Analysis of the Function and Dysfunction of the ALS Gene *C9ORF72* using *C. elegans*

Anna Corrionero and Bob Horvitz
HHMI, Dept. Biology, MIT, Cambridge, MA 02139 USA

An expansion of a GGGGCC hexanucleotide repeat in an intronic region of a gene of unknown function, *C9ORF72* (*chromosome 9 open reading frame 72*), is the most common known genetic cause of familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Among the mechanisms proposed for the pathogenic effects of the *C9ORF72* hexanucleotide expansion in the etiology of ALS is the loss of wild-type *C9ORF72* gene function.

The *C. elegans* genome contains an uncharacterized gene homologous to *C9ORF72*, *F18A1.6*. Both C9ORF72 and F18A1.6 show structural similarities to DENN domain-containing proteins, guanine exchange factors for Rab GTPases (Levine et al., 2013; Zhang et al., 2012). However, the molecular function of C9ORF72 and F18A1.6 remains unknown.

We have observed that *F18A1.6* mutants show slow embryonic development. A translational reporter of *F18A1.6* is expressed during embryogenesis, localizing in the cytoplasm. We are using a candidate-gene approach to identify genes with a similar abnormal embryonic development and that might genetically interact with *F18A1.6*.

Our goals are to determine the molecular function of F18A1.6, its role during embryonic development and to establish if C9ORF72 and F18A1.6 are functionally related. We hope to help elucidate how the most common ALS-causing mutation, a non-coding hexanucleotide repeat expansion in a conserved gene of unknown function, exerts its pathogenic effects.

Poster
No of characters with spaces: 1,508 (2,500 max)
Research area: Cell Biology (Cell Polarity and Intracellular Trafficking)