# Research reveals DNA-protecting gene's crucial role in brain disorders

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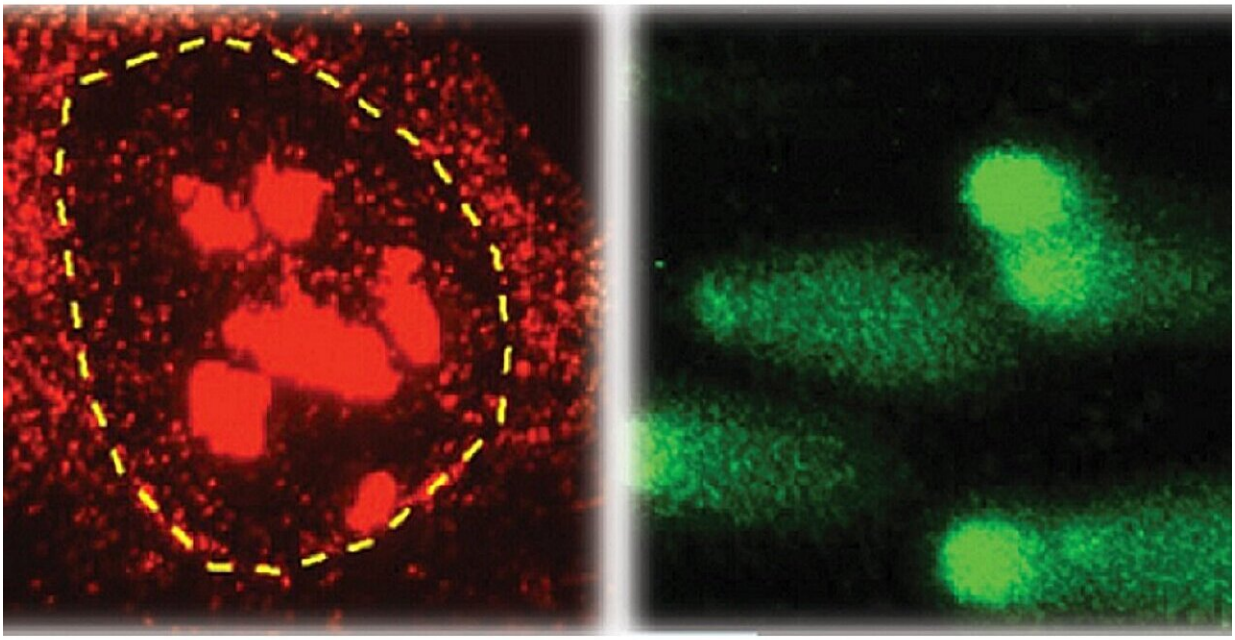

L–R: Microscopic images showing bright red spots on a cell, indicating an increase in detrimental RNA:DNA Hybrids. Second image shows cells with high DNA damage forming a 'comet' shape, where the distinct tail contains fragmented DNA. Credit: University of Adelaide

University of Adelaide researchers now know more about a mysterious

gene's role in maintaining healthy DNA—a crucial development that could lead to new treatments for life-threatening illnesses including neurodevelopmental disorders, some types of cancer and neurodegenerative diseases.

THOC2 is an essential gene for the development and function of brain cells but not much is known about the exact role it plays in normal brain development and neurodevelopmental disorders.

To find out more about its function, researchers at the University of Adelaide used gene editing technology to create the first mammalian model to examine THOC2's molecular pathology.

"We now know more than ever before about the role THOC2 plays in maintaining healthy DNA and the essential cellular processes that are impacted by this gene, resulting in neurodevelopmental disorders," said the University of Adelaide's Dr. Rudrarup Bhattacharjee from the Adelaide Center for Epigenetics, who was the first author on this study.

"Our findings show when THOC2's function is compromised by genetic mutations, normal brain development is impacted. This opens up new opportunities to explore ways to safeguard DNA and help patients with a THOC2-related disorder."

The findings have been published in *Nature Communications* and were part of a collaborative study into THOC2 involving researchers at SAHMRI, who played a key role in generating the preclinical model.

THOC2-related disorders typically affect males and are linked to developmental delays and intellectual disabilities. Some of the characteristics of these disorders seen in human patients were also observed in the mouse model, including learning and memory deficits.

"In our preclinical model, THOC2's function was compromised and that allowed us to assess its impact on the brain. This revealed how a small change in the THOC2 protein can lead to an avalanche of consequences in the form of learning and memory problems, body movement and size," said University of Adelaide's Dr. Raman Sharma, a senior co-author on this study from the Adelaide Medical School.

Further analysis also found the deletion of a small region of the THOC2 gene (towards its C-terminal end) resulted in DNA damage. In particular, it seemed to have a significant effect on the transcription process, where the DNA sequence of a gene is copied to build proteins. Cell death was also observed.

"Our work on the THOC2 gene and its new preclinical model will stimulate research and contribute to better health care," said senior/corresponding author of the study Professor Jozef Gecz, Head of Neurogenetics at the Adelaide Medical School.

"Recent studies have shown that certain cancer cells can become more vulnerable if they have less THOC2 and this is an avenue that could be explored in future studies, along with the role THOC2 plays in neurodegenerative diseases."

**More information:** Rudrarup Bhattacharjee et al, Compromised transcription-mRNA export factor THOC2 causes R-loop accumulation, DNA damage and adverse neurodevelopment, *Nature Communications* (2024). DOI: 10.1038/s41467-024-45121-5

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