Study finds new genetic cause of neurodegeneration

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(Medical Xpress) -- Mayo Clinic researchers have discovered two mutations responsible for a devastating neurological condition they first identified 15 years ago. The researchers say their study -- appearing in *Nature Genetics* -- has revealed a new neural pathway that may help understand a variety of similar conditions.

"We were able to do this now because of Next Generation genomic sequencing technology," says Christopher Klein, M.D., Mayo Clinic neurologist and lead author of the study. "We also had the invaluable help of our international collaborators who helped identify additional extended families with this condition, making the extensive genetic data available to us."

Called hereditary sensory and autonomic neuropathy type 1 (HSAN1) with dementia and hearing loss, its symptoms begin to appear in the young adult years -- 20 to 35 -- after which an individual's cognitive ability, hearing and ability to sense limbs deteriorate slowly. There is no treatment or cure. It was first identified and described by Peter Dyck, M.D., a senior Mayo neurologist and co-author of this current paper.

In addition to the original family studied by Dr. Dyck, Dr. Klein's team focused on DNA samples and data from three other family groups spanning the United States, Japan, the United Kingdom (U.K.) and Australia (the U.K. and Australian individuals are one family and the other U.S. family makes up the four). In addition to NextGen sequencing

and subsequent bioinformatics studies, team members conducted intracellular and methylation studies. Ultimately, they discovered the mutations on the DNMT1 area cause misfolding of the enzyme, decreased enzyme activity and loss of chromatin binding. They also showed that even moderate alterations in methylation can disrupt normal neural functions, "suggesting that DNMT1 is part of a precise mechanism of dynamic regulation of the nervous system."

Because the condition worsens with age, the researchers say its effect is cumulative and epigenetic. That is, it directly alters the genome after birth.

While the findings offer no immediate treatment for the affected families, the discovery does provide a much greater understanding of how the disease functions, and directions for future research in neurodegeneration.

Provided by Mayo Clinic