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

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Researchers find key mutation that causes FTD and ALS

In two landmark papers published in the online journal *Neuron* September 21, 2011, researchers report successful identification of a long-sought mutation that can cause both FTD and ALS. Found in gene named *C9ORF72* on chromosome 9, 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 researchers caution, however, that this finding will not change the reality of care or treatment in the short term. "It is a difficult thing to acknowledge—that an exciting finding like this, as much as it opens new doors to understanding the disease and will undoubtedly shorten the time to an effective therapeutic, nonetheless does not change the options available today," notes Susan Dickinson, executive director of AFTD. It will take several months to two years for a laboratory to develop a clinical test that can tell a family if this is the mutation that is causing disease in their kindred. Typically such tests must go through a certification process to ensure that they are reliable. And while a test will enable definitive diagnosis and pre-symptomatic testing in relatives who wish to know if they carry the mutation, it will not immediately bring with it additional tools for treatment.

"The pace of science is never fast enough," acknowledges Dickinson. "But advances like this, which are the result of dedicated teamwork on the part of clinicians, researchers, patients and their families, prove that, working together, we will eventually succeed in developing treatments and a cure."

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 were published in tandem in *Neuron*) as an abnormally expanded piece of DNA within a gene on chromosome 9. To date little is known about this gene's normal function, nor how this mutation—called a

"hexanucleotide repeat" because a set of six nucleotides are repeated hundreds to more than 1,000 times in people with the mutation—may interrupt normal functioning and lead to disease.

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. Another interesting finding was that the researchers found this same mutation in a small percentage of sporadic cases (i.e. patients in which there was no family history of FTD or ALS). This means that for some patients with apparently sporadic disease, there may be a genetic cause. More research will need to be done to better understand the presence of the mutation in sporadic cases.

"The identification of this new mutation opens completely new areas of research into these diseases," says Rosa Rademakers, PhD, AFTD MAC member and senior author on the Mayo-led research team. Some of the questions that she and other researchers will pursue over the coming months and years include: Why do some people with this mutation develop FTD, others ALS and still others both? How does this mutation and those found in an unrelated gene, *PGRN*, both cause FTD with TDP-43 pathology? What can we learn from the fact that two unrelated genetic mechanisms can cause the same pathological disease?

"We have learned a lot from studying a similar circumstance in Alzheimer's disease, in which mutations in the genes *APP*, *PSEN1*, and *PSEN2* all result in relatively similar pathology, " Boeve notes. "In that case the interplay of the genes and proteins that they encode has revealed multiple potential targets for therapy. The same may be true as we better understand the interplay of mutations in the FTD-related genes *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," concurs Adam Boxer, MD, PhD, 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."

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