

Concerning ALS-related press releases of 21-22 August 2011

On 21 August 2011, the journal *Nature* posted the online publication of the following paper:

Mutations in *UBQLN2* cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia

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The authors represent five academic institutions, with the lead investigators based at Northwestern University in Chicago.

Synopsis: The underlying causes of most forms of ALS have not been identified. This new study has confirmed a mechanism common to all forms of ALS, reinforcing the need to continue developing therapies related to that mechanism. The problem is a breakdown in the recycling system for damaged proteins in specific neurons in the spinal cord and brain that results in severely damaged cells. Problems with this mechanism also likely play a role in other neurodegenerative disorders such as Alzheimer's and Parkinson's disease.

This study is a validation of much research currently being conducted in Canada. It is a new piece of the puzzle that will help us find a treatment/cure for ALS.

Why is the study of interest?

One, it confirms that pathways and mechanisms we have been focusing on as a research community for the past 15 years are important since the protein (ubiquilin2) which they report in this paper (part of the natural intracellular mechanisms for processing & degrading) has mutations in human ALS patients. However, it is important to note that this study does not identify any brand new mechanisms or pathway.

Two, the results in human patients validate the cellular and animal experimental models of ALS which have been used for the past 15 years, as those models already led to the study of this particular intracellular mechanism. In addition, the person who led the way into this line of study was ALS Society of Canada board member and Research Committee chair Heather Durham, PhD (Montreal Neurological Institute) who began studies of the proteasome and of chaperone molecule functions in the late 1990s.

Three, it should be noted that the presence of neuronal protein accumulations/aggregates/inclusions in a number of adult-onset neurodegenerative disorders -- such as Alzheimer's and Parkinson's as well as ALS -- has already been the impetus behind the development of treatments to counteract the formation of such inclusions. This new study provides additional motivation to pursue preclinical studies and clinical trials to develop and test such therapies.

In summary

A solid and interesting new finding. Hopefully it will attract additional basic scientists to study these mechanisms in ALS, and garner support to develop and test new therapies related to those mechanisms.

Scientific Explanation

There has been considerable publicity surrounding this study with coverage by major news sources.

The authors identify mutations in the gene “*UBQLN2*”, which codes for the ubiquilin 2 protein, in a large family with ALS (FALS). Additional mutations in the same gene were found in four other unrelated FALS families. It is of interest that dementia was a feature of a number of *UBQLN2*-linked patients. Ubiquilin2 is one protein component of a complex system found in all cells which repairs or disposes of proteins as they become damaged. When this protein processing system is unable to remove or repair damaged proteins, the damaged proteins begin to accumulate in the cells. Study of postmortem spinal cord and brain samples from affected *UBQLN2*-family members, and postmortem spinal cord samples from a number of other ALS patients (including both familial and non-familial) demonstrated the accumulation of *UBQLN2* in “skein-like inclusions” in all cases examined.

There is a significant body of published work by a number of investigators in the field which has established that proteins which have been implicated in the pathogenesis of ALS as a result of mutations found in FALS (ie., SOD-1, TDP-43, FUS, and optineurin) clump together inside of motor neurons, forming aggregates or inclusions. The formation of clumped or aggregated proteins in specific subsets of nerve cells has long been identified as a hallmark of other neurodegenerative disorders including Huntington’s, Parkinson’s and Alzheimer’s. Thus, interest in how these aggregates/inclusions arise and how nerve cells normally prevent the process led to investigation of intracellular protein processing and degradation. In the ALS field, studies using cellular and animal models to understand why naturally programmed mechanisms to degrade problem proteins do not work in motor neurons began in the late 1990s. These natural mechanisms are complex and involve a number of protein components which work in several locations inside the cell, and communicate with each other by systems that escort damaged or mutant proteins to the appropriate location. The newly identified FALS protein, *UBQLN2*, is one of the components of this complex mechanism.

This new publication confirms that this well established and significant area of basic science research *does* have direct relevance to ALS, as mutations in the *UBQLN2* protein found in the five FALS families lead to impairment of the protein degrading mechanisms. Further, the study reinforces the validity of the cellular and animal models being used to identify important mechanistic pathways of direct relevance to ALS.

Finally, while confirmation of disruption of intracellular protein processing as a common pathway in ALS is important, it is also important to put the results in context. The results do not explain fully what happens “upstream” which leads to these problems in most cases of ALS. Although there are still further questions to be answered, it is encouraging to know that researchers are indeed on the right track.