Analysis of the Function and Dysfunction of the Human Amyotrophic Lateral Sclerosis 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 the human gene *C9ORF72* (*chromosome 9 open reading frame 72*) is the most common known genetic cause of familial amyotrophic lateral sclerosis (ALS). Little is known about the normal function of *C9ORF72*, or, importantly, about how the repeat expansion causes ALS as well as frontotemporal dementia (FTD). Given the current understanding of other neuromuscular disorders caused by expansions of nucleotide repeats, three mechanisms have been proposed for the pathogenic effects of the *C9ORF72* hexanucleotide expansion in the etiology of ALS and FTD: (1) loss of wild-type *C9ORF72* gene function, (2) altered function of the *C9ORF72* repeat-containing RNA, and (3) altered function caused by a polypeptide containing dipeptide repeats encoded by the *C9ORF72* hexanucleotide repeat.

The *C. elegans* genome contains an uncharacterized gene homologous to *C9ORF72*, *F18A1.6.* We are analyzing the normal spatial and temporal expression pattern and determining the biological function and molecular genetic pathway of action of F18A1.6. Using a translational reporter, we have determined that F18A1.6 is expressed from early in embryogenesis to adulthood in epithelial, muscle, hypodermal and intestinal cells and mainly localizes in the cytoplasm. Preliminary observations of mutants carrying different *F18A1.6* alleles suggest that *F18A1.6* loss-of-function mutants are altered in locomotion and lifespan.

We are also trying to identify phenotypic abnormalities caused by the expression in neurons of the expanded *C9ORF72* GGGGCC repeats that cause ALS and FTD. Animals expressing a pathogenic number but not a wild-type number of repeats show locomotion defects. We will design genetic screens to identify genes that mediate or mitigate the behavioral and cellular defects of *F18A1.6* mutations or of GGGGCC hexanucleotide repeat expansions. These screens could identify molecular genetic pathways of action of normal and abnormal *C9ORF72* and thereby define new potential therapeutic targets for ALS and FTD.

Our goal is 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. More generally, we hope to contribute to the understanding of how repeat-expansion mutations can lead to neuromuscular disorders.

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Research area: Cell death and neurodegeneration