Disruption of MTSS2 function causes a new syndromic intellectual disability

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An Undiagnosed Diseases Network (UDN) study led by Dr. Hugo Bellen, investigator at the Jan and Dan Duncan Neurological Research Institute (NRI) at Texas Children's Hospital and distinguished service professor at the Baylor College of Medicine, has found a spontaneous mutation in MTSS2 gene to be the underlying cause of a new syndromic intellectual disability.

The study provides the first experimental evidence of the association between a variant in MTSS2 gene and a novel neurological disorder in humans. It was published in the *American Journal of Human Genetics*.

The study was initiated when an individual with global developmental delay, intellectual disability, eye defects, microcephaly, facial features, and other symptoms but with no definitive clinical diagnosis presented to UDN physicians. The UDN is a unique national collaborative team that brings together clinical and research experts from across the country to solve the most challenging rare disease cases using advanced technologies. The network assists patients, who despite years of testing have been unable to receive a definitive diagnosis for their medical conditions ('medical mystery cases'), severely limiting their options to receive appropriate clinical treatments and support.

Through genomic matchmaking tools such as MatchMaker Exchange, the researchers identified a cohort of five individuals who shared similar symptoms. Interestingly, exome sequencing showed that all of them had the same single amino acid change in one copy of MTSS2 gene.

MTSS2 is known to be ubiquitously expressed in the human brain and previous studies in mice had shown that this gene is highly expressed in the developing central nervous system (CNS). However, prior to this study, this gene had not been associated with any human disease and very little was known about its biological role.

Based on available human genetic data the team conducted a statistical analysis which showed that slight variations in this gene may result in deleterious effects, providing a clue that the observed mutation in MTSS2 may cause the observed symptoms in these patients. Moreover, the team found that although this genetic variant reduced the level of the intermediate mRNA transcript, it did not reduce the amount of encoded MTSS2 protein, an indication that the genetic alteration likely results in

a functionally-altered MTSS2 protein that is somehow unable to function as effectively as its normal version.

Fruit flies as a diagnostic tool

To investigate how this variation in MTSS2 gene results in the symptoms seen in these patients, researchers in the Bellen lab conducted further studies using the fruit fly version of this gene, known as 'missing-in-metastasis' (mim)—which shares significant sequence homology with the human version of this gene.

"Since this gene had never been studied in flies before, our first order of business was to generate a transgenic fly line in which mim gene and all its isoforms were disrupted," said Dr. Yan Huang, a postdoctoral associate in the Bellen lab and first author of the study. "Using these flies, we found that this gene is widely expressed in the neurons and glia of the developing and adult CNS. These mutants had reduced lifespan, impaired locomotion and vision, and mild 'bang sensitivity', a model of inducing mechanical injury in flies that has long served as a readout for human seizures and epilepsy."

To assess if human MTSS2 gene can revert ('rescue') these symptoms, they generated transgenic flies which carried either the normal human MTSS2 gene (reference) or the disease-causing version of the human MTSS2 gene. The reference was able to rescue all the observed defects associated with the loss of mim function while the mutant was only able to partially restore the function, indicating that the variant encodes an MTSS2 protein with partial function. Moreover, based on other experiments, they found that this partially-functioning MTSS2 protein produced by the pathogenic variants causes some of these defects by interfering with the function of the normal MTSS2 protein (i.e. acts in a dominant-negative fashion).

"Using a combination of in-depth clinical evaluations, exome sequencing and functional studies in fruit flies, our international team has found that disruption of the MTSS2 protein function is the likely cause of the symptoms in these patients," Dr. Bellen said. "This is the first experimental evidence for a role of MTSS2 in a neurological disorder and provides a foundation to further dissect the underlying mechanisms, which could eventually lead to a therapy for this novel disorder".

Others involved in the study are Gabrielle Lemire, Lauren Briere, Fang Liu, Marja Wessels, Xueqi Wang, Matthew Osmond, Oguz Kanca, Shenzao Lu, Frances High, Melissa Walker, Lance Rodan, Kristin Kernohan, David Sweetser and Kym Boycott, Undiagnosed Diseases Network and Care4Rare Canada Consortium.

More information: Yan Huang et al, The recurrent de novo c.2011C>T missense variant in MTSS2 causes syndromic intellectual disability, *The American Journal of Human Genetics* (2022). DOI: 10.1016/j.ajhg.2022.08.011

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