Figure S1.
Quality control of hypoxia mutant data. To establish the veracity of our measurements, we searched for three genes that are reported to change expression upon induction of HIF-1: *rhy-1*, *egl-9*, *nhr-57*. All three genes exhibited previously reported expression patterns. *nhr-57* is a classical reporter of *hif-1* activity—the fact that *nhr-57* expression was not significantly lower in *hif-1* and *egl-9 hif-1* mutants in particular serves as an important control that indicates the wild-type samples did not become hypoxic prior to RNA extraction. As a negative control we selected *lam-3*, which is not reported to be downstream of *hif-1*. Stars indicate that genes were differentially expressed in the relevant mutant relative to the wild-type control with $q<0.1$

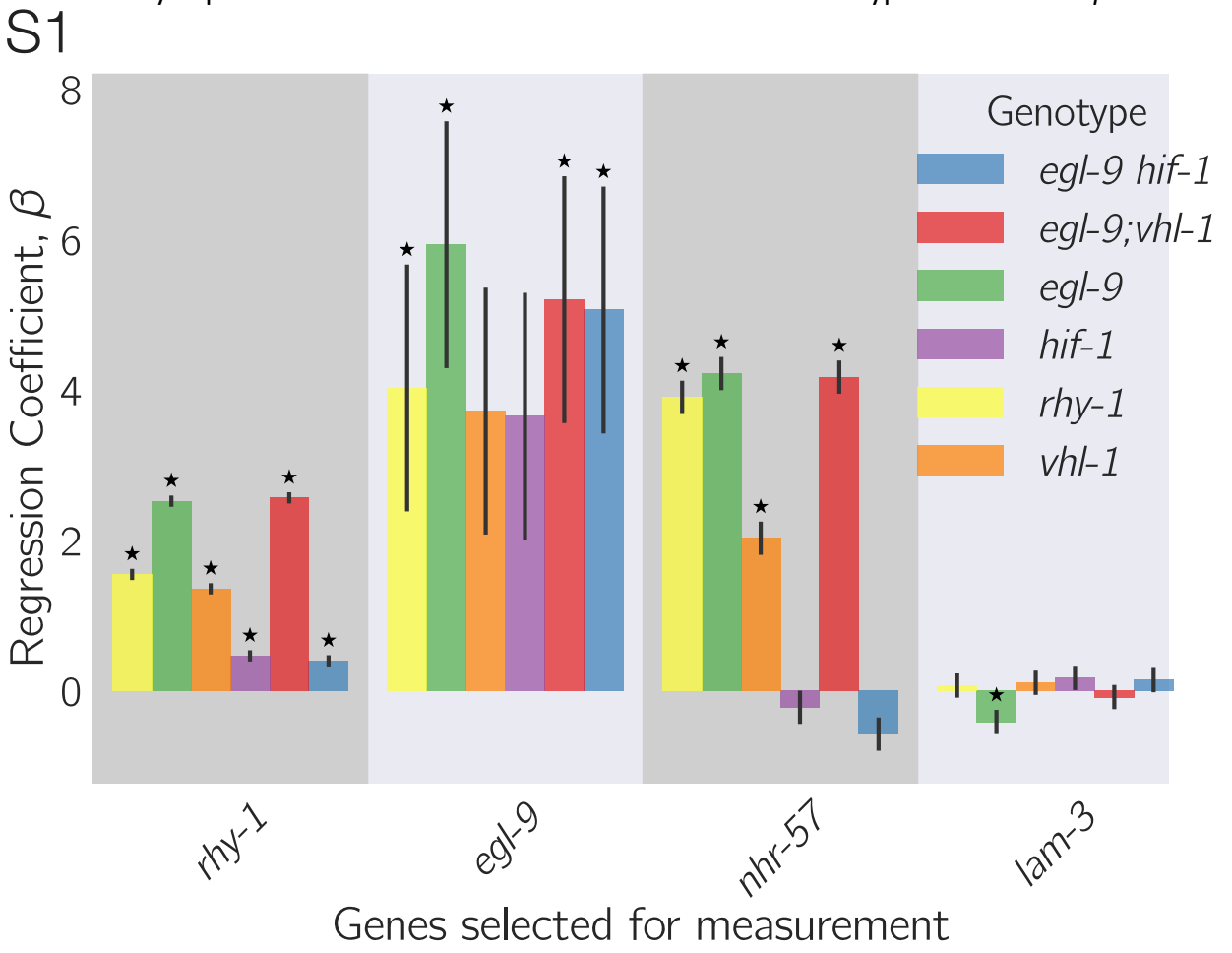


Figure S2.
Epistasis measurements of *hif-1* and *egl-9* show that the *egl-9 hif-1* double mutant recapitulates the phenotype of the *hif-1* single mutant, resulting in an epistasis coefficient, $s_{hif\text{-}1,egl\text{-}9}$=-0.8. This epistasis coefficient suggests that *hif-1* is inhibited by *egl-9*.

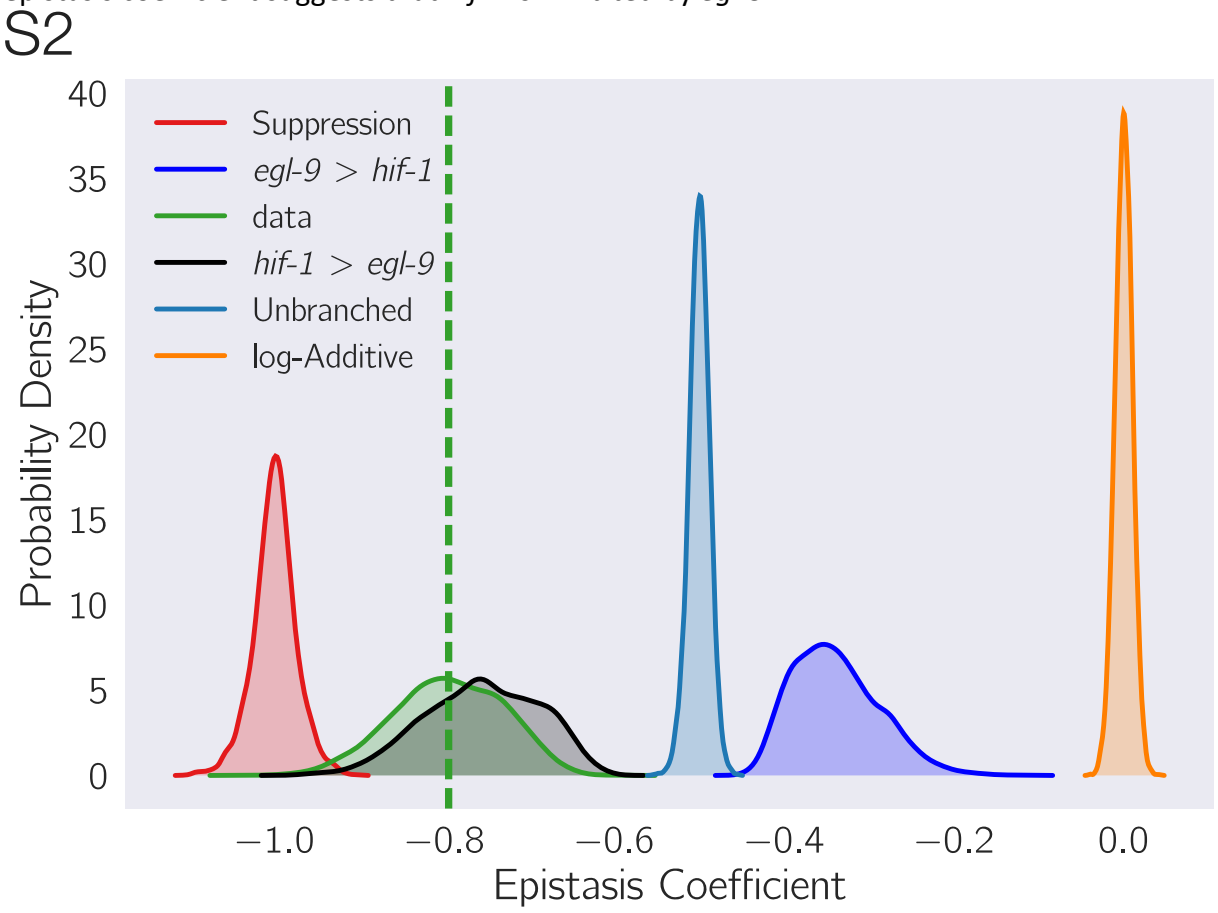
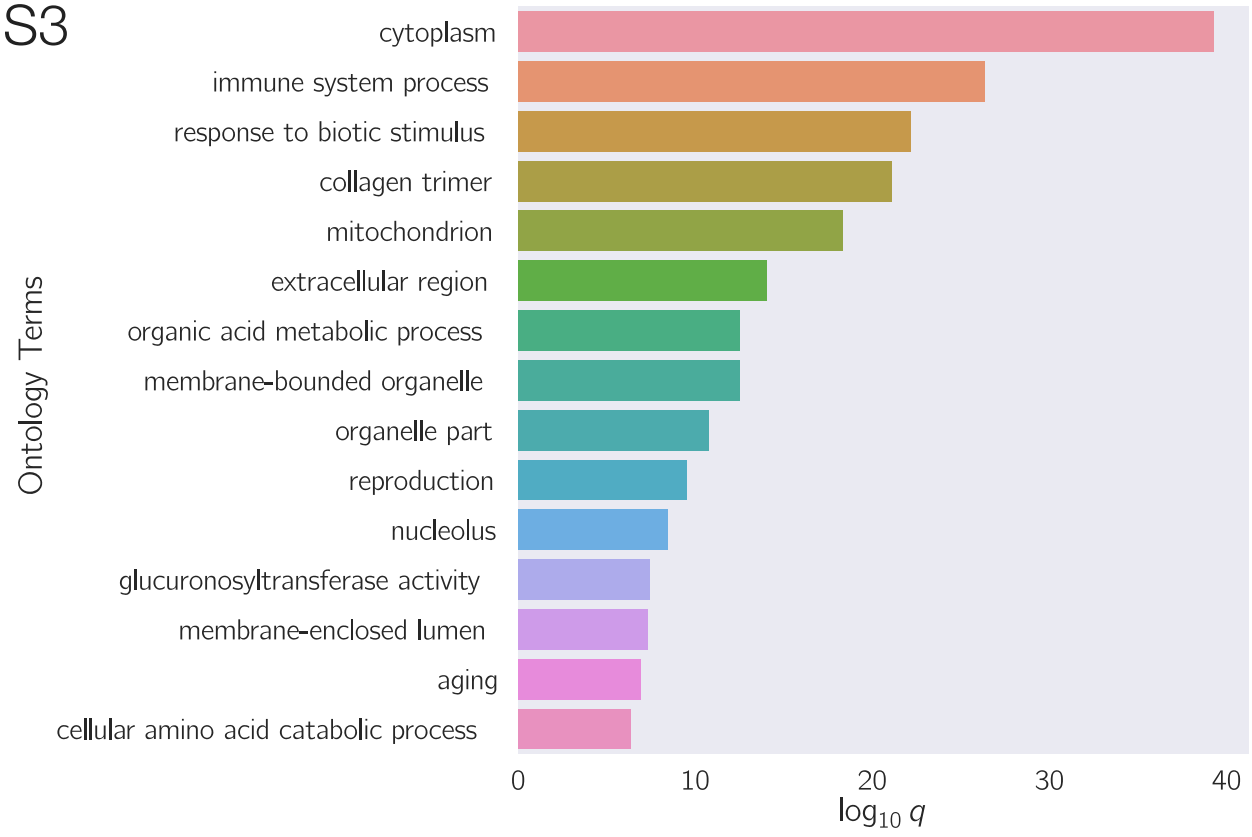


Figure S3, 4.
GO and Tissue Enrichment Analyses of the hypoxia response. The hypoxia response genes we identified are enriched in a variety of molecular processes that are known to be impacted by hypoxia. Moreover, the two most enriched tissues, the intestine and hypoderm, have been previously observed to respon



d strongly to hypoxia.

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