



The Association for
Frontotemporal Degeneration
Opening the gateway to help and a cure

September 21, 2011

Researchers find key mutation that causes FTD and ALS

Researchers have long recognized that a large group of families with members who develop FTD and/or ALS share a distinct region of chromosome 9. Groups from laboratories around the world have worked for more than 10 years to decipher the precise genetic change that these families share. The elusive mutation was finally identified independently by two groups of researchers (whose papers are published in tandem in this issue of *Neuron*) as an abnormally expanded piece of DNA known as a “hexanucleotide repeat expansion” dubbed *C9ORF72*. This is by far the most common mutation for familial FTD and/or ALS discovered to date.

“This finding provides us with a window into understanding the basic science of both FTD and ALS,” says Brad Boeve, MD of the Mayo Clinic, co-author on one of the papers and chair of AFTD’s Medical Advisory Council. “Our job now is to understand how this mutation starts a cascade of events in the cell that results in malfunction and death of neurons in specific parts of the brain. The obvious hope is that along the way we will identify specific steps in this pathway where we can design interventions for treatment and prevention.”

The finding is groundbreaking for several notable reasons: The mutation is responsible for a greater proportion of familial FTD and ALS than any previously identified genetic change. In one of the papers, preliminary estimates state that this mutation causes at least 12% of familial FTD and 22% of familial ALS. In the other paper, the frequencies of the mutation in the groups of cases with familial FTD or familial ALS were even higher. Of equal importance, the researchers found this same mutation can be present in familial and sporadic cases. This means that it is a genetic change that, whether inherited from a parent or it just “happens” by some unknown mechanism in an individual, sets the same molecular process in motion that causes disease.

“The identification of this new mutation really opens completely new areas of research into these diseases,” says Rosa Rademakers, Ph.D., senior author on the Mayo-led research team.

“This is a classic scientific finding, in that this one new finding opens up several sets of new and interesting questions,” concurs Boeve. “Why do some people with this mutation develop FTD, others ALS and still others both? Why do some families seem to show that signs of the disease in one generation may begin at a much younger age than in another generation? We know that this mutation and those found in an unrelated gene, *PGRN*, both cause FTD with TDP-43 pathology. How can two apparently separate genetic mechanisms cause the same type of syndrome and pathology? We have

learned a lot from studying a similar circumstance in Alzheimer's disease, in which mutations in *APP*, *PSEN1*, and *PSEN2* all result in relatively similar pathology, and the interplay of the genes and proteins that they encode have revealed multiple potential targets for therapy – the same may be true as we better understand the interplay of mutations in *C9ORF72*, *PGRN*, *FUS*, *TARDBP* and the common protein link of TDP-43.”

“What we have discovered is a single genetic change that is related to both FTD and ALS,” says Adam Boxer, M.D., Ph.D., a collaborator on the paper from UCSF. “This will allow us to better understand the common pathological process and should be a big leap forward in the effort to develop biomarkers and to identify appropriate targets for therapeutic intervention in both diseases.”

Follow these links for news reports on this scientific discovery:

http://www.eurekalert.org/pub_releases/2011-09/mc-ngm091911.php

http://www.eurekalert.org/pub_releases/2011-09/cp-hgs091611.php

<http://www.cell.com/neuron/home>

[http://www.cell.com/neuron/abstract/S0896-6273\(11\)00828-2](http://www.cell.com/neuron/abstract/S0896-6273(11)00828-2)

[http://www.cell.com/neuron/abstract/S0896-6273\(11\)00797-5](http://www.cell.com/neuron/abstract/S0896-6273(11)00797-5)