YKT6 gene variants cause a new neurological disorder, finds study

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A recent collaborative study has discovered rare variants in the YKT6 gene as the cause of a new neurological disorder characterized by developmental delays along with severe progressive liver disease and a potential risk for liver cancer.

The study, published in Genetics in Medicine, was led by Dr. Hugo

Bellen, Distinguished Service Professor at Baylor College of Medicine and Principal Investigator at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital, and Dr. Wendy Chung, the Chief of the Department of Pediatrics at Boston Children's Hospital.

"It is known that the YKT6 gene plays important roles in many intracellular vesicular trafficking events in the cells but this is the first time it has been linked to a genetically- inherited disorder," Dr. Bellen said. "This study, using patient samples and fruit flies, provides a solid experimental foundation for future studies to better understand this new disease and to develop therapies."

YKT6 gene variants disrupt brain development and sometimes, liver function

In collaboration with Dr. Mythily Ganapathi at Columbia University Irving Medical Center, Drs. Paula Hertel and Davut Pehlivan at Texas Children's Hospital and Dr. James Lupski at Baylor College of Medicine, and by using the GeneMatcher tool and Baylor Genetics clinical diagnostics laboratory, this team of researchers and clinicians found three unrelated individuals with missense (analogous to misspellings in a word) variants in both copies of the YKT6 gene.

All three individuals had early onset of disease (four to six months of age) with failure to thrive. Two of them had an identical missense variant because of which the tyrosine amino acid at position 185 was changed to cysteine (Tyr185Cys).

On the other hand, the third child carried a variant that caused the same amino acid change but in a different location (Tyr64Cys) of the YKT6 protein. Interestingly, in addition to developmental delays and

neurological defects which were observed in all three children, only the two individuals with the Tyr185Cys variant had liver dysfunction and a potential risk for developing liver cancer.

"Interestingly, both individuals with the Tyr185Cys variant belong to the Syrian/Saint Thomas Christians of Kerala, India, a group currently estimated to be comprised of about 5 million individuals worldwide," Dr. Mythily Ganapathi said. "Our genetic lineage analysis suggests this variant likely originated from a common ancestor before the community split."

YKT6 gene variants impair autophagy

To assess how YKT6 variants result in the observed disease pathologies, the Bellen team studied the fruit fly version of this gene which is quite similar to its human counterpart.

"We found that the fly version of this protein is expressed in the fat body and brain which are analogous to the human liver and central nervous system respectively," Dr. Mengqi Ma, one of the first authors and a postdoctoral fellow in the Bellen lab, said. "Moreover, fly strains with loss of function mutations in this gene were lethal."

Further, they observed that Ykt6 mutant flies expressing the normal fly version of the Ykt6 gene flies had an average lifespan. However, transgenic flies expressing the fly versions of the disease variants were less effective in restoring lifespan and other symptoms.

While Ykt6 mutant flies expressing Tyr65Cys (equal to human Tyr64Cys) had normal lifespan and locomotion, those expressing Tyr186Cys (equal to human Tyr185Cys) had severely reduced lifespan and locomotor defects.

"Our results showed that the fly Ykt6 Tyr186Cys cause more severe defects than Tyr65Cys," Dr. Ma added, "suggesting that the corresponding human YKT6 Tyr185Cys is a more severe variant than Tyr64Cys."

To understand why these variants behaved differently, they delved deeper into their biology.

YKT6 belongs to the SNARE family of proteins that regulate the flow of protein traffic to various compartments within the cell. In mammalian cells, YKT6 mediates the fusion of two cellular organelles—the autophagosomes and lysosomes to form autolysosomes—within which 'used' cellular proteins, lipids, and other molecules are degraded and recycled back for future use. This process called autophagy is critical for the proper function and health of the cells.

The team found that the loss of fly Ykt6 led to an abnormal accumulation of proteins involved in autophagosome formation and autophagic cargo receptor, indicating a block in the autophagy pathway.

Further studies revealed that just like lethality and other defects, fly Tyr186Cys (equal to human Tyr185Cys) was less efficient in reverting the symptoms compared to a normal copy of the Ykt6 gene. Furthermore, they observed that while autophagy initiation was normal, the steps involved in the breakdown of cellular waste were impaired in the absence of Ykt6.

"Based on our findings, we recommend the YKT6 gene as a candidate for carrier screening in the Syrian/Saint Thomas Christian community of Kerala," Dr. Mythily Ganapathi said.

"Our work suggests children diagnosed with YKT6 liver disease will also need to be screened for hepatocellular carcinoma," Dr. Paula Hertel said.

"In summary, we have discovered YKT6 variants as the cause of a novel developmental disorder affecting brain function and in certain cases, also liver function, providing us valuable insights into a new genetic disease. However, additional studies with more patients will be needed to precisely understand the pathogenesis and to identify potential therapeutic targets for this condition," Dr. Bellen added.

More information: Mengqi Ma et al, Homozygous missense variants in YKT6 result in loss of function and are associated with developmental delay, with or without severe infantile liver disease and risk for hepatocellular carcinoma, *Genetics in Medicine* (2024). DOI: 10.1016/j.gim.2024.101125

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