The *C. elegans* homolog of the ALS gene *C9orf72* functions in endomembrane trafficking

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 (FTD) (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 accumulate yolk proteins in the perivitellin fluid. This defect can be completely rescued by overexpression of *F18A1.6* or partially rescued by expression of a wild-type *C9orf72* cDNA. Rescue experiments in which we expressed *F18A1.6* in different cell types and at different stages of development in *F18A1.6* mutants suggest that *F18A1.6* does not act in the gut primordium to promote yolk protein endocytosis. Suppression of this phenotype by knock down of the late endosome-specific Rab GTPase *rab-7* and Rab

GTPases involved in secretion indicate that the defect observed in these embryos is caused by an abnormal release of yolk proteins and that *F18A1.6* might be involved in the retention of yolk proteins during the proliferative stage before its release for subsequent uptake by the gut primordium during morphogenesis.

We have also observed that mutations in *rab-2*, which encodes the *C. elegans* homolog of human Rab2 GTPase, cause a similar defect and that *rab-2; F18A1.6* double mutants exhibit an enhanced defect in yolk protein transport. RAB-2 clusters around yolk granules in the absence of *F18A1.6*.

Finally, we have also observed that lysosomes and exocytic vesicles are abnormally localized in *F18A1.6* mutant embryos.

Our goal is to understand the function of *F18A1.6*, determine the functional conservation between *F18A1.6* and *C9orf72* and help understand how the mutation of *C9orf72* causes the development and progression of ALS.