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Gene for axon degeneration identified through international gene matching

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A research group from the University of Helsinki, Finland, has identified a new disease gene for early-onset axonal neuropathy and mild intellectual disability through an international research network.

"Thousands of human inherited diseases are known, but many disease genes for neurological diseases are waiting for discovery. Despite new technologies that allow the sequencing of an individual's entire genome, it is often difficult to confirm that a certain genomic variant causes the disease of that patient," says Associate Professor Henna Tyynismaa from the University of Helsinki.

The best proof would be to identify potentially harmful variants in the same gene in multiple individuals who suffer from a similar disease. In the case of rare diseases, this may require finding patients from several countries.

Tyynismaa's research group studied a family from Finland with three affected children who had an early-onset degeneration of the peripheral nerves. Using genome-wide DNA sequencing, they identified promising variants in a gene called MCM3AP, which was not a previously confirmed human disease gene.

Clinical researcher Emil Ylikallio submitted the gene name to a freely accessible website called GeneMatcher, a kind of "Tinder for geneticists." It connects individuals who post the same gene by sending an email notification to the submitters. No other information than the

gene name is required for the matching, and the follow-up is up to the submitters once they receive a notification for a matching interest.

Ylikallio was pleased to receive several gene matches for MCM3AP from doctors and geneticists around the world, which appeared to associate with a similar disease. Four additional families were identified in Australia, Canada, Turkey and Belgium, with different combinations of mutations in a recessive disease gene causing axonal neuropathy and mild intellectual disability.

The disease has progressed at different rates in the individual patients, but most had lost ambulation at a young age.

"MCM3AP is an interesting gene, which was not previously known to have such a crucial role in nerves. Its function is likely to be related to messenger-RNA export from the nucleus. Disease mechanisms related to defective messenger-RNA export are important for example in the progressive motor neuron disease ALS," Tyynismaa says.

Doctoral student Rosa Woldegebriel, who participated in the study, is now investigating the disease mechanisms of mutant MCM3AP in cultured motor neurons, which have been differentiated from reprogrammed stem cells that were derived from the from the patients' skin biopsies. These studies will hopefully clarify the function of MCM3AP in motor neurons and identify ways to prevent the harmful effects of the mutations.

More information: Emil Ylikallio et al. MCM3AP in recessive Charcot-Marie-Tooth neuropathy and mild intellectual disability, *Brain* (2017). DOI: 10.1093/brain/awx138