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THE *C. elegans* LISSENCEPHALY (LIS1)-LIKE GENE *lis-1* IS REQUIRED FOR EMBRYONIC DEVELOPMENT

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In the human disease lissencephaly, abnormal neuronal migration during brain development leads to reduced cerebral convolutions. Patients with lissencephaly suffer from epilepsy and mental retardation. The most common cause of lissencephaly is haploinsufficiency of the gene LIS1. The predicted *C. elegans* LIS-1 protein is 58% identical to human LIS1. We have isolated two deletion alleles of *lis-1*. One deletion removes 1,465 nucleotides, including predicted exons 4-5, and a second deletion removes 2,019 nucleotides, including predicted exons 4-6. These two mutations fail to complement each other for the defects described below.

Deletion homozygotes are Unc, Egl, and Mel. Progeny of deletion homozygotes arrest at the 50-100 cell stage and contain enlarged, heterogeneous, asymmetrically distributed nuclei. We have analyzed the cell biological basis of the defects in embryonic development and in egg-laying. A *lis-1::gfp* transcriptional fusion gene driven by the *lis-1* promoter is expressed in multiple tissue types in transgenic worms; expression in the nervous system is restricted to a subset of neurons. We are now attempting to confirm this expression pattern using antibody staining. To test whether the human and worm genes might be orthologous, we are attempting to rescue the phenotype of the worm deletion mutants with the human LIS1 cDNA driven by either the heat-shock promoters or the endogenous *lis-1* promoter.

We are seeking *lis-1* interactors both by screening for suppressors of the *lis-1* Mel phenotype and by testing candidate genes. A preliminary F1 screen of ~10,000 haploid genomes failed to yield suppressors of the *lis-1* Mel phenotype. We now plan to extend this screen to the F2 generation.