Scientists Uncover Hidden RNA Defect Behind Rare Childhood Brain Disorders

Press Release, 19 May 2026

An international research team led by Hana Hanzlikova from the Institute of Molecular Genetics of the Czech Academy of Sciences has uncovered a hidden problem inside cells that contributes to a group of rare neurodevelopmental disorders affecting children. Their work reveals that defects in an important cellular RNA-processing system cause misprocessed RNA molecules to accumulate inside the cells. The researchers also identified this build-up as a measurable signal that reflects disease severity and could help improve future diagnosis of these conditions.

For children affected by rare neurodevelopmental disorders, symptoms often appear early and can be severe, ranging from developmental delay and motor difficulties to seizures and structural changes in the brain. In some cases, doctors can identify mutations in specific genes, but a key question has remained unanswered: how do these mutations disrupt normal cell function, and why do they lead to very different disease outcomes from one patient to another?

Without understanding the underlying processes at the molecular level, these conditions remain difficult to interpret. Why are some patients only mildly affected while others develop severe symptoms? And is it possible to directly observe what is going wrong inside their cells? These are the questions that Hana Hanzlíková and her colleagues set out to investigate.

When the cell's messages cannot be completed

Our cells constantly copy information stored in DNA into temporary molecules called RNA, which carry instructions needed for normal cell function. Before these RNA messages can be used, they must first be carefully processed and "finished" by specialized cellular machinery.

The researchers discovered that in patients carrying mutations in the genes BRAT1 or INTS11, this process does not work properly. As a result, some RNA molecules remain unfinished and start to accumulate inside the cell nucleus instead of being normally processed.

"We were surprised by how consistently these unfinished RNA molecules accumulated in patient cells," says Zuzana Poláčková. "It showed us that this is not a rare mistake, but a fundamental problem affecting how cells handle genetic information."

A molecular “traffic jam”

The affected genes, BRAT1 and INTS11, help maintain a cellular complex called Integrator, which is responsible for processing certain RNA molecules. When this system fails, the cell can no longer properly complete some RNA messages.

“It’s similar to a traffic jam inside the cell,” explains Beatrice Valtorta. “The unfinished RNA molecules start piling up because the cell cannot process them correctly.”

Importantly, the team found that the amount of accumulated unfinished RNA closely matched how severe the disease was in different patients. Patients with greater accumulation tended to have more severe symptoms. This means the RNA build-up could serve as a biomarker — a measurable sign that helps doctors better understand and interpret these disorders.

Toward better understanding of rare disorders

To further confirm their findings, the researchers also studied the same process in a living model organism and observed similar defects in brain development together with the same RNA accumulation.

The study helps explain, for the first time, how mutations in BRAT1 and INTS11 disrupt normal cellular function and contribute to disease. Although the findings do not yet provide a treatment, they offer an important step toward better diagnosis and understanding of these rare neurological conditions.

“For a long time, we could identify the genetic mutations in these patients, but we did not fully understand how they contribute to disease,” says Hana Hanzlikova. “Now we can directly observe the cellular process that is failing. This gives us a way to better interpret genetic findings and understand why some patients are more severely affected than others. It brings us closer to understanding how these conditions develop and eventually, how we might intervene in the future”.

Publication: https://link.springer.com/article/10.1186/s13073-026-01667-1
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