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DNA detectives track down nerve disorder cause

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Better diagnosis and treatment of a crippling inherited nerve disorder may be just around the corner thanks to an international team that spanned Asia, Europe and the United States. The team had been hunting DNA strands for the cause of the inherited nerve disorder known as spinocerebellar ataxia, or SCA. The disease causes progressive loss of balance, muscle control and ability to walk. Thanks to their diligence and detective work they have discovered the disease gene in a region of chromosome 1 where another group from the Netherlands had previously shown linkage with a form of SCA called SCA19, and the Taiwanese group on the new paper had shown similar linkage in a family for a form of the disease that was then called SCA22. The international team, from France, Japan, Taiwan and the USA have published their discovery in the *Annals of Neurology*. The Dutch group has also published results in the same issue of the journal.

Their paper reveals that mutations in the gene KCND3 were found in six families in Asia, Europe and the United States that have been haunted by SCA. Their results will allow for a better understanding of why nerves in the brain's movement-controlling centre die, and how new DNA mapping techniques can find the causes of other diseases that run in families.

Margit Burmeister, Ph.D., a geneticist at University of Michigan Health System (U-M), helped lead the work and stressed that the gene could not have been found without a great deal of DNA detective work and the cooperation of the families who volunteered to let researchers map all

the DNA of multiple members of their family tree. 'We combined traditional genetic linkage analysis in families with inherited diseases with whole exome sequencing of an individual's DNA, allowing us to narrow down and ultimately identify the mutation,' she says. 'This new type of approach has already resulted in many new gene identifications, and will bring in many more.'

The gene is very important as it manages the production of a protein that allows nerve cells to 'talk' to one another through the flow of potassium. Pinpointing its role as a cause of ataxia will now allow more people with ataxia to learn the exact cause of their disease, give a very specific target for new treatments, and perhaps allow the families to stop the disease from affecting future generations.

U-M neurologist Vikram Shakkottai, M.D., Ph.D., an ataxia specialist and co-author on the paper, also notes that the new genetic information will help patients find out the specific cause of their disease. He and his colleagues are already working to find drugs that might alter potassium flow, and provide a treatment for a group of diseases that currently are only treated with supportive care such as physical activity and balance training as patients deteriorate. 'Many of the families who come to our clinic for treatment don't have a recognised genetic mutation, so it's important to find new genetic mutations to explain their symptoms,' says Shakkottai. 'But at the same time, this research is helping us understand a common mechanism of nerve cell dysfunction in progressive and non-progressive disease.'

Their findings however are not restricted to just ataxia. The researchers were also able to show that when KCND3 is mutated, it causes poor communication between nerve cells in the cerebellum as well as the death of those cells. This discovery could aid research on other neurological disorders involving balance and movement.

The Dutch team, that also published its findings about KCND3 at the same time, studied families in the Netherlands and found that mutations on the gene are responsible for SCA19, the cause of which had up until now been a mystery. 'In other words, mutations in this gene are not uncommon and present all over the world,' says Burmeister. 'This means that in the future, this gene should be tested for mutations as part of a clinical genetic test panel for patients with ataxia symptoms. Because a generation can be skipped, it may even be relevant in some sporadic cases—those where the patient isn't aware of any other family members with a similar disease.'

More information: Yi-chung Lee, et al. 'Mutations in KCND3 cause spinocerebellar ataxia type 22', *Annals of Neurology*, 2012. doi:10.1002/ana.23701

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