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Getting off tract: Polyglutamine disease involves other regions of protein

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Many genes code for proteins that have a "polyglutamine tract," several glutamine amino acid residues in a row. Nine inherited neurodegenerative diseases, including Huntington's disease and spinocerebellar ataxia type 1 (SCA1), are associated with mutations that cause abnormally long polyglutamine tracts. One theory suggests that accumulation of proteins with extra glutamines damages and kills neurons. However, there is evidence that glutamine tract expansion alone is not sufficient to cause disease.

Now, new research published by Cell Press in the September 23 issue of the journal *Neuron,* reveals that initiation and progression of SCA1 are distinct from cell death and that changes outside of the polyglutamine tract are critical for disease pathogenesis. These findings could help to direct future therapeutic strategies for treating polyglutamine diseases.

SCA1 is thought to be caused by an expanded polyglutamine tract in an ataxin (ATXN1) protein that leads to damage and loss of Purkinje cells in the cerebellum. In addition, phosphorylation of a serine amino acid reside at position 776 (Ser776) is thought to be critical for pathogenesis. Recent research led by Dr. Harry T. Orr from the University of Minnesota showed that replacing Ser776 with a phospho-mimicking aspartic acid residue in ATXN1 with a normal polyglutamine tract seemed to elicit biochemical properties that resembled ATXN1 with an expanded polyglutamine tract.

To investigate the biological relevance of this earlier observation, Dr.

Orr's group created transgenic mice that expressed different versions of ATXN1 in cerebellar Purkinje cells. "We found that a single amino acid change—one that mimics phosphorylation at residue 776—converts wild type protein in a disease-causing protein. Clearly, phosphorylation is critical for this disease," explains Dr. Orr. The researchers went on to show that although the amino acid substitution caused the normal version of the protein to induce disease in cerebellar neurons, the pathogenesis did not progress to cell death.

Taken together, these results suggest that Ser776 is critical for initiating neuronal dysfunction, while an expanded polyglutamine tract is essential for neuronal death. "Obviously, the two are linked in that initiation is a prerequisite of later stages. Regardless, a treatment targeted at initiation, perhaps S776 phosphorylation, is likely to have a major impact clinically. Conversely treating just the cell death phase of the disease is unlikely to improve the neurological status of patients," concludes Dr. Orr.

Provided by Cell Press