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Defective carnitine metabolism may play role in milder forms of autism

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The deletion of part of a gene that plays a role in the synthesis of carnitine – an amino acid derivative that helps the body use fat for energy – may play a role in milder forms of autism (non-dysmorphic autism), said a group of researchers led by those at Baylor College of Medicine and Texas Children's Hospital.

"This is a novel inborn error of metabolism," said Dr. Arthur Beaudet, chair of molecular and human genetics at BCM and a physician at Texas Children's Hospital, and the senior author of the report that appears online in the *Proceedings of the National Academy of Sciences*. "How it is associated with the causes of autism is as yet unclear. However, it could point to a means of treatment or even prevention in some patients."

Beaudet and his international group of collaborators believe the gene deletion leads to an imbalance in carnitine in the body. Meat eaters receive about 75 percent of their carnitine from their diet. However, dietary carnitine levels are low in vegetarians and particularly in vegans. In most people, levels of carnitine are balanced by the body's ability to manufacture its own carnitine in the liver, kidney and brain, starting with a modified form of the amino acid lysine.

Carnitine deficiency has been identified when not enough is absorbed through the diet or because of medical treatments such as kidney dialysis. Genetic forms of carnitine deficiency also exist, which are caused when too much carnitine is excreted through the kidneys.

In this new inborn error, there is a deletion in the second exon – the protein-coding portion of a gene – of the TMLHE gene, which includes the genetic code for the first enzyme in the synthesis of carnitine (TMLHE stands for trimethyllysine epsilon which encodes the enzyme trimethyllysine dioxygenase).

Studies in the laboratory that identified the deletion were led by Dr. Patricia B.S. Celestino-Soper, as a graduate student in Beaudet's laboratory at BCM and by Dr. Sara Violante, a graduate student in the laboratory of Dr. Frédéric M. Vaz of the Academic Medical Center in Amsterdam.

To determine the frequency of the gene deletion, Beaudet and his colleagues tested male autism patients who were the only people with the disorder in their families (simplex families) from the Simons Simplex Collection, the South Carolina Early Autism Project and Houston families. In collaboration with laboratories and researchers in Nashville, Los Angeles, Paris, New York, Toronto and Cambridge (United Kingdom), they tested affected male siblings in families with more than one male case of autism (multiplex families).

When they looked at the TMLHE genes in males affected by autism and compared them to normal controls, they found that the gene alteration is a fairly common one, occurring in as many as one in 366 males unaffected by autism. It was not significantly more common in males within families in which there is only one person with autism. However, it is nearly three times more common in families with two or more boys with autism.

Beaudet said most of the affected males with the deletion did not have syndromic autism that is frequently associated with other serious diseases. In many instances, syndromic autism affects physical development as well as cognitive, which is reflected in their facial

features as well as other parts of their bodies. None of the six boys affected with autism (where information was available) had the syndromic form of disease. Their intelligence quotients and cognitive scores varied, with some being far below normal and others normal.

"Most of the males we identified with the TMLHE deficiency were apparently normal as adults," said Beaudet, although detailed information on learning and behavior was not available on these "control" males. "The gene deletion is neither necessary nor sufficient in itself to cause autism."

"TMLHE deficiency itself is likely to be a weak risk factor for autism, but we need to do more studies to replicate our results," Beaudet said. He estimated that at the rates found in his study, the deficiency might be a factor in about 170 males born with autism per year in the United States. This would equate to about one-half of one percent of autism cases.

The authors from Amsterdam found major increases in some carnitine-related chemicals and absence of others in both urine and plasma. These metabolic alterations were found to be predictive of the dysfunction of the TMLHE gene and therefore can be used to identify males with this disorder

It remains uncertain whether TMLHE deficiency is benign or causes autism by affecting the function of neurons through toxic accumulation or deficiency of a variety of chemical metabolites.

"We believe that the most attractive hypothesis at this time is that the increased risk of autism is modified by dietary intake of carnitine from birth through the first few years of life," said Beaudet.

He and his colleagues are undertaking three studies to further their understanding of the TMLHE deficiency. In one, they will attempt to

replicate the findings in multiplex families. In a second, they will study carnitine levels in the cerebrospinal fluid of infants with autism – both those who have the gene deficiency and those who do not. In a third study, they plan to begin giving boys under age 5 with autism carnitine or a related supplement and determine whether this improves the behavior of those with the TMLHE deficiency and those without.

More information: "A common X-linked inborn error of carnitine biosynthesis may be a risk factor for non-dysmorphic autism," by Patrícia B.S. Celestino-Soper et al. *PNAS*, 2012.

Provided by Baylor College of Medicine