

Frontotemporal Disorders



The frontotemporal disorders are a group of rare diseases that involve shrinkage of specific areas of the brain that regulate behavior, personality, and language, a process termed *frontotemporal lobar degeneration* (FTLD). Frontotemporal disorders usually develop between ages 40 and 60, with early symptoms that can include personality or behavior changes, loss of ability to use or comprehend language, or difficulties with movement, followed by more general cognitive impairment and, ultimately, death. A frontotemporal disorder may sometimes be diagnosed in combination with another neurological disorder such as amyotrophic lateral sclerosis (ALS) or Parkinson's disease. The exact prevalence of these disorders is unknown, but some researchers estimate that as many as 10 percent of all cases of dementia are actually frontotemporal disorders.

Yesterday

- In 1892, neurologist Arnold Pick first identified clumps of protein in the brain that became known as Pick bodies, which are characteristic of the disorder known as Pick's disease. However, it was not until the 1980s that the frontotemporal disorders were widely recognized as clinical entities separate from Alzheimer's disease (AD).
- Until recently, many of these conditions were routinely misdiagnosed as AD or a psychiatric disorder, and very little was known about the underlying pathologies of the frontotemporal disorders.

Today

- In a very short period of time we have made tremendous inroads into understanding the pathology, early symptoms, and disease course of many frontotemporal disorders. Improved imaging and laboratory techniques have allowed us to pinpoint more specifically and understand the characteristic changes that occur in the brains of affected individuals.

- Our increased understanding of characteristic underlying pathologies and typical patterns of symptoms improves our ability to distinguish among the different types of frontotemporal disorders. The most common form is known as behavioral variant frontotemporal dementia (bvFTD), which is characterized (in its early stages) by changes in personality, behavior, and judgment. Other disorders under the "frontotemporal disorders" umbrella include Pick's disease, primary progressive aphasia, primary nonfluent aphasia, semantic dementia, corticobasal syndrome, progressive supranuclear palsy, frontotemporal dementia (FTD) with parkinsonism, and FTD with ALS.

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 frontotemporal lobar degeneration, the underlying pathological mechanism responsible for most forms of frontotemporal disorder. It is believed that almost all cases of FTLD result from dysfunction in either TDP-43 or tau, another protein found naturally in the brain. The next question to answer is "how does the disease develop?"

- 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 dysfunction in TDP-43. MAPT mutations result in dysfunction of the tau protein.
- As many as 40 percent of patients with a frontotemporal disorder 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 frontotemporal disease, 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 a frontotemporal disorder. These criteria are being

reassessed as new information about the disorders' 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 a frontotemporal disorder.

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 as well as greater precision in identifying which specific type of disorder 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 preclinical testing. 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 pathologic links between frontotemporal lobar degeneration and several 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.

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