

“Amyotrophic Lateral Sclerosis (ALS) & Related Motor Neuron Diseases”

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A *C9orf72* ALS/FTD ortholog acts in endolysosomal degradation and lysosomal homeostasis

The most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is the expansion of a hexanucleotide repeat in a non-coding region of the gene *C9orf72*. We report that loss-of-function mutations in *alfa-1*, the *Caenorhabditis elegans* ortholog of *C9orf72*, cause a novel phenotypic defect: endocytosed yolk is abnormally released into the extra-embryonic space, resulting in refractile “blobs.” The *alfa-1* blob phenotype is partially rescued by the expression of the human *C9orf72* protein, demonstrating that *C9orf72* and *alfa-1* function similarly. We show that *alfa-1* and *R144.5*, which we identified from a genetic screen for mutants with the blob phenotype and renamed *smcr-8*, act in the degradation of endolysosomal content and subsequent lysosome reformation. The *alfa-1* abnormality in lysosomal reformation results in a general dysregulation in lysosomal homeostasis, leading to defective degradation of phagosomal and autophagosomal contents. We suggest that aspects of the pathogenic and clinical features of ALS/FTD caused by *C9orf72* mutations, such as altered immune responses, aggregation of

autophagy targets and excessive neuronal excitation, result from a reduction in *C9orf72* gene function and consequent abnormalities in lysosomal degradation.