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Neurobiologists identify animal model for a deadly human metabolic disorder

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In medical research, finding a reliable and cost-effective animal model can greatly enhance success in identifying disease mechanisms and genetic pathways, potentially cutting years off drug testing regimes and development of new treatment strategies.

Now, University of Massachusetts Amherst neuroscientist Gerald Downes and colleagues have developed just such a model, a mutant zebrafish, to study Maple Syrup Urine Disease (MSUD). It is an inherited metabolic disorder that causes affected individuals to smell like maple syrup. Untreated, it can result in mental retardation, profound neurological damage, severe dystonia, coma and death. This new model is described in an early online version of the March issue of the journal Disease Models *and Mechanisms*.

A mouse model does exist and has been useful to provide new insight into the disorder, Downes says, but mouse studies can be expensive and time-consuming. Many of the cellular and molecular mechanisms that promote brain injury in MSUD are not known, and new platforms are needed to better understand how this disease causes brain injury and to develop new therapies. MSUD affects about one in every 185,000 children but the rate of incidence can be about 10 times higher in certain religious communities.

Downes, who leads a research team using zebrafish to investigate human neurological disorders, explains that MSUD causes disease by disrupting the proper metabolic breakdown of three amino acids: Isoleucine,

leucine and valine, found in protein-rich foods such as eggs, meat and milk. These amino acids and their by-products accumulate to toxic levels in the body, with devastating effects on the brain and nervous system. A major symptom is severe dystonia, a neurological condition that results in twisting, abnormal postures due to sustained muscle contractions.

As part of this study supported by the National Institute of Neurobiological Disorders and Stroke at the National Institutes of Health, Downes and doctoral student Timo Friedrich examined a zebrafish mutant named questschkommode, or que that exhibits abnormal swimming behavior. They analyzed high-speed video of larval zebrafish swimming in response to a light touch and found that que mutants perform what is called "accordion behavior."

Instead of normal swimming with left and right tail flips, the mutant que fish compress like an accordion along the nose-to-tail axis (questschkommode means "squeezebox" in German). This behavior is believed to be similar to the dystonia MSUD-affected human patients display during periods of severe metabolic distress.

Collaborating with Aaron Lambert and Mark Masino at the University of Minnesota to record and measure nerve activity, the UMass Amherst researchers further confirmed that dystonia in the que mutant originates in the brain and spinal cord, not in muscle, indicating that the nervous system functions abnormally.

Downes and Friedrich then spent about four years identifying a mutation in the zebrafish dihydrolipoamide branched chain transacylase E2 (dbt) gene. The human version is known to be required for isoleucine, leucine and valine metabolism, and mutations can cause MSUD, they say. Mirroring MSUD, que mutants also have abnormal amino acid metabolism. "The same three amino acids that accumulate in humans also accumulate in this fish, anywhere from six to 10 times higher than

normal for each, which is the same profile as in humans," Downes points out.

Due to this defect, que larva die young, after about five days of life, the researchers say. They also show that que mutants contain reduced levels of the neurotransmitter glutamate, known to be important for nervous system function in many species including humans. Abnormal glutamate levels could be a key trigger of dystonia seen in untreated MSUD.

"It's fantastic to solve this mystery," says Downes. "We've been looking at this mutant for five years. To actually put together a model of what's going on, to take it all the way from a fish that can't swim normally to come up with a useful model to benefit human treatment is incredibly satisfying."

"We'd like to take it farther in the future and use this to develop new MSUD therapies by systematically screening hundreds, even thousands of chemical compounds. We can raise large numbers of zebrafish because of their small size and easy care."

Since discovering the new model, Downes has accepted an invitation to speak at the 16th Biennial MSUD Family Support Group Symposium in Philadelphia in June 2012. "I'm thrilled that our work might be helpful to people in a direct way. I very much look forward to meeting people affected with MSUD and hearing what they are interested in, to figure out how I can help fight this disease."

Provided by University of Massachusetts at Amherst