Mutations in noncoding DNA are found to protect the brain from ALS

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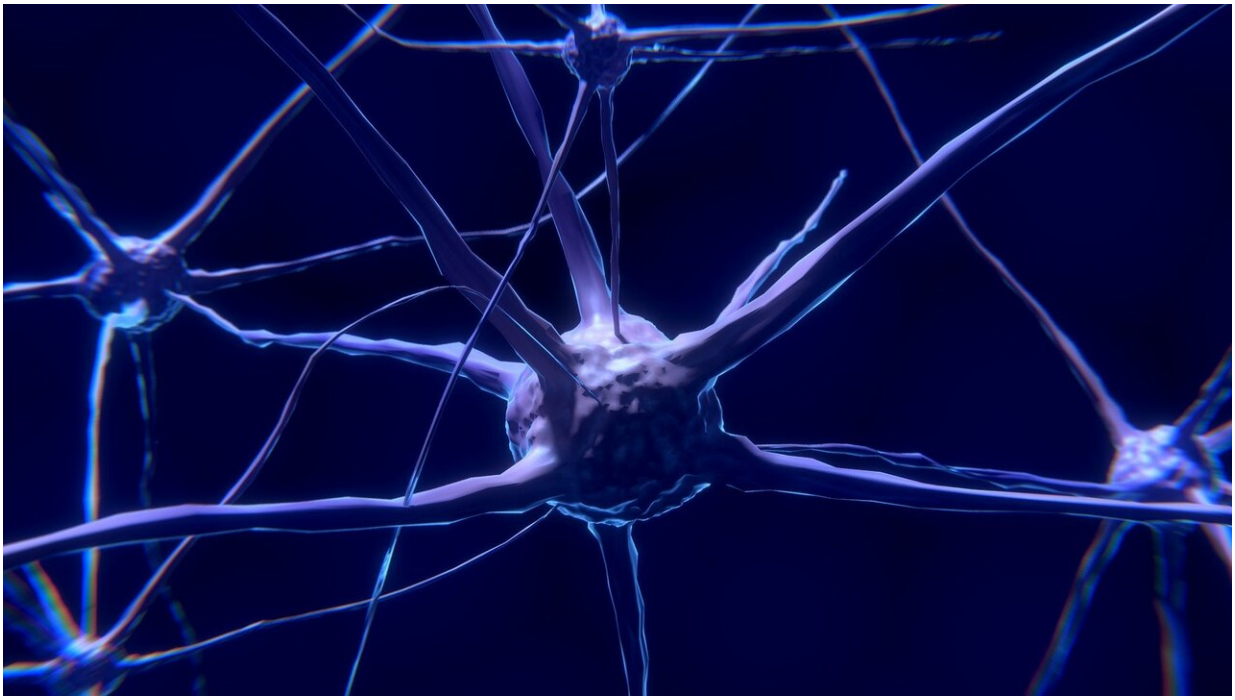

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Genetic mutations linked to a disease often spell bad news. Mutations in over 25 genes, for example, are associated with amyotrophic lateral sclerosis, or ALS, and they all increase the risk of developing this incurable disorder. Now, a research team headed by Prof. Eran Hornstein of the Weizmann Institute of Science has linked a new gene to ALS, but this one contains mutations of a different sort: They seem to

play a defensive rather than an offensive role in the disease.

The gene newly linked to ALS is located in the part of our genome once called "junk DNA." This DNA makes up over 97 percent of the genome, but because it does not encode proteins, it used to be considered "junk." Today, though this noncoding DNA is still regarded as biological dark matter, it's already known to serve as a crucial instruction manual. Among other things, it determines when genes within the coding DNA—the ones that do encode proteins—are turned on and off.

Hornstein's lab in Weizmann's Molecular Neuroscience and Molecular Genetics Departments studies neurodegenerative diseases—that is, diseases in which neurons degenerate and die. The team is focusing on our noncoding DNA. "This massive, noncoding part of the genome has been overlooked in the search for the genetic origins of neurodegenerative diseases like ALS," Hornstein explains. "This is despite the fact that for most ALS cases, proteins cannot explain the emergence of the disease."

Many people know about ALS thanks to the Ice Bucket Challenge that went viral a few years ago. This rare neurological disease attacks motor neurons, the nerve cells responsible for controlling voluntary muscle movement involved in everything from walking to talking and breathing. The neurons gradually die off, ultimately causing respiratory failure and death. One of the symptoms of ALS is inflammation in the brain regions connected to the dying neurons, caused by immune mechanisms in the brain.

"Our brain has an immune system," explains Dr. Chen Eitan, who led the study in Hornstein's lab together with Aviad Siany. "If you have a degenerative disease, your brain's immune cells, called microglia, will try to protect you, attacking the cause of the neurodegeneration."

The problem is that in ALS, the neurodegeneration becomes so severe that the chronic microglial activation in the brain rises to extremely high levels, turning toxic. The immune system thus ends up causing damage to the brain it set out to protect, leading to the death of more motor neurons.

That's where the new findings, published today in *Nature Neuroscience*, come in. The Weizmann scientists focused on a gene called IL18RAP, long known to affect microglia, and found that it can contain mutations that mitigate the microglia's toxic effects. "We have identified mutations in this gene that reduce inflammation," Eitan says.

After analyzing the genomes of more than 6,000 ALS patients and of more than 70,000 people who do not have ALS, the researchers concluded that the newly identified mutations reduce the risk of developing ALS nearly fivefold. It is therefore extremely rare for ALS patients to have these protective mutations, and those rare patients who do harbor them tend to develop the disease roughly six years later, on average, than those without the mutations. In other words, the mutations seem to be linked to a core ALS process, slowing the disease down.

To confirm the findings, the researchers used gene-editing technology to introduce the protective mutations into stem cells from patients with ALS, causing these cells to mature into microglia in a laboratory dish. They then cultured microglia, with or without the protective mutations, in the same dishes with motor neurons. Microglia harboring the protective mutations were found to be less aggressive toward motor neurons than microglia that did not have the mutations. "Motor neurons survived significantly longer when cultured with protective microglia, rather than with regular ones," Siany says.

Eitan notes that the findings have potential implications for ALS research and beyond. "We've found a new neuroprotective pathway," she

says. "Future studies can check whether modulating this pathway may have a positive effect on patients. On a more general level, our findings indicate that scientists should not ignore noncoding regions of DNA—not just in ALS research, but in studying other diseases with a genetic component as well."

More information: Chen Eitan et al, Whole-genome sequencing reveals that variants in the Interleukin 18 Receptor Accessory Protein 3′UTR protect against ALS, *Nature Neuroscience* (2022). DOI: 10.1038/s41593-022-01040-6

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