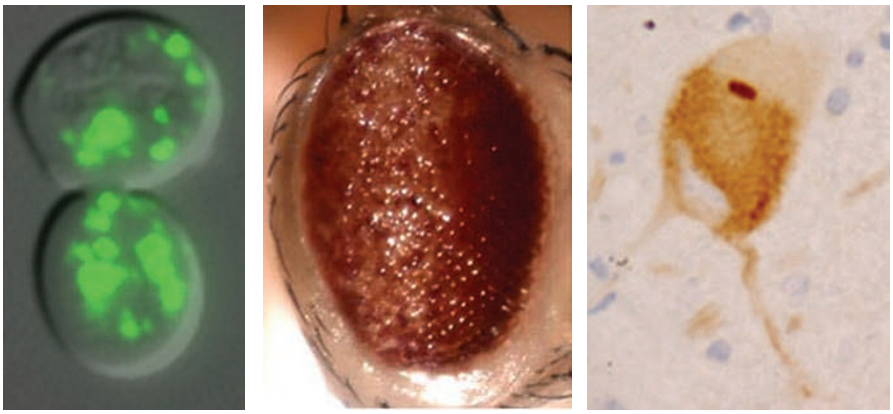
MOTOR NEURON DISEASE

PolyQ expansions in ataxin-2—a risk factor for amyotrophic lateral sclerosis?

Intermediate-length polyglutamine (polyQ) expansions in the ataxin-2 (*ATXN2*) gene could confer an increased risk of developing amyotrophic lateral sclerosis (ALS), according to research from a team led by Aaron Gitler and Nancy Bonini at the University of Pennsylvania, USA. Their findings indicate that ataxin-2 enhances the toxicity of TAR DNA-binding protein 43 (TDP-43)—a molecule that has already been strongly implicated in ALS pathogenesis—and the interaction between these two proteins could provide a lead for the development of much-needed new therapies for ALS.



A combination of approaches involving yeast cells (left), *Drosophila* (center) and human motor neurons (right) has identified a role for ataxin-2 in amyotrophic lateral sclerosis. Images provided by Professor Nancy Bonini and Professor Aaron Gitler. Permission obtained from Nature Publishing Group © Elden, A. C. *et al. Nature* **466**, 1069–1075 (2010).

Long polyQ expansions (>34 glutamines) in the *ATXN2* gene have previously been shown to cause the hereditary neurodegenerative disease spinocerebellar ataxia type 2 (SCA2). Gitler, Bonini and colleagues measured *ATXN2* polyQ repeat lengths in 915 patients with sporadic or familial ALS, and in 980 controls. The researchers found a significant association between ALS and polyQ expansions of 27–33 glutamines, which are thought to be below the threshold for development of SCA2.

As Gitler explains, the study, which was published in *Nature*, employed "multiple different approaches, from yeast genetics and cell biology, to fly genetics, to biochemistry, human cell lines, mutation screening in human patients, immunohistochemisty with human postmortem tissue, and cell biology with disease-specific patient cell lines." Bonini adds "we had previously recognized the enormous potential of combining fly and yeast approaches in the study of α-synuclein; thus, we decided to apply the power of these two systems to this new problem."

The researchers initially set out to identify factors that influence the toxicity of TDP-43. A genetic screen performed in yeast cells uncovered 27 genes that, when overexpressed, increased TDP-43 toxicity. One of these genes was *PBP1*, the yeast ortholog of *ATXN2*.

To examine the effects of the ATXN2–TDP-43 interaction in the context of the nervous system, the researchers switched their attention to a *Drosophila* model. They found that both wild-type and ALS-linked mutant forms of human TDP-43 induced neurodegeneration when expressed in the *Drosophila* eye, and shortened the flies' lifespans when expressed in the nervous system. These effects were more pronounced with the mutant form of the protein than with the wild-type form, and were exacerbated further by upregulation of *Atx2*, the *Drosophila* homolog of *ATXN2*.

By use of immunoprecipitation experiments, the team confirmed that ataxin-2 could physically interact with TDP-43 in human cells. Moreover, spinal cord neurons from patients with ALS showed abnormal intracellular localization of ataxin-2, which was characterized by the presence of distinct foci of accumulated protein in the cytoplasm. Further *in vitro* studies provided evidence that intermediate-length polyQ repeats in ataxin-2 can stabilize the protein and/or inhibit its degradation, thereby increasing its concentration in the cell.

These new findings identify *ATXN2* as a susceptibility gene for ALS, as well as providing a number of avenues for further investigation of the underlying disease mechanisms. "My laboratory, in additional studies with Aaron, is focused on going after the pathway of toxicity using fly genetics," says Bonini. "Aaron and I are also determining the potential role of ataxin-2 in other human degenerative diseases, and how its interactions with TDP-43 may feature in those situations."

At present, the only available treatment for ALS is riluzole, which only marginally slows disease progression, so the development of new therapies for this condition is an urgent priority. "The genetic data in yeast and fly raise the possibility that the ataxin-2–TDP-43 interaction may be an important target therapeutically," says Gitler.

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