NEWS

# Molecular mechanisms: Mouse models autism, Rett syndrome

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Painted peaks: Mice lacking CDKL5 (bottom) have weaker brain waves, suggesting weaker connections between distant neurons, compared with controls (top).

Mice lacking **CDKL5**, a gene linked to both Rett syndrome and autism, show features associated with both disorders, according to a study published 26 December in the *Proceedings of the National Academy of Sciences*[1].

The study also found that CDKL5 regulates pathways involved in cell growth and development.

Cells send signals through choreographed cascades in which proteins activate and inactivate each other. CDKL5's role is to add a phosphate group to other proteins, priming them for activity. Ultimately, CDKL5 helps **stabilize active neuronal connections**, a process that underlies learning, memory and brain development.

Mutations that inactivate CDKL5 lead to an **atypical form of Rett syndrome**, characterized by seizures that begin early in life and problems with motor skills. And large disruptions to chromosomal regions that encompass CDKL5 are **more common in people with autism** than in controls, linking the gene to autism as well.

In the new study, researchers engineered male mice to carry a mutation that prematurely shortens the CDKL5 protein. CDKL5 is on the X chromosome, so male mice have only one copy of the

gene.

These mice spend an equal amount of time in an empty chamber and one that contains another mouse, whereas controls prefer to visit a potential playmate. The mutant mice are also not good at building nests. Both features suggest social deficits similar to those seen in people with autism.

When placed on a rotating cylinder, the mutant mice fall off more often than controls do. They get better with practice, but remain clumsier than controls, suggesting that they have problems with motor coordination, but not motor learning.

The mice are also hyperactive and clasp their paws together, a feature seen in other mouse models of Rett syndrome. This clasping is reminiscent of the hand flapping common in people with Rett syndrome.

CDKL5 mice have normal brain rhythms as measured by electroencephalography, the study found. This is inconsistent with the susceptibility to seizures seen in people with a mutation in CDKL5. However, neurons in the brains of the mutant mice don’t work in sync the way neurons in control mice do.

The mutant neurons also have fewer proteins with a phosphate tag than those from controls, the study found. Many of the proteins affected feed into one of two autism-linked signaling pathways — **PTEN** and mTOR.

## References:

**1: Wang I.T.** *et al.* **109**, 21516-21521 (2012) **PubMed**