

Frontotemporal lobe degeneration

Recent advances in understanding the genetics and pathology of Frontotemporal lobe degeneration

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Frontotemporal lobar degeneration (FTLD) is a debilitating condition that affects approximately 4 per 100,000 people in the 45 to 64 year old population (Rabinovici and Miller, 2010). FTLD has a mean age of onset of 52.8 years and after Alzheimer's disease (AD), it is the second most common form of early-onset dementia (Rabinovici and Miller, 2010). Dementia is an umbrella term describing a progressive loss of cognitive ability (thinking) that may include memory, executive function (planning, reasoning and attention), skilled movements and language. There are many changes to the brain that can result in dementia but it is most commonly caused by neurodegenerative diseases of aging. First classified as a disease separate from AD in 1994 (The Lund and Manchester Groups, 1994), FTLD is particularly characterised by degeneration of the frontal and temporal lobes of the cerebral cortex, and with pathological features that are distinct from AD. FTLD is fatal and patients generally succumb to the disease within 6 to 11 years after symptom onset (Rabinovici and Miller, 2010).

Clinically, FTLD impairs many aspects of human activity due to the areas of the brain that are most affected. It presents as a disorder of behaviour including loss of personal and social awareness, disinhibition, and lack of emotions. Speech disorders are often seen as well as loss of ability to negotiate the environment (The Lund and Manchester Groups, 1994). Memory is relatively spared in the early stages (Rademakers et al., 2012). Several different subtypes of FTLD have now been described in terms of their key clinical features. These include behavioural variant FTLD (bvFTLD), semantic variant primary progressive aphasia (PPA), nonfluent/agrammatic variant PPA (PNFA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and FTLD with amyotrophic lateral sclerosis (FTLD-ALS) (Roberson, 2012; Sieben et al. 2012).

Relationship between FTLD and ALS

It is thought that FTLD is closely related to the neurodegenerative disease, amyotrophic lateral sclerosis (ALS). ALS is the most common form of motor neuron disease and is characterised by progressive loss of movement due to the loss of upper and lower motor neurons. Although physical symptoms of the two disorders may differ, many clinical, genetic and pathological characteristics overlap. ALS and FTLD frequently occur in the same family with many ALS sufferers having impairments in frontotemporal functions such as cognition and behaviour, and also a large proportion

of FTLD patients suffering from motor neuron dysfunctions (Lomen-Hoerth et al., 2002; Phukan et al., 2007). The close relationship between the disorders was strengthened in 2006 when the protein TDP-43 was determined to be the main pathological protein in a large number of ALS patients and the most common pathological subtype of FTLD (Neumann et al., 2006). The identified similarities between these aspects of ALS and FTLD have contributed greatly to the elucidation of pathological and genetic mechanisms by which the two disorders operate, although no effective treatments for either disorder are available.

Genetics of FTLD

FTLD appears to have a larger genetic component than many other neurodegenerative diseases, such as AD, with approximately 50% of FTLD patients having a positive family history. 10 to 20% of these inherit the disease in an autosomal dominant fashion (The Lund and Manchester Groups, 1994; Paulson & Igo, 2011) emphasising the important contribution that genetic factors play in this disease. The remaining cases of FTLD are suspected to be sporadic and to date, have no known cause.

Insight into the genetic basis of FTLD has accelerated in the last 15 years with the identification of mutations in the microtubule associated protein tau (*MAPT*) (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998; Ratnavalli et al., 2002) and progranulin (*PGRN* or *GRN*) genes (Baker et al., 2006; Cruts et al., 2006), both located on chromosome 17. Mutations within the chromatin-modifying protein 2B (*CHMP2B*) gene were discovered in a large Danish family, and also mutations in the valosin-containing protein (VCP) have also been associated with FTLD (Watts et al., 2004). As noted above, ALS mutant genes, *TARDBP*, and fused in sarcoma (*FUS*) have mutations in a smaller number of FTLD cases (Wang et al., 2013), increasing the evidence that these two diseases are within the same spectrum of disorders. The most recent discovery has been the identification of an expansion of the hexanucleotide repeat, GGGGCC, in the *C9ORF72* located on chromosome 9, which was shown to cause a majority of familial cases (Renton et al., 2011; DeJesus-Hernandez et al., 2011). The repeat expansion in the *C9ORF72* gene occurs in a non-coding region and is often associated with brain TDP-43 pathology (FTLD-TDP). It is currently unclear how these mutations cause disease. The discovery of these genes has allowed for clinical genetic testing to be carried out on the more common genes in some countries (Paulson & Igo, 2011).

Pathological changes associated with FTLD

The pathology of FTLD is complex and as with other neurodegenerative diseases there is overlap in pathology between subtypes of pathology and between other diseases such as AD. Upon gross examination, FTLD is characterised by atrophy of the frontal and temporal lobes, as well as other brain areas depending on the subtype of disease observed. At the microscopic level, loss of neurons is observed, as well as an increase in the number of astrocytes (astrocytosis) within atrophied areas of the brain (Sieben et al., 2012). In individual cases, the observed pattern of atrophy in FTLD is variable and clinical symptoms of disease are reflected by these patterns

(Sieben et al., 2012), suggesting that FTLN is a heterogeneous group of disorders. FTLN is similar to many other neurodegenerative diseases in that it is characterised by the presence of abnormal intracellular protein aggregates in surviving cells. The protein content of these aggregates is frequently used to classify the type of FTLN. The most common pathological inclusions consist of tau or TDP-43 proteins. Tau is accumulated in FTLN cases caused by MAPT mutations and TDP-43 inclusions are present in cases caused by mutations present in progranulin, C9ORF72 and TARBP. Links between mutations and protein aggregates and the relationship to cell loss are currently unclear.

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