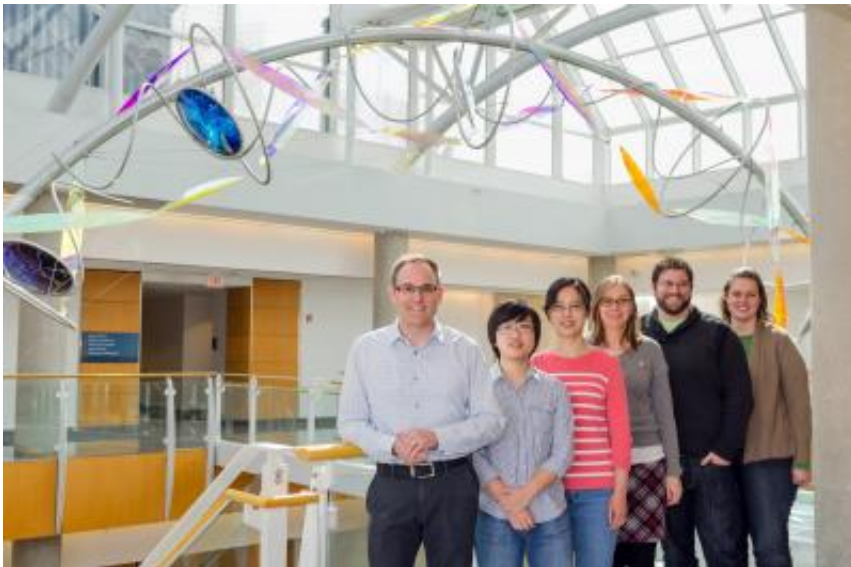


# Discovery helps explain how children develop rare, fatal disease

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Michael Petris (left), an associate professor of biochemistry, and his research team found that the gene *ATP7A* is essential for the dietary absorption of the nutrient copper, a mineral deficient in those with a rare genetic disorder called Menkes disease. Credit: Aaron Duke/University of Missouri

One of 100,000 children is born with Menkes disease, a genetic disorder that affects the body's ability to properly absorb copper from food and leads to neurodegeneration, seizures, impaired movement, stunted growth and, often, death before age 3. Now, a team of biochemistry researchers at the University of Missouri has published conclusive scientific evidence that the gene *ATP7A* is essential for the dietary

absorption of the nutrient copper. Their work with laboratory mice also provides a greater understanding of how this gene impacts Menkes disease as scientists search for a treatment.

Humans cannot survive if their bodies are lacking the ATP7A gene, yet children can develop Menkes disease when the gene is mutated or missing. Previously, scientists did not have a good model to test the gene's function or develop an understanding of the underlying causes of the disease symptoms. In his new study, Michael Petris, associate professor of biochemistry, was able to modify mice so that they were missing the ATP7A gene in certain areas of the body, specifically the intestinal track where [nutrient absorption](#) takes place.

"These findings help us to understand where in the body the function of this gene is vital and how the loss of the gene in certain tissues can give rise to Menke's disease," said Petris, who is a researcher in the Bond Life Sciences Center and holds an appointment in the Department of Nutrition and [Exercise Physiology](#). "We want to continue to explore the underlying biology of Menke's disease to determine where we should focus our research efforts in the future. If we know which organs or tissues are most responsible for transporting copper throughout the body, we can focus on making sure the gene is expressed in those areas. This disease is ideal for [gene therapy](#) down the road."

Petris found that young mice missing the ATP7A gene in their [intestinal cells](#) were unable to absorb copper from food, resulting in an overall copper deficiency that mimics symptoms of Menkes disease in children. Petris says it's vital to ensure that the developing newborns absorb enough copper during the neonatal period when the demand for the mineral is highest.

"Copper is a little-appreciated but essential trace mineral in all body tissues," Petris said. "Cells cannot properly use oxygen without copper; it

helps in the formation of red blood cells, and it helps keep the blood vessels, nerves, skin, immune system and bones healthy. Normally, people absorb enough copper through their food. However, in the bodies of those with Menkes disease, copper begins to accumulate at abnormally low levels in the liver and brain and at higher than normal levels in the kidney and intestinal lining."

Newborn screening for this disorder is not routine, and early detection is infrequent because it can arise spontaneously in families, Petris said. Many times, the disease is not detected until the symptoms are noticed, and by that time, it can be too late for any aggressive treatments.

"The clinical signs of Menkes disease are subtle in the beginning, so the disease is rarely treated early enough to make a significant difference," he said. "However, a single dose of copper injected into mice within a few days of birth restored normal growth and life expectancy. Early intervention was critical because treatment that began after symptoms developed wasn't successful."

Petris says that understanding the roles of copper in biology may have far-reaching health implications for the general population because copper underpins many facets of biology, including the growth of cancer tumors and the formation of toxic proteins in Alzheimer's disease.

The development of these mice provides a novel experimental system in which to test treatments for patients with this disease. The early-stage results of this research are promising, but additional studies are needed.

The study, "Maternofetal and neonatal copper requirements revealed by enterocyte-specific deletion of the Menkes disease protein," was published in the *American Journal of Physiology-Gastrointestinal and Liver Physiology*. Co-authors were Yanfang Wang, Sha Zhu and Gary Weisman, researchers in the MU Department of Biochemistry; Joseph

Prohaska from University of Minnesota Medical School; and Jonathan Gitlin from the Marine Biological Laboratory in Woods Hole, Mass. The research was funded by a grant from the National Institutes of Health.

Provided by University of Missouri-Columbia

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