NEWS

Medley of models reveals misbehaving pathways in autism-linked condition

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Genes involved in axonal guidance and other key pathways are expressed differently in people with mutations in the autism-linked gene KMT5B, according to a new **study**.

KMT5B codes for an enzyme that adds **methyl group tags** to histones, the protein component of chromosomes. The chemical tags wrap DNA more tightly around histones, which tends to diminish gene expression. The gene may also help **fix rips** in the genetic code, but scant research has explored how it contributes to autism.

“This gene doesn’t get enough love,” says lead investigator **Holly Stessman**, assistant professor of neuroscience at Creighton University in Omaha, Nebraska.

KMT5B methylates a histone region called H4K20, a process that appears to be necessary for typical **brain development**. Previous work from **Stessman**’s lab points to a role in regulating social behavior: Mice missing the gene are smaller and **less social** than their wildtype littermates. But it’s unclear which pathways are affected in people harboring KMT5B variants.

To begin to try to bridge that gap, the new study combined deep phenotyping of people who have KMT5B mutations with experiments in mice and zebrafish.

“This is a great example of the combined clinical and basic science project,” says **Zhen Yan**, professor of physiology at the University of Buffalo in New York, who was not involved in the study.

Stessman and her colleagues collected genetic and detailed clinical data from 43 people with KMT5B mutations, the largest sample analyzed to date. Within the cohort, 17 people have missense mutations, which alter a single amino acid in the protein and often have mild effects. The remaining 26 have loss-of-function mutations, substantial DNA changes that disrupt the gene's function. All participants who had been assessed were found to have intellectual disability or developmental delay.

Of the participants for whom data were available, many have distinctive facial features and **macrocephaly**. In contrast to previous reports — in which entire cohorts met the diagnostic criteria for autism — only 59 percent of the group had received a diagnosis. But it's not clear whether the condition is underdiagnosed among people with KMT5B variants or just not a defining feature of KMT5B syndrome, Stessman says.

Almost all of those who were assessed exhibited hypotonia, or low muscle tone, and about one-third had heart problems at birth. Both traits had not been reported before in the literature.

The researchers took blood samples from seven participants aged 3 to 12 years and extracted RNA from lymphoblast cells. Compared with neurotypical children matched for age and sex, the participants showed skewed expression in 1,302 genes. Many of these genes contribute to axonal guidance and cell signaling.

Turning to animal models, the team identified dysregulated genes in mice missing one or both copies of KMT5B. Loss of KMT5B turned up the expression of 161 genes and weakened the activity of 35, including the autism-linked genes **GRIN2B** and **WDFY3**.

Just eight genes showed expression changes in both people and mice. "Comparing identical brain regions of humans and mice might give more convergent gene targets," Yan says.

When they analyzed KMT5B expression in wildtype mice and zebrafish, the group found brain-wide expression during development. But in adult mice, expression is restricted to select brain regions where neurogenesis takes place, such as the hippocampus.

Maturing mice: KMT5B RNA is expressed most strongly in the developing nervous system.

Because KMT5B expression peaks when neuronal production is highest, mutations in it likely perturb the creation and differentiation of neurons, says **Margarita Behrens**, research professor at the Salk Institute in San Diego, California, who was not involved in the research. It will be interesting to learn KMT5B's role during neurogenesis, which appears to drive its link with intellectual disability and autism-like traits, she adds.

The findings were published 10 March in *Science Advances*.

The study provides detailed reference data and the animal tools needed to move the field forward, says **Zhaolan Zhou**, professor of genetics at the University of Pennsylvania in Philadelphia, who was not involved in the study.

But whether KMT5B alters gene expression directly — through changes in histone methylation — or by some other route is unknown, Zhou says. “The mechanism remains unclear.”

Stessman next plans to tease apart the gene’s dual functions to uncover which phenotypes arise from altered histone methylation versus reduced DNA repair. Doing so may help pinpoint which function is most relevant to the condition, she says.

Probing KMT5B’s role in fixing broken DNA may also shed light on the connection between **autism and cancer**, she adds. Studies have linked the gene to **leukemia** and other **cancers**, possibly caused by defective DNA repair. Because the brain develops quickly, it accumulates mutations faster than other tissues, and so a lack of DNA repair in people with KMT5B mutations may increase the burden of mutations more than the brain can tolerate, she says.

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