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More genes for Lou Gehrig's disease identified

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In recent months a spate of mutations have been found in a disease protein called TDP-43 that is implicated in two neurodegenerative disorders: amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, and certain types of frontotemporal dementia (FTD). These mutations could potentially become candidates for drug targets.

Recently, colleagues at the University of Pennsylvania School of Medicine and Veterans Affairs in Seattle, WA have found two more mutations. They published their findings online in advance of print publication in the May issue of *The Lancet Neurology*.

"Now we have a direct link between the genetics and the clinical pathology of these diseases," says co-author Vivianna M. Van Deerlin, MD, PhD, Assistant Professor of Pathology and Laboratory Medicine at Penn. "This solves the question of whether TDP-43 is involved in the disease itself or a just a byproduct of it."

"Put this all together and it becomes completely convincing that there are mutations in this gene that causes some forms of ALS," says co-author Gerard D. Schellenberg, PhD, Associate Director for Research, Veterans Affairs Puget Sound Health Care System, in Seattle, WA

Essentially, these mutations are hard evidence that TDP-43 is critical for the disease process. In some cases the accumulation of TDP-43 may initiate disease; in others, it might be a downstream player in the onset of pathology.

In late 2006, Virginia Lee, PhD and John Trojanowski, MD, PhD at the Center for Neurodegenerative Disease Research at Penn found that TDP-43 accumulated abnormally in post-mortem brain tissue from individuals diagnosed with either disease. The misfolded, disease protein was recovered from only affected central nervous system regions, which include the hippocampus, neocortex, and spinal cord. TDP-43 is normally involved in RNA and DNA processing, among other cellular tasks.

The research team surveyed 259 individuals with either ALS or ALS combined with FTD and brains with pathological TDP-43 protein present and determined the DNA sequence of the gene for TDP-43 and compared it to the normal TDP-43 sequence in people without these diseases.

“By doing this, we found two families in which a mutation was present and showed that the mutated gene tracked with the disease,” says Van Deerlin. “Within the same family, all people tested who have the disease carry the mutated form of TDP-43 and it was absent in the unaffected people tested.”

With this, the research group then asked: Do we see this same change in people that don’t have the disease outside of the families as controls? The group tested 747 Caucasian and 380 Chinese elderly people without the disease and didn’t find the mutated form of TDP-43 in any of them.

“What makes our paper completely distinctive is that we have post-mortem brain tissue from some individuals in one of the ALS families,” says Schellenberg. “We showed that people with a mutated form of TDP-43 actually have TDP-43 deposited in their brain.”

The researchers stress the implications beyond ALS and FTD: TDP-43 shows up in a variety of diseases, for example 20 percent of Alzheimer’s

cases. “These findings are not just important to ALS, it’s every disease where there is a pathological form of TDP-43,” notes Schellenberg. The next step will be to gain a better understanding of how the mutation in TDP-43 causes disease.

Source: University of Pennsylvania