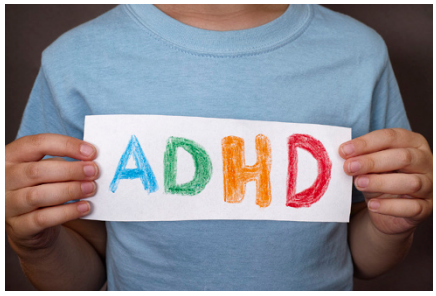
A new research path into attention disorders

The gene *PTCHD1* is mutated in about 1% of human patients suffering from intellectual disability and autism spectrum disorders, and *PTCHD1* deletion is associated with attention-deficit hyperactivity disorder (ADHD). To bridge the gap between this gene and ensuing behavioral deficits, a group led by Guoping Feng (Massachusetts Institute of Technology, Cambridge, MA) and Michael Halassa (New York University, NY) examined the effects of deleting *Ptchd1* in a transgenic mouse model (*Nature* **532**, 58–63; 2016). Their experiments uncover several important aspects of the role of this gene in a small brain structure, the thalamic reticular nucleus (TRN), in neurodevelopmental syndromes related to ADHD.

The *PTCHD1* gene encodes a transmembrane protein that is believed to act as a membrane receptor. The research team discovered that, during early development, *Ptchd1* is expressed selectively in the mouse TRN, which regulates neuronal activity between



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the thalamus and cortex. In order to study the effects of *Ptchd1* deletion, the researchers created mice that lacked a functional *Ptchd1* gene, and examined neuronal and behavioral effects of this manipulation.

When neuronal recordings in the TRN were compared between *Ptchd1*-knockout mice and control mice, the researchers found a significant reduction in repetitive bursting activity, a reduction in intracellular calcium, abnormal sleep-related activity, and altered responses to visual stimuli. These findings suggest a strong role for *Ptchd1* in normal and stable TRN activity. In addition to these neural deficits, the *Ptchd1*-knocokout mice exhibited hyperactivity and weaker performance on a task involving attention. The researchers performed further experiments to restrict *Ptchd1* deletions primarily to the TRN, providing convincing evidence that the altered attention of the knockout animals was the result of dysfunctional TRN activity and not a loss of *Ptchd1* in other brain regions.

Importantly, the team of researchers attempted to rescue the aberrant neuronal activity by applying a drug that they hypothesized could mitigate the changes observed in the TRN. After drug injection, *Ptchd1*-knockout mice no longer exhibited hyperactivity and showed improved performance on an attention-based task in the presence of distractors. The results of this study provide a potential molecular pathway for future studies and treatment in humans afflicted with attention disorders.

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