**CYLD is a causative gene for frontotemporal dementia-amyotrophic lateral sclerosis**

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Frontotemporal dementia (FTD) is a disease that causes degeneration of the areas of the brain that control cognitive, auditory and visual function. Amyotrophic lateral sclerosis (ALS) and FTD exist on the same spectrum, with many overlapping disease-causing mechanisms. For example, the leading cause of both ALS and FTD is a mutation in the C9orf72 gene. Ordinarily this gene provides a template for production of the C9orf72 protein, but mutation impairs this, triggering development of either disease. Constant work is being carried out to illuminate the causes of ALS/FTD in order to find as yet elusive therapies. Researchers from the University of Sydney now believe they have identified a new genetic mutation that results in the development of these conditions and could help in the search for treatments.

In 2013 research into an Australian family, genetically predisposed to develop either ALS or FTD and without a mutation in any known ALS genes, showed a mutation in the gene for CYLD (Dobson-Stone et al., 2013). At the time this mutation was assumed not to be disease-causing; a recent publication in *Brain* now suggests this may not be the case.

Dobson-Stone et al. (2020), set out to further investigate the mutant gene reported in 2013. They first analysed brain samples from two deceased members of the family, finding the CYLD mutation caused significant levels of CYLD-immunoreactivity, a measure of the brain's immune response, suggesting CYLD was in fact harmful. Their next goal was to investigate whether the mutation would have any effect in a cellular model. To do this they expressed the mutated CYLD gene in mouse neuron cells finding that, most notably, the CYLD mutation impaired cellular autophagy (the body's method for clearing out damaged cells) and altered the location of TDP-43 protein in the cells, two clinical hallmarks of ALS/FTD. Mechanistically, the mutation caused an increase in activity of the CYLD protein, indicating the CYLD mutation is disease-causing due to a gain of function (as opposed to a loss of function).

CYLD is therefore a cause of, and link between ALS and FTD, albeit a rare one. Though this discovery does not necessarily mean immediate changes for patients it highlights a new disease-causing mechanism that could be applicable in wider ALS/FTD. Further research should now focus on establishing how common this mutation is (in this study it was only observed in this family and not other, larger databases of patients) and more in-depth investigations into the mechanisms behind CYLD ALS/FTD.

**References**
