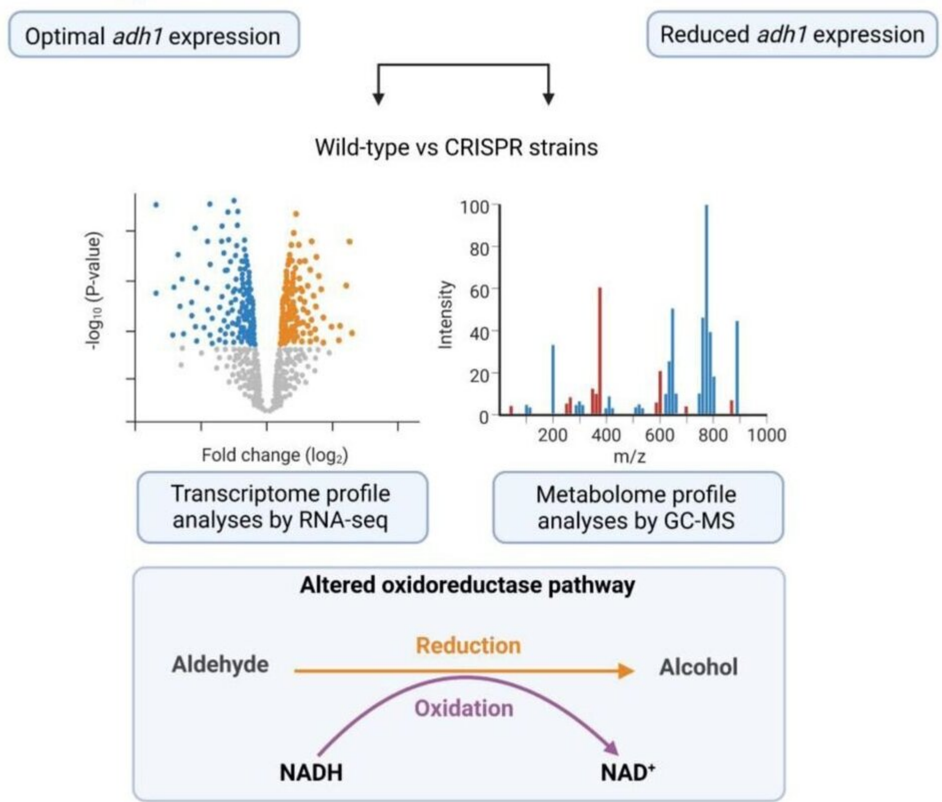
DNA folding more important for cell function than previously thought

September 17 2025



Credit: Ikenna Obi et al

Tiny tweaks in DNA folding can have big effects. A study from Umeå University shows that even the most subtle changes in DNA's shape have an important influence on gene activity and energy production. This discovery challenges the view of DNA as passive storage of information and points to its active role in cell behavior, offering new possibilities for understanding diseases like cancer and diabetes.

"We are very excited about these results, as they broaden our understanding of DNA's role as a dynamic regulator, not just as a static blueprint," says Nasim Sabouri, Professor at the Department of Medical Biochemistry and Biophysics, who led the study published in *Nucleic Acids Research*.

Just like a single piece of paper can be folded into different origami shapes, like a bird or a plane, DNA can also fold in ways beyond the classical double helix. One of these shapes, called a G-quadruplex or G4, appears in parts of the genome that are crucial for how cells grow, manage energy and regulate which genes are turned on or off.

"In humans, G4 structures have often been associated with disruptive and negative effects, linked to cancer and neurodegenerative diseases. But we wanted to explore a different angle: Could a single G4 structure actually play a constructive, positive role in regulating gene activity?" asks Sabouri.

Using yeast and the gene editing tool CRISPR-Cas9, they introduced subtle mutations into G4 that sits near genes important for the cell's energy balance. Their goal was to see how changing the shape of the G4—not removing it entirely—would affect the cell's behavior.

Nasim Sabouri, Pallabi Sengupta, and Ikenna Obi at the Department of Medical Biochemistry and Biophysics have used the gene-editing tool CRISPR-Cas9 to alter the shape of a DNA structure in yeast, which affected the yeast cells' energy production. Credit: Rebecca Forsberg

"What we found was both exciting and unexpected," says Ikenna Obi, staff scientist in Sabouri's research group and first-author of the study.

They discovered that the mutations to the G4 structure triggered widespread changes in the cell's metabolism and expression of genes. Most notably, it disrupted one of the central energy systems in cells.

"We've shown that even a small tweak to DNA's shape can ripple through the entire cell, affecting how it grows and functions," says Pallabi Sengupta, postdoc in Sabouri's research group, who also contributed to the study.

This is the first time scientists have shown that a single G4 structure in yeast can regulate both gene activity and metabolism, challenging the idea that G4s are mostly problematic. It also highlights DNA's role not just as a static blueprint, but as a dynamic regulator of cellular function.

"We expected some change in gene expression," Sabouri explains, "but the scale of the downstream metabolic shifts was surprising."

By revealing how G4 regulates gene activity and energy balance in the cell, this research can lead to new ways of understanding—and potentially treating—conditions like cancer and metabolic disorders like diabetes, where gene regulation and energy balance go awry.

"Our findings open up exciting possibilities for both basic biology and applied science," Sabouri concludes.

More information: Ikenna Obi et al, CRISPR-Cas9 targeting of G-Quadruplex DNA in ADH1 promoter highlights its role in transcriptome and metabolome regulation, *Nucleic Acids Research* (2025). DOI: 10.1093/nar/gkaf853.
academic.oup.com/nar/article/53/17/gkaf853/8252031

Provided by Umea University