NEWS

Loss of CHD8 from cerebellum disrupts movements, not social behaviors

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26 APRIL 2021

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Deleting the gene CHD8 from specific cells in the cerebellum, a brain region important for coordinating movement, **leads to motor deficits** but does not alter social behaviors in mice, a new study suggests.

CHD8 is one of the genes most frequently mutated in people with autism, but researchers haven't been able to pinpoint how these mutations relate to **core autism traits**.

The cerebellum seemed like a prime candidate area for the gene's involvement, says **Keiichi Nakayama**, professor of molecular and cell biology at Kyushu University in Fukuoka, Japan, who led the new study. Previous studies showed that removing other autism-related genes, including **TSC1**, **SHANK2** and **PTEN**, from this region **causes social difficulties** in mice.

"But our study shows that CHD8 deficiency in the cerebellum is not related to [autism traits]," Nakayama says.

Still, the findings provide evidence that disrupting CHD8 in particular cell types can seriously impair development of the cerebellum and contribute to **motor coordination problems**, says **Alex Nord**, associate professor of neurobiology, physiology and behavior at the University of California, Davis, who was not involved in the study.

"It's a negative result," Nakayama says. "But it's an important one."

Gene tinkering:

Nakayama's team began by engineering mice that were missing both copies of CHD8 in neural stem cells, which give rise to neurons throughout the brain. These mice had slowed growth, reduced body weight and malformations of the cerebellum compared with control mice.

The team then targeted specific cell types that make up the cerebellum. Deleting the gene from neurons called Purkinje cells, which send information from the cerebellum to other brain regions, had virtually no effect on cerebellar development, they found. However, mice missing the gene in cerebellar granule cells — tiny, densely packed cells that make up around three-quarters of brain neurons — had unusually small cerebellums.

The granule cells in these mice divided less and differentiated prematurely compared with such cells in control mice. The cells also showed dampened signaling to other neurons.

Compared with control mice, those lacking CHD8 in granule cells performed poorly on tests requiring balance and coordination but showed no difference on tasks that assess social behaviors.

The results appeared in *Cell Reports* in April.

Under construction:

The findings show that CHD8's loss may cause significant structural changes to the cerebellum in autistic people, says **Peter Tsai**, assistant professor of neurology at the University of Texas Southwestern in Dallas, who was not involved in the study. He also says it's still too soon to rule out the cerebellum's involvement in shaping autism-related behaviors.

The granule neurons targeted in the study are located largely in the frontal region of the cerebellum, an area critical for regulating movements. Targeting granule neurons in more posterior regions of the cerebellum, which are associated with social and behavioral processes, might have resulted in autism-related traits in the mice, Tsai says.

He also questions the Purkinje cell results: The study looked at how CHD8 deletion affected these cells from 6 days after birth onward, but it's possible that targeting the cells earlier in development would have produced different results, he says.

"[Purkinje cells] really may just not have a role," Tsai says. "But I think with the caveat that it may actually have a role earlier in development and just we don't know."

Both limitations reflect inherent constraints of the genetic tools the team used, Nord says. An interesting alternative approach might involve introducing a virus into the cerebellum to selectively target specific cells or regions, he adds.

Nakayama says his team plans to conduct studies to look at how CHD8 mutations may be

implicated in other brain regions and cell types. In particular, his team is interested in exploring the effects CHD8 may have on other regions of the brain such as the prefrontal cortex.