A nutrient called carnitine might counteract gene mutations linked with autism risks

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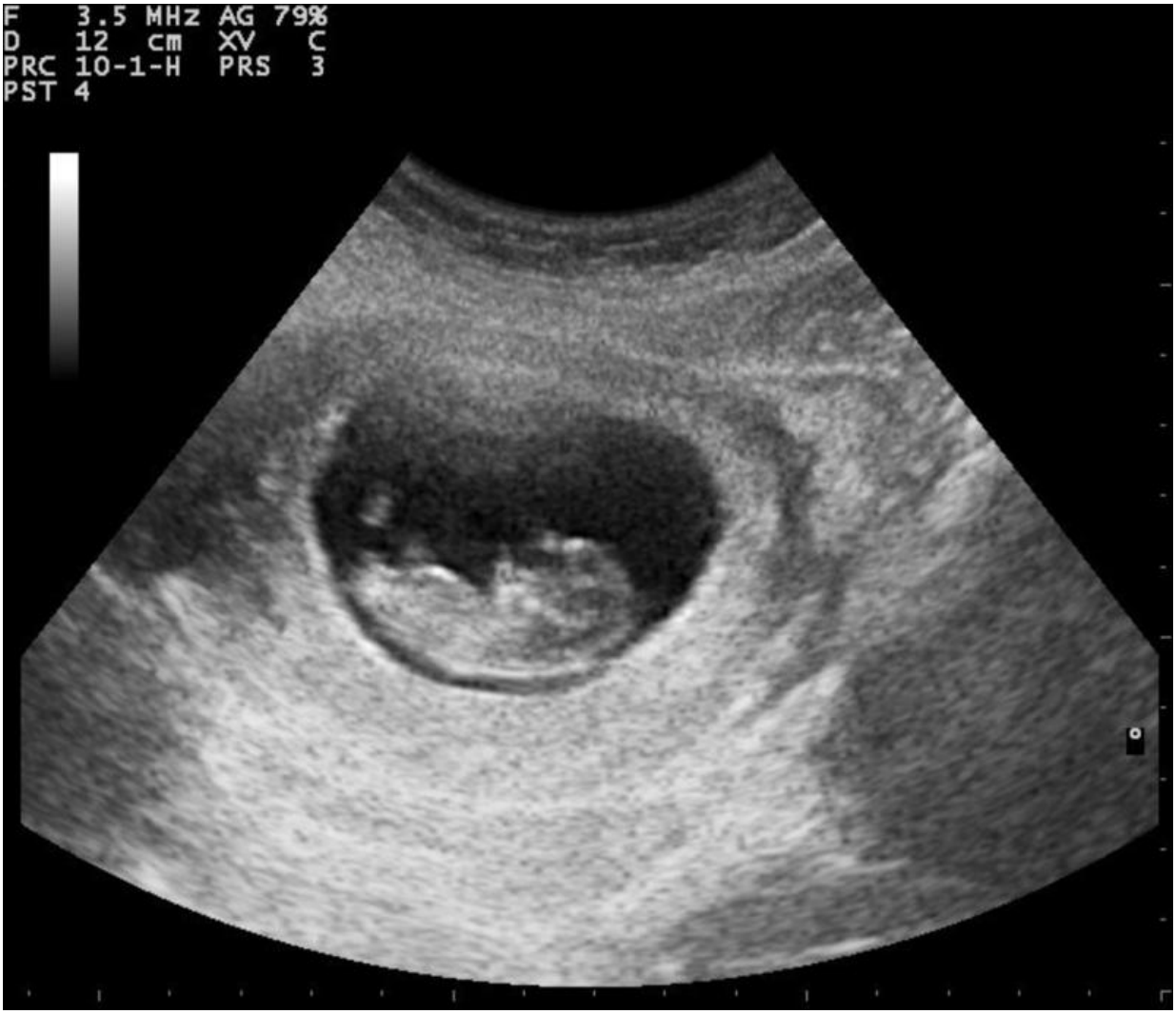

TLMHE mutations could affect fetal brain development. Credit: Wikimedia Commons, CC BY-SA

Autism spectrum disorders (ASDs) affect about one percent of the world's population. In the United States alone, about 1 in 68 children are on the spectrum, and between 40 and 60 percent of them are also diagnosed with some degree of intellectual disability.

The annual cost associated with ASD in the United States is high - presently estimated to be US$236-$262 billion. If diagnoses continue to grow at the current pace, it will exceed $460 billion by 2025, more than the total cost of diabetes.

Scientists still aren't sure what causes ASD, but evidence suggests it's probably the result of complex interactions between genetic and environmental factors that affect brain development. So far hundreds of genes whose mutations are associated with ASD have been identified. Many of them are known or predicted to play critical roles in the cells that make up the building blocks of the brain.

Learning more about these genes – and their mutations – might help us understand some of the root causes of ASD, and perhaps find ways to lower the risk that a child will have it.

We decided to take a closer look at mutations in one of these genes, called TMLHE, which is required for a critical chemical reaction that lets cells burn fat molecules to produce energy. We wanted to understand how a TMLHE mutation could increase autism risk and whether we could counteract the effect of the mutation.

Neural stem cells and the developing brain

When we examined the effect of TMLHE mutations in mice, we found these mutations specifically affect neural stem cells during early stages of brain development.

Neural stem cells create all of the specialized cells that make up the brain. When they divide to create two "daughter" cells, one typically becomes a specialized brain cell, such as a neuron, and the other remains a neural stem cell.

This means that the population of neural stem cells is maintained, and the brain building work can continue. Although this process occurs throughout one's lifetime, it is the most active during embryonic brain development.

If the neural stem cell population is not maintained at the proper level when the brain is developing, there won't be enough stem cells left to produce the right number and right kind of specialized brain cells. The result is an abnormally wired brain.

We find this to be precisely the problem that TMLHE mutations created in mice. Too often, neural stem cell division created two specialized cells, instead of one specialized cell and one neural stem cell.

What does a TMLHE mutation do to neural stem cells?

TMLHE mutations make it difficult for neural stem cells to produce energy, or to maintain a correctly oxidized environment, which is why they often don't divide properly.

Cells produce energy by processing fat molecules. For this to happen, fat molecules need to get to the mitochondria, the powerhouses of the cell, to be broken down. A nutrient called carnitine helps transport fat to these parts of the cell.

This is where TMLHE comes in. While we can get carnitine from food –

milk and meat, for instance – our bodies can also produce it. But the TMLHE gene is required for carnitine synthesis, so a mutation in this gene can lead to carnitine deficiency. This affects energy production in cells and can also result in a cellular environment that is too oxidized for the cell to function properly, which makes problems for the neural stem cell when it divides.

But we also found that this neural stem cell defect is corrected when carnitine is added to TMLHE-deficient cells. This restores their ability to burn fat into energy and to maintain a proper environment within mitochondria, and restores proper cell division behavior to TMLHE-deficient neural stem cells.

TMLHE mutations are surprisingly common

Two recent studies have found that the prevalence of TMLHE mutations in human populations may range from about 1 in 350 to about 1 in 900. In most cases, these people would be unaware that they carry a copy of the defective gene.

Our research raises the possibility that the increased autism risk associated with TMLHE mutations might be effectively managed by making sure the embryo has enough carnitine during critical stages for brain development. It also seems that sufficient carnitine is required at very early stages of pregnancy – far earlier than previously suspected.

Either parent can pass on a defective TMLHE gene. Girls have two copies of the gene, inheriting one from each parent. Boys, however, have only one copy of the gene, which they inherit from the mother. If a male fetus inherits the mutant TMLHE gene, it will be unable to produce its own carnitine and will rely on the mother for its carnitine supply.

Hypothetically, a woman who carries a TMLHE mutation could take

supplemental dietary carnitine during pregnancy to try to minimize the associated ASD risk – particularly for male babies.

Carnitine deficiency may be an underestimated ASD risk

While hundreds of genes are associated with ASD risk, the surprisingly high incidence of TMLHE mutations in human beings suggests the impact of carnitine deficiency on ASD risk may be badly underestimated. This is a particularly interesting possibility given that diet might be a significant contributing factor to ASD risk associated with TMLHE mutations.

Results from our mouse study, and a recent study in which an autistic child with a TMLHE mutation was treated with carnitine supplementation, suggest that prenatal carnitine supplementation might well be worth considering. However, more research, particularly clinical trials on human populations, will be needed to further establish the role of carnitine in autism prevention.

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