CHARACTERIZATION OF *SUP-11* AND *SUP-18*, TWO REGULATORS OF THE SUP-9/SUP10/UNC-93 TWO-PORE POTASSIUM CHANNEL COMPLEX

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Rare altered-function mutations in the genes *unc-93*, *sup-9*, and *sup-10* result in the abnormal regulation of muscle contraction. These mutants move sluggishly, are unable to lay eggs, and exhibit the rubber-band phenotype: when worms are prodded on the head, they contract and relax along their entire bodies without moving backwards. Genetic studies suggest that these three genes act at the same step and likely encode subunits of a protein complex. We have shown that *sup-9* encodes a two-pore K^+ channel subunit with similarity to mammalian TASK. *unc-93* and *sup-10* encode novel putative transmembrane proteins.

Loss-of-function mutations in a fourth gene, *sup-18,* completely suppress the rubber-band phenotype caused by a *sup-10(gf)* mutation and partially suppress the *unc-93(gf)* and *sup-9(gf)* rubber-band phenotypes. We have shown that *sup-18* encodes a single-pass transmembrane protein. Its intracellular domain shares sequence similarity with a family of bacterial NADH oxidases. A *sup-18::gfp* fusion is expressed in muscle and is localized to dense bodies, along with SUP-9 and UNC-93::GFP. We are making deletions in the *sup-18::gfp* reporter to identify regions of SUP-18 required for colocalization with SUP-9. In addition, we are assaying recombinant SUP-18 for nucleotide binding and dehydrogenase activities *in vitro*.

Rare gain-of-function mutations in *sup-11* cause a small scrawny phenotype, completely suppress the *unc-93(gf)* rubber-band defects and act as partial suppressors of the *sup-10(gf)* and *sup-9(gf)* rubber-band phenotypes. Loss-of-functions mutations in *sup-11* cause embryonic lethality. While *sup-11(gf)* and *sup-18(lf)* mutations each only partially suppress the *sup-9(gf)* rubber-band phenotype, *sup-11(gf)*; *sup-9(gf)*; *sup-18(lf)*animals are completely suppressed for the rubber-band phenotype, suggesting that *sup-11* and *sup-18* act in parallel. Since *sup-11* is an essential gene, SUP-11 may interact with channels in addition to SUP-9, with the gain-of-function mutations affecting mainly its interaction with the SUP-9/SUP-10/UNC-93 complex but not with other channels. *sup-11* has been mapped to a small interval on LGI. We are further mapping *sup-11* against polymorphisms in the region and determining the sequences of candidate genes from *sup-11* mutants.