Researchers drill down into gene behind frontotemporal lobar degeneration

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Seven years ago, Penn Medicine researchers showed that mutations in the TMEM106B gene significantly increased a person's risk of frontotemporal lobar degeneration (FTLD), the second most common cause of dementia in those under 65. While the data confirmed the gene's clinical relevance, it didn't tell researchers how it caused the disease - which is vital to developing new therapeutics.

Now, a new study published online this week in the *American Journal of Human Genetics* from Penn researchers helps answer that question by uncovering the mechanisms of the genetic mutations, or variants, associated with the gene. By functionally dissecting the TMEM106B gene first linked to FTLD, the researchers have shown how its variants directly affect the architecture and expression of it, and thus how it may lead to disease.

This is among the first functional studies of gene variants known to be associated with neurodegenerative diseases.

"Approximately 200 variants linked to these diseases—Alzheimer's, Parkinson's, FTLD, ALS—have been discovered, but how they actually influence them is not fully understood," said senior author Alice S. Chen-Plotkin, MD, an associate professor of Neurology at the Perelman School of Medicine at the University of Pennsylvania. "In general, more functional studies like this one need to be conducted downstream of the genes, so we can get to the root of the problem. Otherwise, what's the point of finding variants? We need to determine what they mean in a biological sense in order to find targetable pathways."

FTLD is characterized by the progressive loss of neurons in the frontal and temporal regions of the brain. It affects approximately 15 people out of 100,000 between the ages of 45 and 64. It is a fatal disease with death typically occurring within eight years of diagnosis. As is the case with all neurodegenerative diseases, there are no disease-modifying therapies available today to treat FTLD.

Through a combination of data-mining of publicly available databases of genetic information and laboratory studies using multiple tissue types, such as neurons and white blood cells, the researchers confirmed that the genetic variants known to increase a patient's risk of FTLD correlated with an increased expression of TMEM106B. And that it depended on whether cells recruited more CTCF or less CTCF, a key protein that helps dictate and organize the structure of the genome. A "causal' variant known as rs1990620 was responsible for recruiting CTCF, the authors found.

That variant attracted more CTCF to the cells, which translated into more long-range interactions, particularly between the promoters and the enhancers, the researchers found. The promotor is a region of DNA that starts the transcription of a particular gene, while an enhancer helps close the deal.

Those long-range interactions are what led to the

increased levels of TMEM106B in the cells, the study suggests, which then caused abnormal lysosome activity and cellular toxicity. The "trash cans" of those cells essentially became out of order.

"If you are a cell, you only have two ways to get rid of junk: your proteasomes and lysosomes. If one of those trash cans doesn't work as well, especially if you are a neuron, it can cause problems," Chen-Plotkin said. "Neurons can't just die and renew. They have super long processes that they need to regulate themselves. This break down may be what ultimately puts people on the path toward neurodegeneration."

Researchers at Penn will continue to drill down even further into the TMEM106B gene to better understand the downstream cell biology, Chen-Plotkin said. The team also plans to further investigate other variants associated with neurodegenerative diseases. Too few functional studies, she said, have been initiated, not only in neurology, but also in all disease types.

"This type of approach can be applied to the other 199 or so neurodegenerative disease risk loci," she said. "Given that so much investment has already been made to identify them, we want to derive the maximum biological meaning from them, because we may hit a pathway that is very meaningful and really targetable."

Provided by Perelman School of Medicine at the University of Pennsylvania