

Motor neuron disease and toxic substances: Possible link?

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Motor neuron disease is a rare, devastating illness in which nerve cells that carry brain signals to muscles gradually deteriorate. One form of it, Lou Gehrig's disease or ALS (amyotrophic lateral sclerosis), is familiar to the public in the lives of scientist Stephen Hawking and Morrie Schwartz, about whom Mitch Albom's "Tuesdays with Morrie" was written.

For most MND patients, the cause is unknown. Figuring out why these people develop the disease, which causes muscles to weaken, atrophy and cease to function, is an important step in developing therapies to treat or prevent motor neuron disease.

Now a team of University of Michigan scientists has gotten a step closer:

- They have discovered mutations in one key gene (neuropathy target esterase, or NTE) that cause a previously unknown type of inherited motor neuron disease.
- The discovery paves the way for better diagnosis and research on treatments.
- Most intriguing, the scientists found the mutations caused changes in a protein already known to be involved when people develop neurologic disorders as a result of exposure to toxic organophosphates—chemicals commonly used in solvents and insecticides and also as “nerve gas” agents. This discovery points to a new lead in the search to understand MND.

“We speculate there may be gene-environment interactions that cause some forms of motor neuron disease,” says John K. Fink, M.D., professor of neurology at the U-M Medical School and senior author of the new study, which appears in the March issue of the American Journal of Human Genetics. He also is a researcher at the VA Ann Arbor Healthcare System.

“Our findings support the possibility that toxic organophosphates contribute to motor neuron disease in genetically vulnerable people,” says Fink. He believes the results suggest that altered activity of the gene found in patients in the study may also contribute to other motor neuron disorders, possibly including ALS. Motor neuron disease affects five per 100,000 people.

The findings are an exciting first step in uncovering a possible link between the environment and motor neuron disease, says Shirley Rainier, a research assistant professor at the U-M Department of Neurology and the first author of the study. “Why does one person in a family get it, and another doesn’t?”

Piecing together a puzzle

In the 1930s, an estimated 50,000 people in the U.S. became lame or otherwise neurologically affected by neurotoxic organophosphates when they drank a contaminated batch of “ginger jake,” an alcohol-containing potion that was legal during Prohibition.

Ginger jake suppliers substituted a lubricating oil for the oil usually used, castor bean oil, when castor bean prices went up. A 2003 article in the New Yorker detailed the sad results, which led bands like the Mississippi Sheiks to write songs about the “ginger jake blues.”

More recently, there have been incidents in Fiji, India and Africa when

accidental consumption of oils containing neurotoxic organophosphates (instead of cooking oil) caused death or nerve damage for tens of thousands of people. Although scientists don't yet know the exact manner in which toxic organophosphate exposure leads to progressive and permanent nerve damage, they have learned that this process involves disturbance of an enzyme, NTE, contained within nerves.

Fink examined members of two families who had progressive weakness and spasticity (tightness) in their legs, as well as muscle atrophy in their hands, shins and feet. James Albers, M.D., Ph.D., a U-M professor of neurology and an expert in neuromuscular disorders, studied nerve and motor function. Rainier performed genetic studies and determined that the gene for the condition was on a region of chromosome 19.

Mark Leppert, Ph.D., co-chair of human genetics at the University of Utah, and his team performed genetic analysis that confirmed this location and excluded other areas in the genome. Among the many genes in this region of chromosome 19, one gene stood out as particularly likely: the gene that encodes for NTE. Because of its known role in organophosphate-induced neurological disease, the NTE gene was considered an important candidate gene and was studied immediately.

Analysis showed that the affected people in each family had NTE gene mutations. These mutations altered a critical part of the NTE protein called the esterase domain. Fink has named the inherited condition "NTE motor neuron disease." It begins in childhood and progresses slowly, with symptoms of weakness and spasticity in the legs and muscle atrophy in the hands and lower legs.

Next, Fink and his team want to learn if mutations in the NTE gene happen in other types of motor neuron disease such as ALS, and if the mutations make a person more vulnerable to neurological damage from organophosphate exposure. Fink's lab is currently using fruit flies as a

model to study the NTE mutations, with the goal of finding treatments for people with motor neuron disease.

Source: University of Michigan

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