25. *egl-41*, which may act in sex determination, is identical to *sel-10*, which encodes an F-box protein and negative regulator of *lin-12*/Notch

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Hermaphrodites carrying dominant mutations in the gene *egl-41* (*egl*, egg-laying defective) lack the hermaphrodite-specific HSN neurons but have the male-specific CEM neurons and therefore are weakly masculinized (1, 2). Our analyses with a deficiency (*nDf42*) and a duplication (*ctDp8*) that span the *egl-41* locus indicate that *egl-41* is not haplo-insufficient and that the dominant mutations cause an altered function that is antagonized by wild-type activity. The existing *egl-41* alleles (*n1069, n1074, n1077, e2055, n3717*) therefore most likely represent gain-of-function (gf) mutations causing altered function. It has previously been shown that *egl-41*(gf) mutations enhance the masculinizing effect of weak loss-of-function (lf) mutations in *tra-2* (*tra*, transformer) and suppress the feminizing effect of a *tra-2*(mx) (mx, mixed character) allele (1, 3). In addition, a null mutation of *fem-1* (*fem*, feminization) was found to be epistatic to *egl-41*(gf) mutations (3). Our analyses furthermore indicate that lf mutations of *fem-2* and *fem-3* are epistatic to *egl-41*(gf) mutations as well and that *egl-41*(gf) mutations are epistatic to a *her-1*lf) (*her*, hermaphroditization) mutation. We suggest the gene defined by *egl-41*(gf) mutations is part of the genetic pathway that specifies sexual fate and acts between *her-1* and the *fem* genes. To determine the lf phenotype of *egl-41* and to facilitate the cloning of the gene by transformation rescue, we performed an F1 screen for dominant revertants of the phenotype caused by the *egl-41*(gf) mutation *n1077*. We screened 20,000 haploid genomes and identified one mutation, *bc189*, that is closely linked to the *egl-41* locus. *bc189* completely suppresses the *egl-41*(*n1077*gf) phenotype but causes no obvious additional abnormalities. We therefore cloned the gene by combining fine mapping, using SNPs, and our observation that the dominant phenotype of *egl-41*(*n1077*gf) is antagonized by wild-type activity. *egl-41* proved to be identical to a gene previously characterized, *sel-10* (*sel*, suppressor/enhancer of *lin-12*). *sel-10* was identified as a negative regulator of *lin-12*/Notch (*lin*, lineage abnormal) signaling and encodes an F-box protein (4, 5). The *egl-41*(gf) mutations as well as *bc189* are missense mutations in the *sel-10* ORF (G566R and D482N, respectively). We will therefore now refer to *egl-41* as *sel-10*. *sel-10*(*bc189 n1077*) suppresses a partial lf mutation of *lin-12*, enhances a gf mutation of *lin-12*, and suppresses a lf mutation of *sel-12* and therefore genetically behaves like the canonical lf allele of *sel-10*, *ar41*. Surprisingly, using the same criteria, *sel-10*(*n1077*gf) also behaves like a *sel-10*(lf) mutation. Furthermore, preliminary data indicate that, just like *sel-10*(gf) mutations, *bc189 n1077* as well as *ar41* enhance the masculinizing effects of weak *tra-2*(lf) mutations. These results suggest that *sel-10* is normally involved in the determination of sexual fate and that *sel-10*(gf) mutations share certain characteristics with *sel-10*(lf) mutations. Using biochemical and molecular approaches, we are currently seeking potential targets of the F-box protein SEL-10 in the sex determination pathway.

1. C. Desai, H. R. Horvitz, Genetics 121, 703-21 (1989). 2. C. Desai, G. Garriga, S. L. McIntire, H. R. Horvitz, Nature 336, 638-46 (1988). 3. T. Doniach, Genetics 114, 53-76 (1986). 4. M. Sundaram, I. Greenwald, Genetics 135, 765-783 (1993). 5. E. J. Hubbard, G. Wu, J. Kitajewski, I. Greenwald, Genes Dev 11, 3182-93. (1997).