

A New Map of Frontotemporal Dementia: Defining How Tau Mutations Cause FTD

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A version of the MAPT (Tau) gene in transgenic mice has been shown to cause frontotemporal dementia (FTD)-like symptoms and neural degeneration through the aggregation of the tau protein. These findings highlight a new cause for FTD, and may lead to a novel diagnosis and treatments for the disease.

Frontotemporal dementia (FTD) is a lesser-known neurodegenerative disease in humans. FTD (initially called Pick's disease) was made known to the scientific world by Arnold Pick in 1892. It has both behavioral and psychological symptoms, including binge eating, language difficulties, as well as a characteristic degradation of the frontal and temporal lobes of the brain (Vossel and Miller, 2008). Although it is ultimately incurable, treatment options that alleviate the symptoms of FTD have been approved. The lack of a cure for FTD is partially due to the number of types within the disease and the lack of extensive research. Unfortunately, most cases are spontaneous and difficult to identify. However, about 10% of FTD cases are considered familial, leading to the discovery of some genetic components. Many genetic links are being investigated for familial FTD, including the C9orf72 and progranulin genes, as well as the tau gene. These genes have been correlated with FTD, but few studies have identified an underlying mechanism that includes these genes. If a definitive link could be identified, treatment options that target these molecular mechanisms could be explored.

One gene that has been correlated with some forms of FTD is the microtubule-associated protein tau (MAPT) gene, often called the tau gene. This gene codes for the tau protein which is shown to be involved in the progression of Alzheimer's disease (another type of dementia) (Lindquist, 2008). In Alzheimer's disease, the tau protein forms tangles, causing neurological degeneration within the brain. It has been hypothesized that the tau protein also forms tangles in some forms of FTD. This tau-associated FTD type is often called Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17). The symptoms associated with FTDP-17 include reduced movement (also present in Parkinson's disease), as well as other behavioral abnormalities (National Institute on Aging, 2014). In the study entitled "Tau-Mediated NMDA Receptor Impairment Underlies Dysfunction of a Selectively Vulnerable Network in a Mouse Model of Frontotemporal Dementia", Warmus et al. examines the link between the MAPT gene and FTD (2014)

Based upon the known symptoms of FTD, the researchers hypothesized that MAPT mutations in mice result in a connectivity reduction and atrophy of the salience network. The salience network was examined because of its connection to the symptoms of FTD (in humans), as well as known degradation in some FTD cases (as found by an earlier study) (Seeley, 2010). This network is involved in determining which aspects of the outside world should be consciously perceived by the individual and some regions of it also manage specific behaviors. The salience network resides in the insular cortex and striatum regions of the brain. These regions are located deep within the brain and have many important functions. To simulate this disease in mice, the researchers used mice with the human tau V-337M genetic mutation (called hT-337M in mice) and compared them with transgenic hT-WT mice (which have the non-mutated or wild-type human tau gene)

To understand how hT-337M mutations might affect these regions and mouse behavior in general, the researchers examined several aspects of both mouse behavior and physiology, including grooming, nest building and behavior in the elevated plus maze (which consists of two open arms and two closed arms connected to each other, elevated above the ground). To examine the physiology of the mice, the researchers obtained subsections of their hindbrains. Additionally, synaptosomal preparations (samples of neural synapses) were made for later use. Other laboratory tests conducted on brain samples included electrophysiology, western blotting and immunohistochemical staining. Although the behavior experiments were important in establishing the

mice had FTD, the data gained using the physiological techniques resulted in an understanding of how hT-337M mutations affect cells.

When the researchers compared the experimental results of the hT-WT and hT-337M mice, they found a striking pattern. There was an age-dependent increase in time spent grooming for the hT-337M mice, but not for the hT-WT mice. This age-dependency was evidence in the larger number of self-induced facial lesions compared with the hT-WT mice. The hT-337M mice spent more time in the maze but covered the same average distance as the hT-WT mice. Physiologically, NMDAR-dependent neuronal transmission in the ventral striatum was below normal in the hT-337M mice. This transmission is essentially communication between neurons that is regulated by the NMDA glutamate receptor on neurons. Reduced dendritic spine PSD size was also found in older hT-337M mice. The PSD (post-synaptic density) is a mass near the synapse, or gap between two neurons, and is associated with the NMDA receptor (Camp et al, 2011). This mass is partially involved in the regulation of the effects of some commonly used drugs and the regulation of certain behaviors. In ventral striatum and insular cortex synaptosomes (samples of neural synapses), decreased NMDA and AMPA glutamate receptor levels were observed in hT-337M mice. These changes, however, were not observed in the dorsal striatum brain region. Finally, increased levels of the tau protein were found in the ventral striatum (but not dorsal striatum) of hT-337M mice.

To summarize, hT-337M mice showed increased levels of phosphorylated tau in regions with neuronal degradation, leading the researchers to conclude that phosphorylated tau produced by the mutant MAPT gene may lead to neural degradation, and eventually FTD. The hT-337M mice showed age-dependent abnormalities in many behavioral aspects, revealing a connection between the mice and the symptoms of FTD. These findings provide further insight into the connection between MAPT mutations and FTD, and along with other similar studies, may lead to an investigation into potential diagnosis and treatments for this form of FTD (Pir, Choudhary, Mandelkov, & Mandelkov, 2016). For example, a patient may undergo genetic testing to look for FTD mutations. As a treatment, one could use neural growth factor (NGF) to improve the health of the brain, a course of action currently being investigated in Alzheimer's disease patients (Wolfe, 2006). One could also target the reduced NMDAR function found in hT-337M mice using cycloserine (as suggested Warmus et al). While treatment options for FTDP-17 are being examined, more research into the connection between human MAPT mutations and FTD should be done.

In conclusion, this study offers a unique window into how FTD is influenced by the MAPT gene. This research has many important implications for the scientific community and may lead to new treatments for the disease.

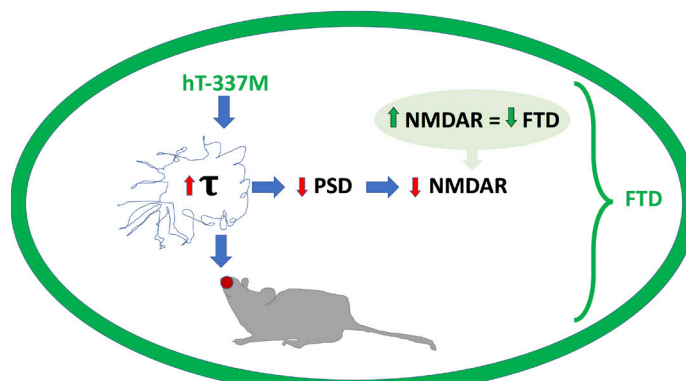


Figure 1: In this new model of FTDP-17, tau mutations (hT-337M) in mice result in an increased production of the tau protein. This leads to behavioral abnormalities in mice (such as repetitive grooming and facial lesions), as well as a smaller post-synaptic density (PSD) size and NMDA receptor impairment. These effects of tau mutations contribute to the development of FTD in mice and quite possibly in humans. As the authors of the study noted, if the health of the NMDA receptors can be improved, then the overall severity of FTD in mice may also be improved.

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