New genetic mutation for ALS identified

A team led by scientists from Johns Hopkins and the National Institutes of Health has discovered a new genetic mutation for amyotrophic lateral sclerosis (ALS) and a related disease called frontotemporal dementia (FTD) that appears to account for more than a third of all inherited cases of these diseases. The researchers show in a new study published online on 21 September 2011 in Neuron that this mutation, found within a gene called C9ORF72, is about twice as common as all the other mutations discovered thus far for the disease combined.

The findings, say study leader Bryan J. Traynor, M.D., an assistant professor in the Department of Neurology at the Johns Hopkins University School of Medicine and chief of the Neuromuscular Diseases Research Unit at the NIH, could help scientists develop new animal models of ALS, also known as Lou Gehrig's disease, and eventually new targets for attacking the more common sporadic form of the disease, which isn't inherited and appears to crop up in the population at random.

Though a handful of other genetic mutations have been linked to inherited, or familial, ALS and FTD over the past several years, these mutations appear to account for only about a quarter of cases. Knowing that other ALS- and FTD-causing mutations remain undiscovered in the genome, the team focused their search on a place that other studies had suggested might hold promise: the short arm of chromosome 9. While previous research had suggested this as a likely hotbed for genetic problems that cause ALS and FTD, the exact location of the responsible mutation or which genes might be affected was unknown.

"If you think of chromosomes like geographic regions, we knew what city this mutation was located in, and what part of the city, but we didn't know what street it was located on or which house," explains Traynor. "We were really looking for the exact address for this mutation."

To narrow down the mutation's location, Traynor and his colleagues worked with collaborators around the world, using a next-generation genomic sequencing technique on pieces of chromosome 9 sampled from ALS and FTD patients in unrelated Welsh and Dutch families in which the diseases had been diagnosed in multiple generations. They compared sequences from these affected individuals to healthy people, both unaffected relatives and people outside these families who had never been diagnosed with ALS or FTD.

In just the affected individuals, the sequences turned up an unusual section of chromosome 9 near the C9ORF72 gene in which a six-base DNA sequence (GGGGCC) was repeated over and over. When the researchers looked at DNA samples from other patients with familial ALS and FTD from Finland, the country with the highest incidence of these diseases worldwide, this same unusual segment was present in nearly half of cases, stretching from hundreds to thousands of repeats.

"Together with another mutation in a previously discovered familial ALS gene known as SOD1, this means that we are now

able to explain nearly all of familial ALS disease in Finland," Traynor notes.

Seeking confirmation in other familial ALS and FTD cases around the globe, the researchers tested samples from patients in Italy, Germany, and North America. Sure enough, the repeats were present in about 38 percent of patients, but never in healthy individuals.

Traynor notes that he and his colleagues don't yet know how the repeated segments might cause familial ALS and FTD. It could be that they affect the function of C9ORF72, whose purpose is not yet known. However, the team thinks a more likely mechanism is that the repeated segments cause affected cells to manufacture a slew of toxic RNA, genetic material that clogs up cells and eventually leads to their demise. The slow buildup of toxic RNA could be the reason why ALS and FTD tend to show up in middle age, rather than earlier in life. The researchers note that previous work has already shown abnormal RNA metabolism in ALS patients now known to carry this new mutation, lending support for this theory.

Eventually, Traynor adds, the finding could help scientists find new ways to treat both familial ALS and FTD, as well as the more common sporadic forms of these diseases. Creating mouse models with the newly found mutation and other genetic anomalies linked to ALS and FTD could lend insight on what goes wrong in motor neurons, the cells primarily affected by these diseases, potentially leading to new areas to target with drugs or other interventions.

Other Johns Hopkins researchers who participated in this study include Sonja W. Scholz, M.D., PhD, and Jeffrey D. Rothstein, M.D., Ph.D., who also serves as the John W. Griffin, M.D. Director for the Johns Hopkins Brain Science Institute.

In the same issue of Neuron, a team led by scientists from the Mayo Clinic published a paper showing that it independently identified the same repeat expansion as a genetic cause for ALS and FTD.

For more information, go to:
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