NEWS

# Roundworm roundup may reveal function of autism genes

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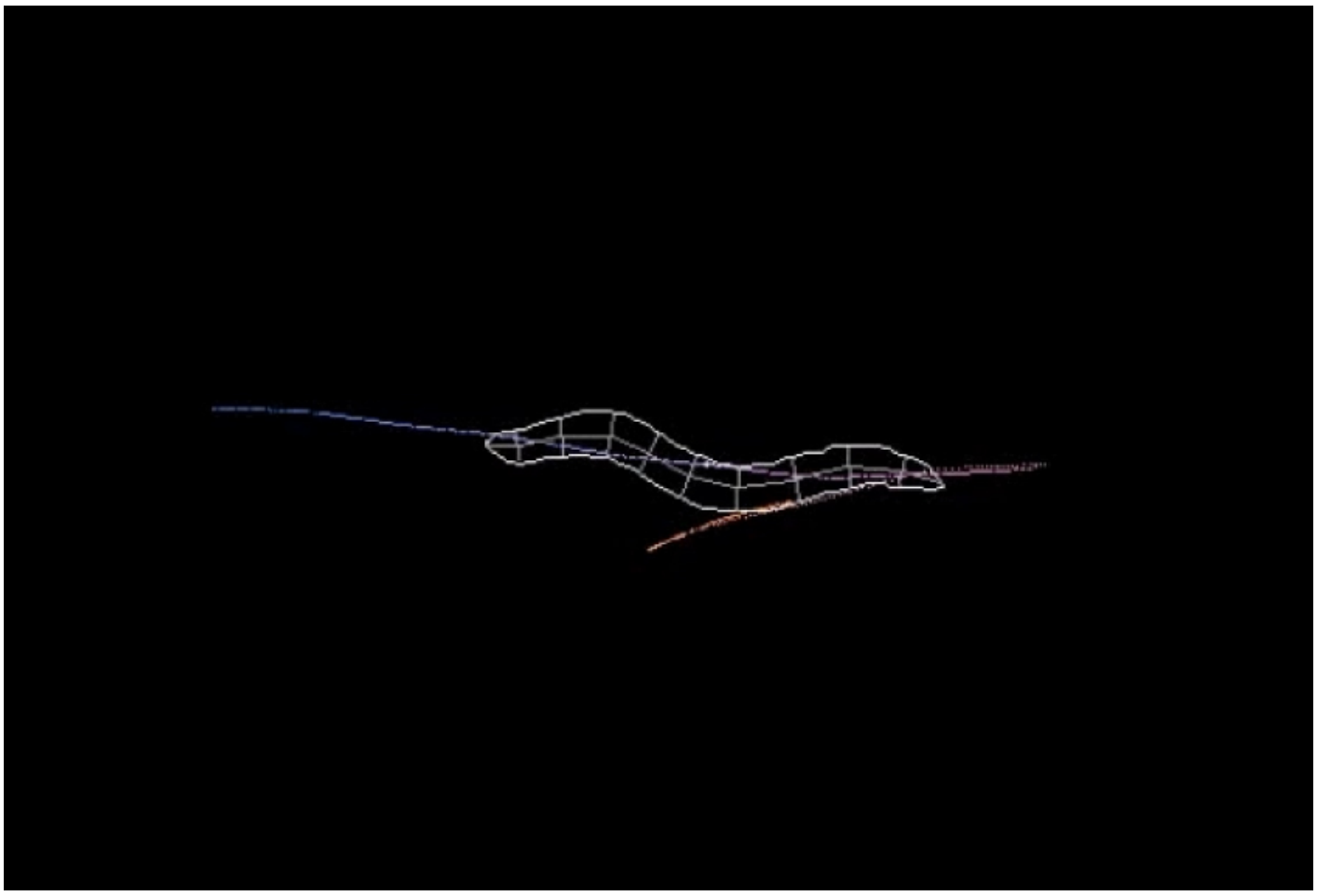

Tracking how roundworms crawl has enabled scientists to determine that many autism genes are involved in sensory processing and learning.

Two problems with autism genetics are that “there are too many genes of unknown function and too many mutations of unknown significance,” says Troy McDiarmid, a graduate student in **Catharine Rankin**’s lab at the University of British Columbia in Vancouver. McDiarmid presented the unpublished findings at the **2018 Society for Neuroscience annual meeting** in San Diego, California.

Enter roundworms, also known less evocatively as *Caenorhabditis elegans*. Despite the worms’ evolutionary distance from people, their genome contains equivalents of many human genes. The worms are easy to manipulate genetically, reproduce quickly and are easy to maintain in the lab.

“We have to go faster than we can in mammals” because genetic information about autism is accumulating at such a rapid clip, McDiarmid says.

In the new study, researchers mail-ordered 87 mutant worm strains, each carrying a different mutation; the mutations are in 79 genes that may be involved in autism. The researchers placed the worms in lab dishes, captured videos of them and analyzed their morphology and behavior using a computer program called Multi-Worm Tracker.

The software can analyze up to 40 worms in a single dish and can evaluate “any metric you can imagine in two dimensions,” McDiarmid says — length, curviness, speed and direction of crawling and so on. The researchers analyzed 26 traits in about 200 worms of each strain.

They recorded 10 minutes of baseline crawling and then tapped the side of the dish holding the worms 30 times. Worms typically reverse direction in response to this stimulus. But all of the autism strains are either hyper- or hyposensitive to this tapping, crawling backward for longer or shorter periods, respectively, than controls do.

After five minutes of quiet, the researchers tapped the dish one more time. Worms typically crawl in reverse, but for a shorter time than they do in response to the first set of taps. This suggests that they can learn to identify and tune out irrelevant information, a process called habituation.

Mutations in 19 of the 79 genes produce worms that reverse-crawl for longer than controls do after this final tap, suggesting impaired habituation.

## Salt swap:

Looking for patterns of similar features among the worms, the researchers found that mutations in 11 of the autism genes produce worms with sensory hypersensitivity and impaired habituation. The mutated genes in this cluster are a mix of well-established autism genes such as **CHD8** and more tenuous ones such as GAPVD1.

The researchers cross-bred worms bearing mutations in these 11 genes and found that baby

worms bearing two mutations are no more severely affected than their parents. This suggests that the 11 genes in this cluster all act in the same molecular pathway, the researchers say.

In a second set of experiments, the team investigated the effects of 20 different mutations in the gene **PTEN**. Mutations in a single DNA base have been **found throughout this gene** in people with autism. Similar mutations are also present in typical people, however, so scientists have been unsure sure which of the mutations are harmful.

The researchers assessed the worms' attraction to salt. Worms typically crawl toward salt because it indicates that food is nearby, but worms lacking DAF-18, the worm version of PTEN, crawl away from it. Inserting PTEN into worms lacking DAF-18 restores their salt-seeking behavior.

The researchers used CRISPR-CAS9 gene-editing technology to replace DAF-18 with versions of PTEN bearing mutations found in autistic individuals[1].

All of the worm strains with autism-linked mutations crawl away from the salt, the researchers found. This was surprising, says McDiarmid, given that some PTEN mutations do not seem to be harmful.

The work is part of a larger effort to screen PTEN mutations in a variety of model organisms, including yeast, flies and rats; a mutation that has harmful effects in multiple species is also likely to be harmful in people.

Worms lacking DAF-18 show a dampened response to taps on their dish but, as with the salt test, swapping in PTEN reverses the effect. McDiarmid plans to conduct the dish-tapping protocol with worms bearing different autism-associated PTEN mutations.

*For more reports from the 2018 Society for Neuroscience annual meeting, please **click here**.*

**REFERENCES:**

1. McDiarmid T.A. *et al. Dis. Model Mech.* Epub ahead of print (2018) **PubMed**