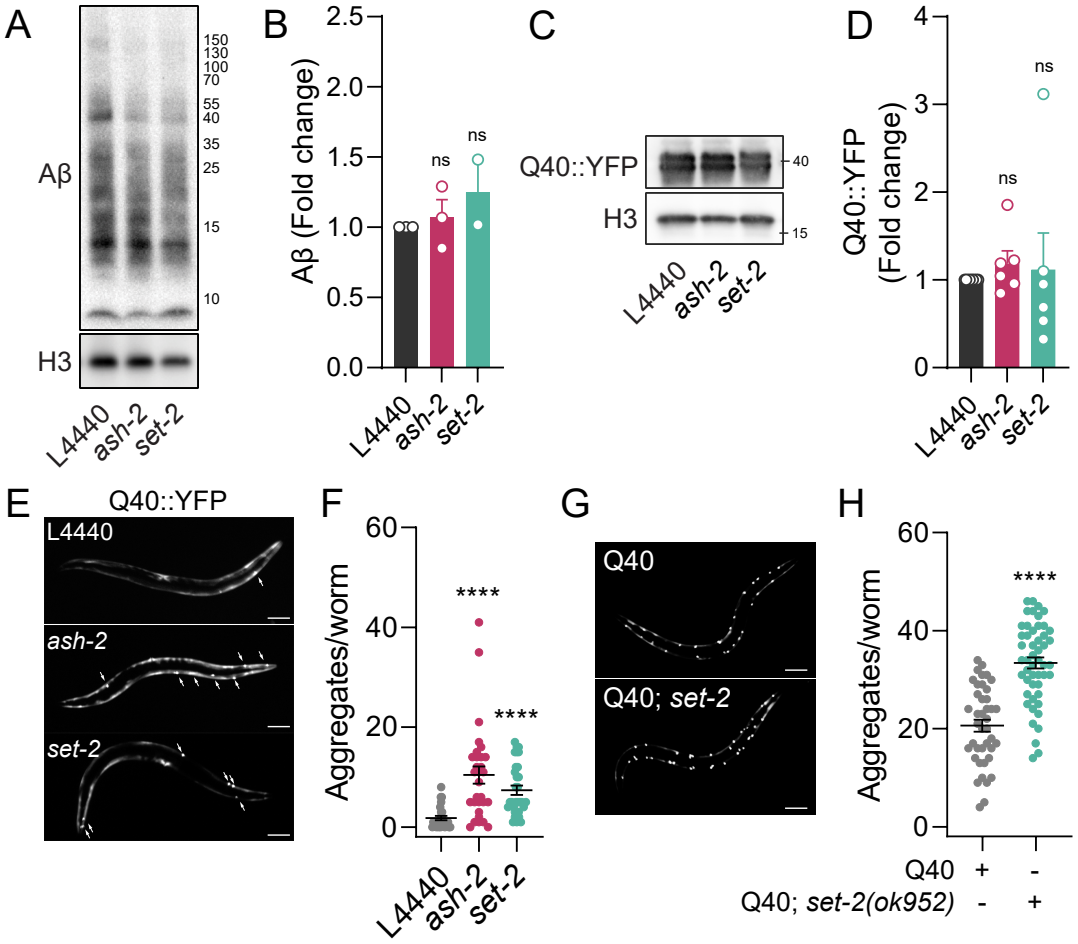

Fig. S1. Amyloid levels and polyQ foci formation in H3K4me3 modifier-deficient *C. elegans* (related to Figure 1).
(A, B) Levels of $A\beta_{1\text{-}42}$ in CL4176 worms maintained on control (i.e. L4440), *ash-2* or *set-2* RNAi were assessed by western blot (*A*) and quantified by densitometry (*B*). *(C, D)* Levels of Q40::YFP in worms maintained on control (i.e. L4440), *ash-2* or *set-2* RNAi were assessed by western blot *(C)* and quantified by densitometry (*D*). (*E, F)* Q40::YFP expressing *C. elegans* strain AM141 was maintained on control (i.e. L4440), *ash-2* or *set-2* RNAi and Q40::YFP aggregates were examined 96 h after egg lay (i.e., day 1 of adulthood) by fluorescence microscopy (*E*) and quantified *(F)*. Each symbol represents an individual worm and at least 30 animals were assessed per condition. *(G, H)* Wild-type or *set-2 (ok592)* Q40::YFP *C. elegans* were examined 96 h after egg lay (i.e., day 1 of adulthood) by fluorescence microscopy (*G*) and aggregates were quantified *(H).* Differences is relative aggregate number between (*E, F)* and *(G,H)* is likely due to the differences in the bacterial strains (RNAi strain L4440 versus OP50) used as food source. Each symbol represents an individual worm. At least 30 animals were assessed per condition. Results are representative *(A, C, E, G)* or the average ± SEM *(*graphs in *B, D)* of four (*E-F*), six (*C, D*), three (*A, B;* L4440 and *ash-2*) or two (*A, B; set-2*) independent experiments. Statistical significance was assessed by one-way ANOVA *(B, D),* Kruskal-Wallis *(F)*, or Mann-Whitney *(H)*; ****, $p<0.0001$. Scale bar = 0.1 mm.

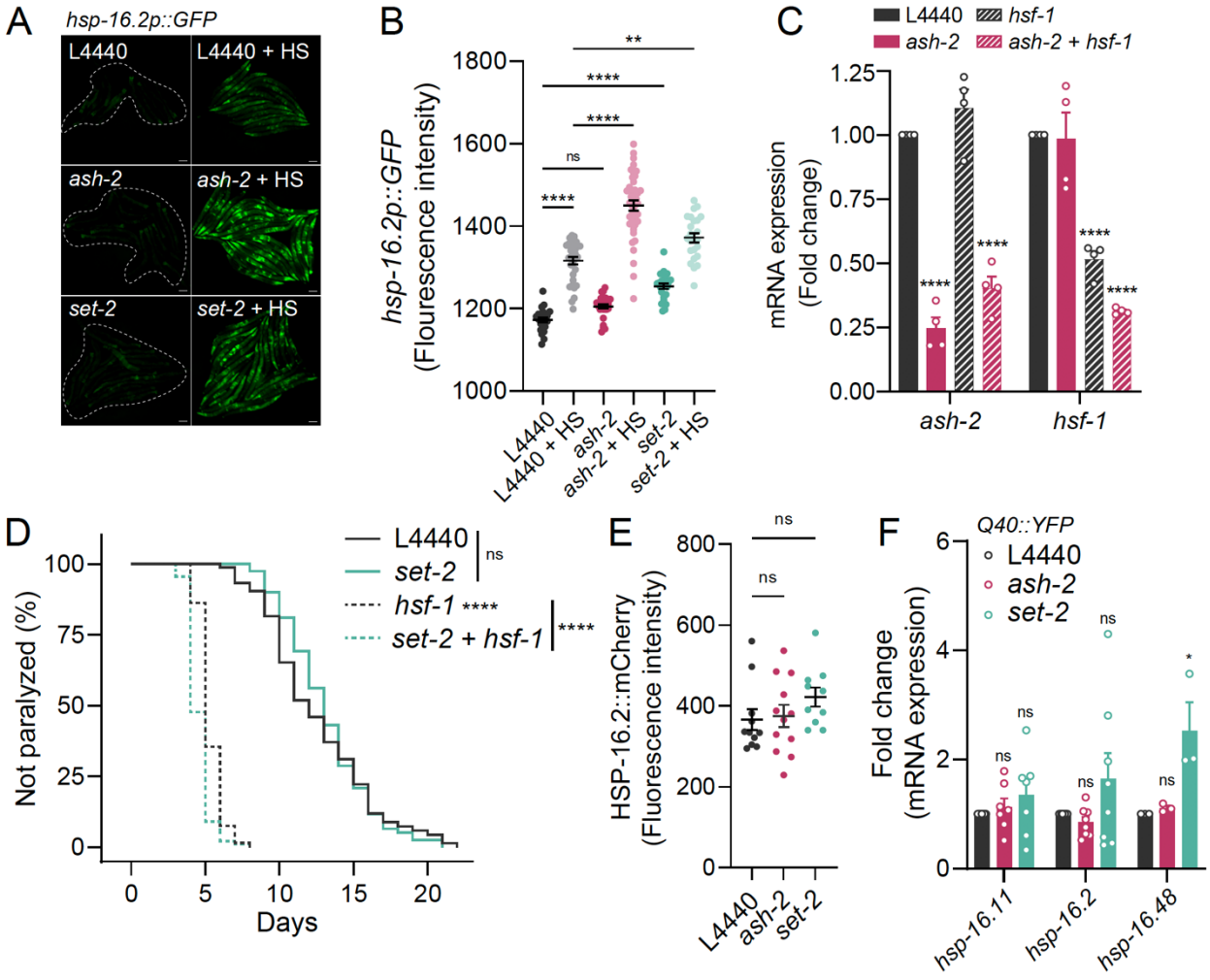

Fig. S2. H3K4me3 modifier depletion does not enhance heat shock gene expression under non-stress conditions (related to Figure 2).
(*A*) Fluorescence images of day 1 adult *hsp-16.2p::GFP* expressing worms maintained on control (L4440), *ash-2* or *set-2* RNAi before and following heat shock (HS). Scale bar is 0.1 mm. (*B*) Quantification of the fluorescence in individual worms (symbols) shown in *(A)*. *(C)* Knockdown efficiency of *ash-2* and *hsf-1* in day 1 adult Q40::YFP animals maintained on L4440, *ash-2, hsf-1,* or *ash-2* + *hsf-1* RNAi. *(D)* Paralysis of Q40::YFP animals maintained on L4440, *set-2, hsf-1,* or *set-2* + *hsf-1* RNAi. *(E)* Quantification of HSP-16.2::mCherry fluorescence in the heads of *hsp-16.2p::hsp-16.2::mCherry* expressing Q40::YFP animals aged to day 5 of adulthood at 20°C on control (L4440), *ash-2* or *set-2* RNAi. At least 10 animals assessed per condition. (*F*) Steady state expression of heat shock genes *hsp-16.11, hsp-16.2, hsp-16.48* in Q40::YFP animals maintained on control (L4440), *ash-2* or *set-2* RNAi as determined by RT-PCR. Statistical significance was determined by Kruskal-Wallis *(B, F),* one-way ANOVA *(C, E)* or log-rank *(D)*; p<0.05, *; p<0.0001, ****. Additional experimental information, and data for biological replicates not shown can be found in Table S1.

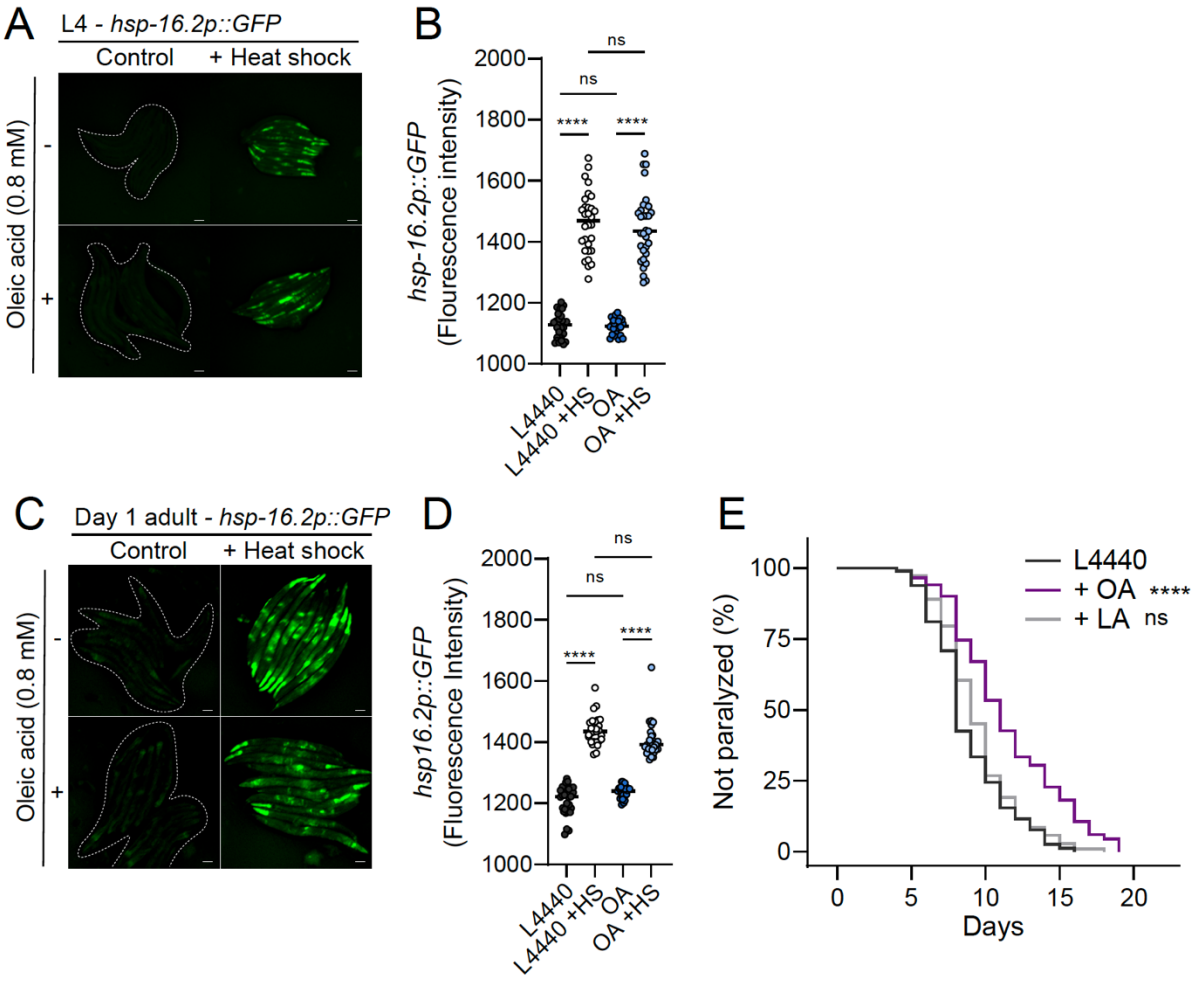

Fig. S3. Oleic acid does not activate or potentiate the heat shock response (related to Figure 3).

(A, B) L4 or (*C, D*) day 1 adults expressing the *hsp-16.2p::GFP* reporter were maintained on control RNAi (L4440) in the absence or presence of 0.8 mM oleic acid. Worms were either left untreated or subjected to heat shock (HS) treatment (35°C for 2 h, 20° for 2 h). Fluorescence images were taken (*A, C*) and quantified *(B, D)*. At least 25 animals were assessed per condition. Scale bar in *A, C* is 0.1 mm. *(E)* Q40::YFP animals were maintained on NGM plates in the absence of supplements or in the presence of oleic acid (0.8 mM) or linoleic acid (0.8 mM). Paralysis was measured as described before. Results are representative of three independent experiments. Statistical significance was assessed by Kruskal-Wallis test *(B, D)* and log-rank *(E)*; *, $p<0.05$; **, $p<0.01$; ****, $p<0.0001$. Additional experimental information, and data for biological replicates not shown, can be found in Table S1.

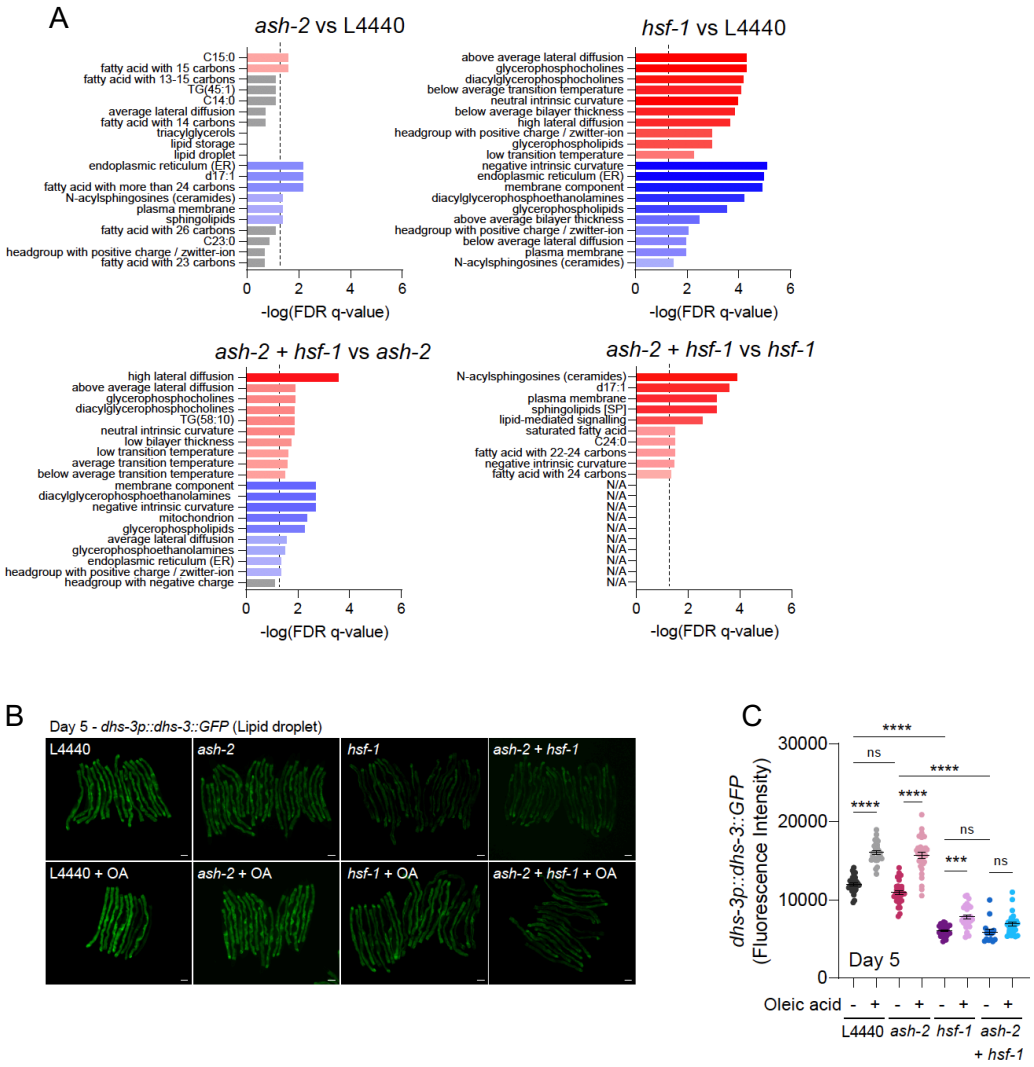

Fig. S4. Effects of H3K4me3 modifier or *hsf-1* depletion and oleic acid supplementation on lipid ontology enrichment and lipid droplet formation (related to Figure 4).
(A) Mass spectrometry analysis of lipid levels in Q40::YFP animals maintained on L4440, *ash-2, hsf-1,* or *ash-2* + *hsf-1* RNAi was conducted, and significantly altered lipids between indicated conditions were analyzed for ontology enrichment using LION/web analysis. Enriched categories in lipids that increased in each comparison are shown in red, and lipids that decreased in each comparison shown in blue, with statistically significant categories being color-coded by –log(FDR q-value). *(B, C)* LIU1 *(dhs-3p::dhs-3::GFP)* lipid droplet reporter animals were maintained on control (L4440), *ash-2, hsf-1,* or *ash-2* + *hsf-1* RNAi, and fluorescence was imaged at day 5 of adulthood. Representative images are shown. Scale bar is 0.1 mm. The *dhs-3p::dhs-3::GFP* fluorescence was quantified in *(C)*. Results are representative of at least three independent experiments. Statistical significance was assessed by one-way ANOVA *(D)*; ***, p<0.001; ****, p<0.0001.

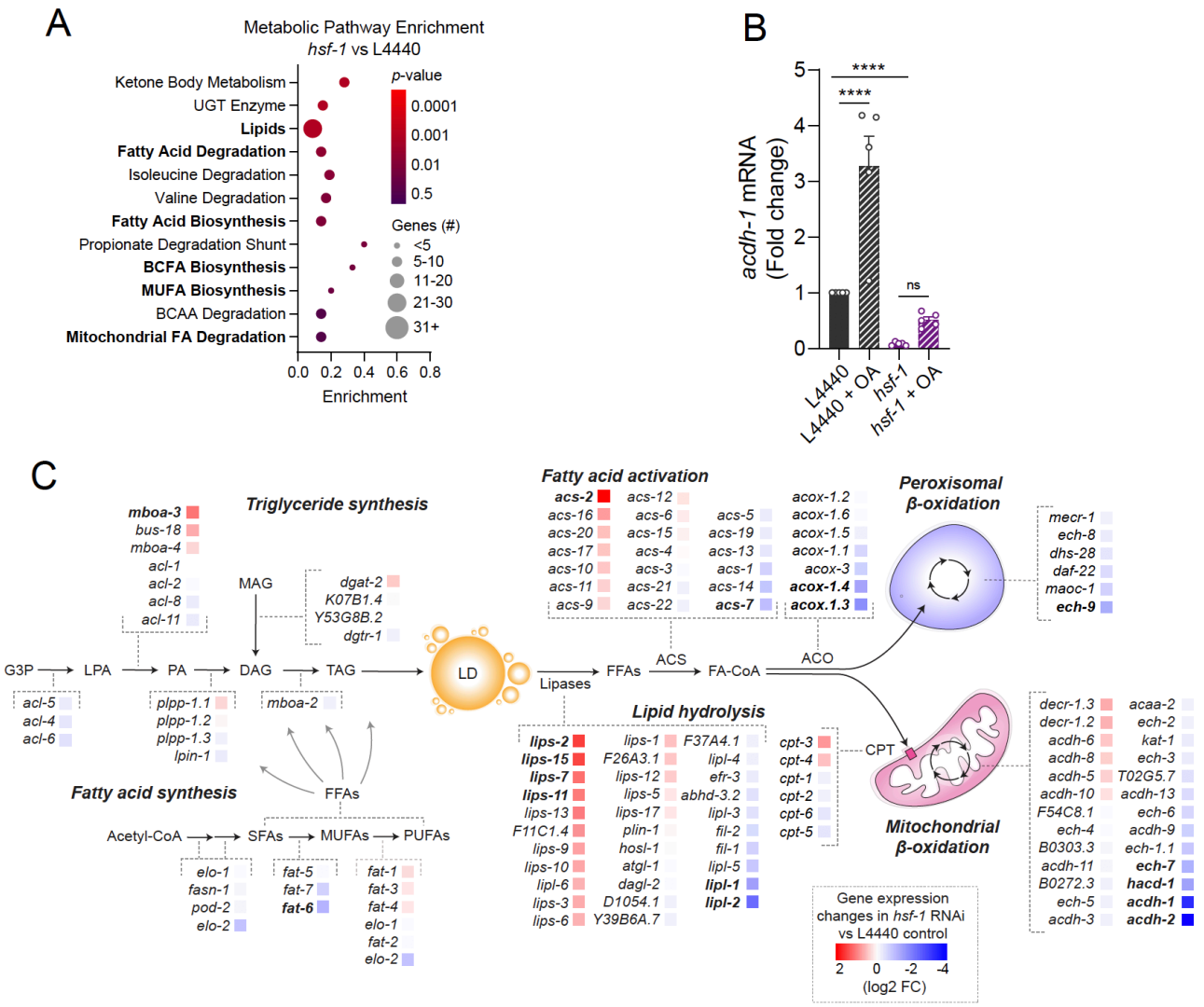

Fig. S5. *Hsf-1* knockdown alters genes involved in lipid synthesis and breakdown (related to Figure 5.)

(A) Differentially expressed genes in day 1 adult Q40::YFP worms maintained on *hsf-1* RNAi vs L4440 control RNAi were analyzed for metabolic pathway enrichment. Significant categories are color-coded by *p*-value. *(B)* Q40::YFP worms maintained on L4440 or *hsf-1* RNAi, and accumulation of *acdh-1* was assessed by qPCR. Levels of the housekeeping gene *pmp-3* were used as a control for normalization. *(C)* Changes in genes involved in fatty acid synthesis and breakdown in Q40::YFP worms deficient in *hsf-1*. Genes with statistically significant differences vs L4440 control are listed in bold. Results are the average *(A, C)* or average ± SEM *(B)* of at least four independent experiments. Additional experimental information on RNAseq analysis can be found in Table S2.