

Uncovering a key relationship in ALS

July 15 2015, by Heidi Singer

A University of Toronto research team has discovered new details about a key gene involved in ALS, perhaps humanity's most puzzling, intractable disease.

In this fatal disorder with no effective [treatment options](#), scientists (including members of U of T) achieved a major breakthrough in 2011 when they discovered mutations in the gene C9orf72, as the most frequent genetic cause of ALS and [frontotemporal dementia](#). But little was known about how this gene and its related protein worked in the cell.

To solve this problem, Professor Janice Robertson and her team at the Tanz Centre for Research in Neurodegenerative Diseases developed novel antibodies that not only specifically detected C9orf72 in human tissues, but could also distinguish between both the long and short isoforms.

"Using these antibodies we have made the remarkable discovery that C9orf72 is localized to the [nuclear membrane](#) in healthy neurons, but is mislocalized to the plasma ([outer membrane](#)) in diseased neurons," says Robertson, whose research was published July 14 online in the journal *Annals of Neurology*.

Robertson and her team also showed that C9orf72 directly interacts with components of the nuclear shuttling complex, which is responsible for the movement of proteins across the nuclear membrane. One such protein is TDP-43, which normally resides in the nucleus but is wrongly

localized to the cytoplasm in diseased neurons in ALS. TDP-43 accumulation and aggregation in the cytoplasm diagnoses most ALS cases - but the link with C9orf72 was absent.

Now through the use of the C9orf72 antibodies the Robertson lab has found that loss of C9orf72 from the nuclear membrane correlates with TDP-43 pathology. These results suggest that defects in C9orf72 affect the proper functioning of the nuclear shuttling complex, resulting in TDP-43 build up in the cytoplasm.

"We've discovered a link between the [genetic cause](#) of ALS and its pathology that appears to be important for all cases, not just familial ones," says Robertson, a Canada Research Chair in ALS. "The possible involvement of C9orf72 in the shuttling between nucleus and cytoplasm opens intriguing new avenues of research into the causes of ALS - and hopefully, one day an [effective treatment](#) or cure."

More information: Isoform Specific Antibodies Reveal Distinct Subcellular Localizations of C9orf72 in Amyotrophic Lateral Sclerosis, DOI: 10.1002/ana.24469

Provided by University of Toronto

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