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New syndrome named, causes a rare intellectual disability

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Pediatric researchers, using high-speed DNA sequencing tools, have identified a new syndrome that causes intellectual disability (ID). Drawing on knowledge of the causative gene mutation, the scientists' cell studies suggest that an amino acid supplement may offer a targeted treatment for children with this condition.

"Intellectual disability is a common diagnosis, but it includes many different diseases, with multiple genetic causes, and few targeted therapies," said first author Elizabeth Bhoj, M.D., Ph.D., a Genetics fellow in the Center for Applied Genomics (CAG) at The Children's Hospital of Philadelphia (CHOP). "This study may represent an early step toward the types of precision medicine treatment that may become more common as we draw on genomic research."

An international team of scientists from five countries collaborated on the study, published online March 31 in the *American Journal of Human Genetics*. The study's senior author, Hakon Hakonarson, M.D., Ph.D., is director of the CAG at CHOP.

The study team analyzed DNA samples from 13 affected children from nine unrelated families, along with DNA from the children's healthy parents. There were four pairs of affected siblings. All the children had developmental delays, ranging from moderate to severe, and all had hypotonia (low muscle tone). Five of the children had seizures.

Although the clinical symptoms varied among the children, all had

mutations in one gene, TBCK (for TBC1-domain-containing kinase), found when the CAG performed whole-exome sequencing. The research built on a 2015 discovery by Saudi scientists who identified TBCK as playing a role in a family with ID.

The parents of all 13 children were healthy, but carried the same gene change found in their affected children, who inherited the recessive trait—one copy from each parent. The researchers propose naming the condition TBCK-related ID syndrome.

The TCBK gene codes for the TBCK protein, which in turn helps to regulate signals along a biological pathway called the mTOR pathway. Abnormal mTOR signaling is already known to play a role in brain abnormalities, epilepsy, autism and ID.

In the current research, the study team showed that cells from the affected children had lower levels of mTOR signaling and of the TCBK protein. However, when the researches added leucine, an amino acid that acts along the mTOR pathway, to cell cultures, they measured an increase mTOR signaling in the patients' cells.

"This raises the possibility that treating affected children with leucine supplements could relieve some of their symptoms," said Bhoj. She compared this to the clinical use of dietary modifications for patients with phenylketonuria (PKU), a long-recognized genetic condition identified in routine newborn screening. In that condition, protein-restricted diets and supplements prevent brain damage.

Pending further research, added Bhoj, a next step will be to perform a pilot study to test the effects of leucine supplements in children identified with TBCK-related ID syndrome.

"This work highlights how modern genetic approaches can uncover

disease-causing variants in phenotypically heterogeneous samples that involve the same gene and molecular pathway," said Hakonarson, who added, "Such molecular phenotyping can help clarify disease relationships and inform future treatments, in keeping with our precision medicine focus."

More information: Elizabeth J. Bhoj et al. Mutations in TBCK, Encoding TBC1-Domain-Containing Kinase, Lead to a Recognizable Syndrome of Intellectual Disability and Hypotonia, *The American Journal of Human Genetics* (2016). DOI: 10.1016/j.ajhg.2016.03.016

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