NEWS

Working with mice? Question their background

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A standard mouse strain used by researchers worldwide harbors a rogue mutation that impairs immune cell development — and may confound results[1]. The findings are a striking reminder that a mouse's genetic background may have a significant influence on its behavior and biology.

The researchers came to this conclusion after they first mistakenly attributed the mice's problems with immune cell development to two mutations they had introduced and could not replicate the results. They later traced the effect to a mutation that inactivates a gene called DOCK2. The mutation, they found, had cropped up in a strain of mice called C57BL/6 (or B6), sold by Harlan Laboratories, an international company headquartered in Indiana. They describe this mutation, and its potential confounds, 31 May in *Cell Reports*.

B6 mice are an inbred strain, meaning that each mouse's genes are identical on both copies of its chromosomes. Researchers like to use inbred strains because the same genetic background persists across generations, allowing for consistency in experiments.

The new study is a sharp reminder that, in fact, mutations may crop up in different stock strains, introducing inconsistencies, says lead researcher **Shiv Pillai**, professor of medicine at Harvard Medical School. B6 mice obtained by another supplier, Jackson Laboratories, do not carry this mutation.

These issues are important because mouse strains with the same mutation linked to a condition may **behave differently** if their genetic background differs. This problem has dogged autism research: Mice that show promising autism-like behaviors in the one lab do not in another, for example. Researchers may ascribe these differences to small variations in the background, but they don't explore further.

"People don't take this stuff as seriously as they should," says **Valerie Bolivar**, assistant professor of biomedical sciences at the State University of New York at Albany. "It's almost swept under the rug: It gets a hand wave, then isn't discussed," she says.

Mystery mutation:

Pillai and his team created mice that lack one of two proteins they thought might play a role in the development of B cells, the immune cells that produce antibodies[2]. When mice missing either protein had problems with B-cell development, it seemed logical that the mutations were to blame, Pillai says. But it turned out they weren't. "We found out the hard way," Pillai says.

The researchers had crossed their mutant mice with B6 mice from Harlan Laboratories to give them a consistent genetic background. But when they bred them with B6 mice from Jackson Laboratories, located in Bar Harbor, Maine, the problem with B-cell development disappeared.

It took two years for the researchers to figure out what was going on. Eventually, their analysis revealed a mutation that inactivates DOCK2.

Another team had found the same mutation in DOCK2 in their mice years earlier and assumed it had arisen spontaneously[3]. Instead, it probably stemmed from the same strain that had waylaid the B-cell study, Pillai says. Several other published findings on immune cell development from other teams might need to be reexamined, Pillai says.

"There are a number of other mice that I'm not saying anything about," he says. "We know what they are likely to be, but without doing the experiments ourselves we cannot make any claims."

Profound pitfalls:

The Harlan B6 mice could also have influenced autism research that focuses on **the role of the immune system**, Bolivar says. However, many autism researchers use the Jackson Laboratories strain that does not carry this mutation.

The findings highlight the pitfalls of using inbred mouse strains, says **Guoping Feng**, professor of brain and cognitive sciences at the Massachusetts Institute of Technology. Having the same variant on both copies of a gene brings the effects of even mild mutations to the surface. “Mixed background might be much better to study for behavior and neurodevelopmental disorders,” he says.

Feng says he has found that inbred mice lacking the autism-linked gene **SHANK3** have less pronounced behavioral abnormalities than do those with a mixed genetic background.

Bolivar also has firsthand experience with the vagaries of mouse strains. Like Pillai’s team, she was unable to replicate problems with learning and memory when she switched to a mouse strain with a different genetic background.

Her team has been tracking down the origin of these differences. “The technology is now getting to the point that we can go after these mutations. And they can be very important,” she says.

REFERENCES:

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