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Studying human disease genes in *C. elegans*

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We are generating worm models of hereditary neurological diseases to study the genetic mechanisms underlying these disorders. Our current efforts are focused on models of the gain-of-function diseases familial amyotrophic lateral sclerosis (FALS) and Huntington's Disease (HD) and the loss-of-function diseases spinal muscular atrophy (SMA) and lissencephaly.

To attempt to model ALS we have generated transgenic worms carrying extrachromosomal arrays of the human copper/zinc superoxide dismutase cDNA driven by conditional or constitutive promoters. We employed a similar strategy to attempt to model HD. We are currently performing western blot analyses to assay expression of the human proteins in our transgenic strains.

We have used RNAi and PCR-based deletion screening to study the loss-of-function phenotypes associated with disruption of *C. elegans* homologs of the known lissencephaly disease genes LIS1 and DCX and the LIS1-interactor *nudC*. RNAi of the LIS1-like gene produced an embryonic-lethal phenotype. We have isolated two deletion mutants of the worm LIS1 homolog and are now characterizing their phenotypes. Studies of *Aspergillus* and mice indicate that LIS1 interacts with a gene similar to the *Aspergillus nudC* gene. RNAi of the *C. elegans nudC* homolog yields an embryonic-lethal phenotype; escapers die at the L3 and L4 stages or become sterile adults. We have also obtained a candidate deletion within the worm *nudC* homolog and are now isolating worms containing this deletion. Mutations of DCX (doublecortin) in humans produce X-linked subcortical laminar heterotopia and lissencephaly syndrome. RNAi of the DCX homolog produced a variety of defects at low penetrance, including embryonic lethality, rollers, and severely malformed bodies. We are currently screening for deletions of the worm DCX homolog. RNAi of the SMA disease gene Survival of Motor Neurons (SMN) homolog yielded sterile progeny, many of which moved with abnormally deep body bends. Abnormalities of the reproductive system included morphologically misshapen gonads and defective oocyte maturation. We have obtained a candidate deletion of the SMN homolog and are isolating worms with this deletion.