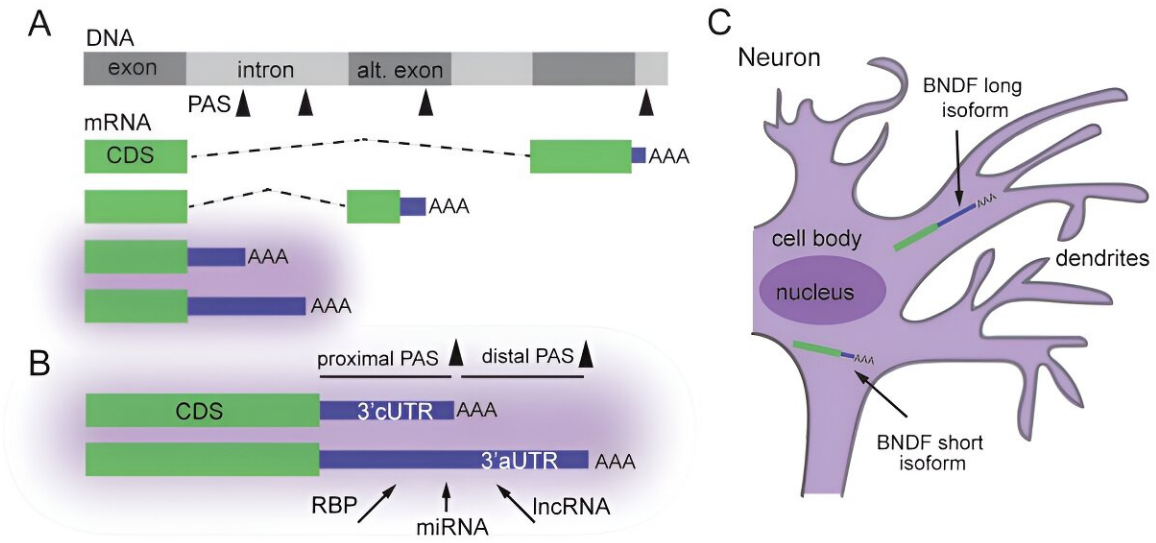
Study reveals hidden genetic mechanisms behind psychiatric disorders

September 3 2024



Alternative polyadenylation (APA). Credit: *Genomic Psychiatry* (2024). DOI: 10.61373/gp024i.0049

In a comprehensive review of recent genetic studies, researchers have identified a hidden layer of complexity in how our genes function, shedding new light on the biological underpinnings of major psychiatric disorders. The study published in *Genomic Psychiatry* reveals that a process called alternative polyadenylation (APA)—which affects how genes are expressed—may be a crucial factor in determining an individual's risk for conditions like schizophrenia, bipolar disorder, and

depression. This discovery opens up exciting new avenues for understanding and potentially treating these complex mental health conditions.

"For years, we've known that psychiatric disorders have a strong genetic component, but pinpointing exactly how genes contribute to disease risk has been challenging," said Dr. Michelle Paff, lead author of the study. "Our research shows that it's not just about which genes you have, but also how those genes are processed and regulated."

The study focuses on APA, a mechanism that affects the stability and localization of messenger RNA (mRNA) molecules, which serve as blueprints for protein production in cells. By altering the length of a gene's 3' untranslated region (3'UTR), APA can significantly impact how much protein is produced from a given gene and where in the cell that protein ends up.

Using sophisticated computational techniques, the researchers analyzed data from multiple large-scale genetic studies, identifying 286 genes whose APA patterns were associated with psychiatric disorders. Remarkably, 60–65% of these genes had not previously been linked to these conditions through other genetic mechanisms.

"This finding suggests that APA may be a 'missing link' in our understanding of psychiatric genetics," explained Dr. Xiangmin Xu, senior author of the study. "It helps explain why some individuals with genetic risk factors develop disorders while others don't."

The study highlights several specific genes where APA appears to play a particularly important role:

- DDHD2: Associated with schizophrenia risk, this gene's APA pattern may affect how neurons communicate.

- FADS1: Linked to bipolar disorder, changes in this gene's APA could influence the metabolism of fatty acids crucial for brain function.
- GABRA2: Also associated with bipolar disorder, APA of this gene may alter the balance of inhibitory signaling in the brain.
- MTCH2: Connected to depression risk, APA of this gene could impact mitochondrial function and energy production in brain cells.

The researchers also found that genes affected by APA in psychiatric disorders tend to be involved in intracellular transport and cellular localization pathways. This suggests that APA may influence how proteins are moved and positioned within neurons, potentially disrupting normal brain function.

"These findings have significant implications for how we approach both research and treatment of psychiatric disorders," said Dr. Paff. "By understanding the role of APA, we may be able to develop more targeted therapies that address the root causes of these conditions at a molecular level."

The study's authors caution that more research is needed to fully understand the implications of these findings. However, they are optimistic about the potential for this work to lead to new diagnostic tools and treatment strategies.

"This line of work opens up a whole new dimension in psychiatric genetics," Dr. Xu concluded. "It's an exciting time in the field, and we believe this work will accelerate our progress towards better outcomes for individuals living with these challenging conditions."

More information: Paff, M. et al. Roles of alternative polyadenylation in psychiatric disorder risk, *Genomic Psychiatry* (2024). DOI:

10.61373/gp024i.0049. gp.genomicpress.com/wp-content … GP0049-Paff-2024.pdf

Provided by Genomic Press