# Frontotemporal dementia: an endosomal problem?

Mutations in an endosomal sorting protein are associated with a rare form of frontotemporal dementia (FTD), report UK and Danish researchers. "We have been trying to identify the gene associated with FTD3 for the past 10 years", explains joint project leader Elizabeth Fisher (Institute of Neurology, University College London, UK). "Our discovery that affected members of a large Danish family with FTD3 have a mutation in *CHMP2B*, which encodes a subunit of the endosomal ESCRTIII complex, throws light on a possible new mechanism of neurodegeneration."

FTD, the second most common cause of presenile dementia, is a heterogeneous disorder. The most common familial form is caused by mutations in the *tau* gene, which lead to widespread tau inclusions in the brain. By contrast, FTD3 has no distinctive neuropathological features but is characterised by onset of dementia in people aged in their late 50s and by behavioural changes.

Fisher and her colleagues linked the FTD3 phenotype to a region of chromosome 3 in an affected Danish pedigree that includes more than 450 people. "Our graduate student Gaia Skibinski searched data from the human genome project for candidate genes in this region and homed in on one known only by an anonymous set of numbers", explains Fisher. "Then, by use of web-based bioinformatic tools, she discovered that this gene is related to a yeast gene involved in endosomal function, and because defective endosomal function has recently been implicated in several neurodegenerative diseases, we investigated this candidate further."

The researchers found a specific mutation within *CHMP2B* in 11 affected members of the Danish family that was not present in unaffected family members or in control DNA samples. They also found a second *CHMP2B* mutation in an unrelated individual with familial FTD. In addition, they discovered that expression of the mutant gene in cultured neuronal cells causes the formation of aberrant endosomal structures (*Nat Genet* 2005; published online July 24, DOI: 10.1038/ng1609).

"These data are original and interesting", comments neurobiologist Andrew Bean (University of Texas Medical School at Houston, TX, USA), "in that they bolster the emerging recognition that defects in intracellular trafficking are a significant cause of neuronal disease. However, finding additional individuals with *CHMP2B* mutations will be important, and mechanistic studies describing how *CHMP2B* mutations affect various aspects of endocytic trafficking are needed to complete the picture."

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