MedicalXpress

Spasticity gene finding provides clues to causes of nerve cell degeneration

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The discovery of a gene that causes a form of hereditary spastic paraplegia (HSP) may provide scientists with an important insight into what causes axons, the stems of our nerve cells, to degenerate in conditions such as multiple sclerosis.

In the Journal of Clinical Investigation today, an international team of scientists led by Dr Evan Reid at the University of Cambridge, and Dr Stephan Zuchner from the University of Miami, report that mutations in the gene known as 'reticulon 2' on chromosome 19 cause a form of HSP, a condition characterised by progressive stiffness and contraction (spasticity) of the legs, caused by selective and specific degeneration of axons

The team identified three mutations in the reticulon 2 gene as causing a type of HSP – in one case, this mutation included an entire deletion of the gene. In addition, the researchers showed that reticulon 2 interacts with another gene, spastin. Mutations in this latter gene cause the most common form of hereditary spastic paraplegia.

Reticulon 2 provides the genetic code for a reticulon protein that is a member of a family of proteins recently shown to play a key role in shaping the endoplasmic reticulum. The endoplasmic reticulum is a network of interconnected sheets and tubules that extends throughout the cytoplasm in nearly all cells. It has a number of functions, including protein synthesis, calcium signalling and regulation of other components of the cell. Recent data suggest that the sheets are involved in protein

synthesis, whereas the tubules are specialised to carry out the other functions.

This new study provides the most direct evidence to date that defects in how the endoplasmic reticulum is shaped and formed could underlie axon degeneration. When axons degenerate, signals are unable to pass through the nerve cells, leading to a breakdown of communication within the central nervous system. This is common in degenerative diseases of the nervous system, such as multiple sclerosis.

"Our work highlights important new disease mechanisms, which may provide a platform for us to study how axons are damaged in devastating illnesses such as HSP, and perhaps even in multiple sclerosis, which in some cases is very similar to HSP," explains Dr Reid, a Wellcome Trust Senior Research Fellow in Clinical Science. "But we must not forget how this work may immediately directly benefit families affected by hereditary spastic paraplegia, for whom the discovery now opens up the possibility of genetic counselling and testing."

More information: Mutations in the ER-shaping protein cause the axon-degenerative disorder hereditary spastic paraplegia type 12, *Journal of Clinical Investigation.*

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