# National Institutes of Health

## Fact Sheet

# Frontotemporal Dementia (Frontotemporal Lobar Degeneration)

Frontotemporal dementia (FTD) is an umbrella term that has been used to describe a group of rare disorders that involve shrinkage of specific areas of the brain that regulate behavior, personality, and language – it is now termed *frontotemporal lobar degeneration* (FTLD) by doctors and researchers to more accurately describe the disorders. FTLD usually develops between ages 40 and 60, with early symptoms that can include personality or behavior changes or loss of ability to use or comprehend language, followed by more general cognitive impairment and, ultimately, death. It is sometimes diagnosed in combination with other neurological disorders such as amyotrophic lateral sclerosis (ALS) or Parkinson's disease. The exact prevalence of FTLD is unknown, but some researchers estimate that as many as 10 percent of all cases of dementia are FTLD.

## Yesterday

- In 1892, neurologist Arnold Pick first identified clumps of protein in the brain that became known as Pick bodies, which are found in one type of FTLD. However, it was not until the 1980s that FTLD was widely recognized as a clinical entity separate from Alzheimer's disease (AD).

- Until recently, FTLD was routinely misdiagnosed as AD or a psychiatric disorder, and very little was known about FTLD's underlying pathology.

## Today

- In a very short period of time we have made tremendous inroads into understanding FTLD's pathology, early symptoms, and disease course. Improved imaging and laboratory techniques have allowed us to more specifically pinpoint and understand the characteristic changes in the FTLD brain.

- Our increased understanding of FTLD pathology improves our ability to distinguish among its different types. The most common form is known as FTLD-U (FTLD with ubiquitinated inclusions, referring to the characteristic accumulations of abnormal protein found in the brains of affected individuals). Other disorders under the FTLD umbrella include Pick's disease, primary progressive aphasia, semantic dementia, corticobasal degeneration, progressive supranuclear palsy, and FTLD with parkinsonism linked to chromosome 17 (FTLD-17).

- Recently, NIH-supported investigators discovered that an abnormal form of the protein TDP-43 in the brain is implicated in a significant number of cases of FTLD. We now know that virtually all FTLD cases result from dysfunction in either TDP-43 or tau, another protein found naturally in the brain.

- NIH-supported investigators also identified mutations in the *PGRN* and *MAPT* genes as the cause of some forms of FTLD. *PGRN* mutations result in underproduction of a protein called progranulin, which in turn causes the dysfunction in TDP-43 associated with FTLD. *MAPT* mutations result in dysfunction of the tau protein.

- As many as 40 percent of FTLD patients have a family history of the disease. In addition to *PGRN* and *MAPT*, scientists have identified mutations in two other genes –*VCP* and *CHMP2B* – that cause familial forms of FTLD, and the search is underway for other related genes, as well as genes involved in sporadic, or non-familial, cases.

- In 2001, an international team of scientists established clinical and neuropathological criteria for a diagnosis of FTLD. These criteria are currently being reassessed as new information about FTLD's neuropathology is uncovered.

- Although there is still no cure or preventive intervention, some treatments – notably anti-depressant medications – can help ameliorate behavioral problems resulting from FTLD.

## Tomorrow

- *Improved tools will facilitate early diagnosis.* Scientists are working to identify biomarkers and develop improved neuropsychological screening instruments that will permit more rapid diagnosis of FTLD as well as greater precision in identifying which specific type of FTLD is present. These tests will allow doctors to identify at-risk individuals during the very earliest stages of disease, before symptoms appear.

- *Effective treatments targeted at the disease's underlying pathology will be available.* Experimental treatments targeting abnormal TDP-43, tau, and progranulin are undergoing testing *in vitro* and in animal models. Scientists hope that these studies will lead to the development of agents to be studied in clinical trials.

- *Cross-disciplinary research will yield big rewards.* Research has uncovered some surprising links between the pathology of FTLD-U and that of other diseases, including AD, ALS, and Paget's disease of bone, raising the possibility that advances in one disease may lead to advances in another.

Contact: Creighton Phelps, Ph.D.,
phelpsc@mail.nih.gov