In this supplemental section we will discuss several distinct sets of differentially expressed proteins that are unique for either *daf-2* or dietary-restricted nematodes (**Supplemental table 1**). In addition we provide an overview of key, previous transcriptome-derived associations between gene categories/functions and longevity are corroborated or not by our present proteomic analysis.

Upregulation of proteasome subunits upon DR

Annotation clustering indicated overrepresentation of proteasome subunits among upregulated proteins in DR worms (**Supplemental table 1**). Indeed, several α and β subunits of the 20S core- and 19S regulator complex of the proteasome were increased significantly in DR worms (**Supplemental figure 1**), which is confirmed by GSEA (NES_{DR} = 2.08; $P < 0.001$; FDR < 0.003). The (oxidative) stress-responsive Nrf/SKN-1 transcription factor is a potent regulator of 26S proteasome subunit gene expression in both mammals and *C. elegans* (Kwak *et al.* 2003; Oliveira *et al.* 2009; Li *et al.* 2011; Niu *et al.* 2011). Furthermore, inhibition of proteasomal gene expression by RNAi results in activation of Nrf/SKN-1 and subsequent compensatory upregulation of proteasomal subunits in both mammals and *C. elegans* (Kraft *et al.* 2006; Kahn *et al.* 2008; Radhakrishnan *et al.* 2010; Li *et al.* 2011). We therefore hypothesize that SKN-1 is responsible for the observed increased levels of 26S proteasome subunits in DR nematodes, since activation of SKN-1 in the ASI neurons is required for lifespan extension by bacterial dilution induced DR (Bishop & Guarente 2007). In response to (oxidative) stress, SKN-1 translocates to the nucleus and regulates the expression of hundreds of genes (An & Blackwell 2003; Tullet *et al.* 2008; Oliveira *et al.* 2009). Since it has been established that the 20S core of the proteasome is responsible for the degradation of the majority of oxidatively damaged proteins, it makes sense that regulation of proteasomal subunit expression should fall under the control of SKN-1 (Davies 2001; Breusing & Grune 2008; Wang *et al.* 2010). It also follows that increased proteasome expression could potentially alleviate

age-related oxidative damage resulting in lifespan extension of diet-restricted animals (Opalach *et al.* 2010).

daf-2-specific upregulation of transthyretin-like proteins

The abundance of several nematode-specific proteins containing a transthyretin-like (TTR-like) domain was significantly increased in *daf-2(e1370)* mutants (NES_{daf-2} = 1.73, *P* = 0.003; FDR = 0.017; **Supplemental figure 2F**). This finding is consistent with reported transcriptional activation of TTR-like genes in *daf-2* mutants and/or dauers (McElwee *et al.* 2004). *C. elegans* encodes 59 genes that contain a transthyretin-like domain, with rather weak similarities to mammalian transthyretin (Sonnhammer & Durbin 1997). In mammals, transthyretin is best known as a transporter for the thyroid hormone, thyroxine (T4) and retinol (vitamin A). However, in recent years, a much larger diversity in function and ligand binding for TTR has been acknowledged, especially as a neuroprotective component in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease (Fleming *et al.* 2009). In nematodes, nothing is known about the ligand-specificity and respective functions of TTR-like proteins, although a predicted signal sequence suggests a transmembrane location (Sonnhammer & Durbin 1997). TTR-like proteins were also found among the most represented in the excreted/secreted proteome of parasitic nematodes (Nagaraj *et al.* 2008). Given the evolutionary conservation of the ligand-binding site, McElwee *et. al.* (2004) have proposed some TTRs may play an active role in binding and excreting potentially toxic lipophilic compounds (McElwee *et al.* 2004). However, affinity-purified transthyretin-like protein 1 (TTL-1) from the nematode *Ostertagia ostertagia,* which shows high sequence similarity with several *C. elegans* TTR-like proteins, was devoid of any lipid and thyroid hormone binding properties (Saverwyns *et al.* 2008). Notably, RNAi against *ttr-1* extends nematode life-span in a *daf-16* dependent fashion and enhances dauer formation, suggesting a role for TTR-1 as part of the IIS pathway

(Hansen *et al.* 2005). Several TTR-like genes were induced upon infection with pathogenic LF82 *E. coli*, which suggests TTR-like proteins could be involved in the immune response (Simonsen *et al.* 2011).

Differential expression of proteins involved in the stress response and innate immunity

We observed DAF-16-induced upregulation of several glutathione-S-transferases (GSTs) and one UDP-glucuronosyltransferase (UGT) (**Supplemental figure 2A**). GSTs and UGTs are key enzymes in phase 2 detoxification by conjugation of xenobiotic or endobiotic lipophilic compounds to glutathione and UDP-glucuronic acid, which greatly facilitates their excretion from the cell (phase 3) (Tukey & Strassburg 2000; Sheehan *et al.* 2001; Ayyadevara *et al.* 2007). Some GSTs are also involved in oxidative-stress resistance (Tawe *et al.* 1998; Leiers *et al.* 2003). The *C. elegans* genome is predicted to encode 44 GSTs and 65 UGTs and several groups have reported DAF-16 and/or SKN-1-dependent transcriptional upregulation of numerous UGTs and GSTs (An & Blackwell 2003; Murphy *et al.* 2003; Wang & Kim 2003; McElwee *et al.* 2004; Ayyadevara *et al.* 2005a; Halaschek-Wiener *et al.* 2005; Tullet *et al.* 2008; Oliveira *et al.* 2009; Jones *et al.* 2010). GST-10 was shown to be required for full *daf-2* longevity and its over-expression increases wild-type mean lifespan (Ayyadevara *et al.* 2005a; Ayyadevara *et al.* 2005b). We note that GST-42 encodes a putative maleylacetoacetate isomerase that participates in tyrosine catabolism, which is upregulated in *daf-2* and requires glutathione as coenzyme. Therefore, GST-42 as such has probably no direct role in detoxification or oxidative stress metabolism.

We also detected two cadmium responsive (CDR) gene products, CDR-2 and CDR-4, which appear induced by DAF-16 (**Supplemental figure 2A**). The CDR gene family in *C. elegans* consists of seven hydrophobic, lysosomal membrane proteins with a conserved glutathione-S-transferase domain (Dong *et al.* 2005; Dong *et al.* 2008; Hunter *et al.* 2009). Their promoter region contains different stress-responsive elements (antioxidant-, heatshock- and metal-responsive elements). However, the exact role of these genes in the stress response remains to be determined.

Another aspect of the stress response is the conservation of existing proteins via molecular chaperones/heat shock proteins (HSPs). Although we detected differential expression of several HSPs, only one (T05E11.3, an ortholog of the GRP94/GP96 branch of HSP90 heat shock factors) was upregulated in *daf-2* mutants (**Supplemental figure 2B**). UGGT-1 which is also DAF-16-induced, encodes one of two *C. elegans* UDP-Glc:glycoprotein glucosyltransferases (UGGTs), which is responsible for monitoring the correct folding of glycoproteins in the ER by glycosylating not properly folded glycoproteins and targeting them for proteasomal degradation (Guerin & Parodi 2003; Buzzi *et al.* 2011).

Strong DAF-16-dependent transcriptional activation of HSP20/α-crystallins or small heatshock proteins (sHSPs) was previously observed in *daf-2* mutants (Hsu *et al.* 2003; Murphy *et al.* 2003; McElwee *et al.* 2004). This activation of sHSPs is required for the full lifespan extension in *daf-2* mutants (Hsu *et al.* 2003). Y55F3BR.6 and HSP12.2 represent two sHSPs in our dataset (Kokke *et al.* 1998). Interestingly, these sHSPs appear specifically activated in DR but not in *daf-2* mutants. This suggests that (a subset of) sHSPs are possibly also involved in DR-induced lifespan extension. Surprisingly, several HSPs are actually down-regulated in *daf-2* mutants (DAF-21, HSP-1, DNJ-19), dietary restriction (T24H7.2), or in both *daf-2* and DR worms (HSP-6). Previously, RNAi of *daf-21* and *hsp-1,* but not *dnj-19*, was shown to result in a small reduction in *age-1(hx546)* lifespan, and RNAi of *daf-21* increased susceptibility to pathogen infection (Morley & Morimoto 2004; Singh & Aballay 2006). DAF-21 is a member of the HSP90 family of heat shock factors, but it is also part of a guanylyl-cyclase-dependent chemosensory pathway that likely underlies DAF-21's involvement in the constitutive dauer formation phenotype (Birnby *et al.* 2000). HSP-6 is a mitochondrial-specific chaperone of the HSP70 superfamily involved in the mitochondrial UPR (mtUPR), which has recently been implicated in ETC-mediated longevity (Yoneda *et al.* 2004; Durieux *et al.* 2011). The level of HSP-6 also appears to correlate with *C. elegans* lifespan; overexpression of HSP-6 results in lifespan extension, whereas RNAi of *hsp-6* was reported to cause mitochondrial dysfunction and decreased lifespan (Yokoyama *et al.* 2002; Yoneda *et al.* 2004; Kimura *et al.* 2007). We note that

other groups have reported similar findings on the expression level of DAF-21 and HSP-6 in *daf-2* mutants (Dong *et al.* 2007; Durieux *et al.* 2011). We can conclude that impaired IIS does not lead to a general upregulation of HSPs, and regulation of HSPs appears more complex. Interestingly, similar conclusions were drawn from an HSP expression study in Ames dwarf mice deficient in growth hormone/IGF-1 signaling, where expression of several HSPs actually correlate positively with the level of IIS (Swindell *et al.* 2009).

Several proteins implicated in the oxidative stress response were upregulated in *daf-2* mutants, including, catalases (CTL-2 and CTL-1/-3), superoxide dismutase (SOD-1), 2-Cys peroxiredoxin (PRDX-3), glutaredoxin (GLRX-10) and glutathione peroxidase (R05H10.5), consistent with increased oxidative stress resistance of *daf-2* mutants (**Supplemental figure 2C**) (Larsen 1993; Vanfleteren 1993; Honda & Honda 1999). Interestingly, protein levels of R05H5.3, a thioredoxin, and MSRA-1, the single methionine sulfoxide reductase A (MsrA) gene in *C. elegans* (Lee *et al.* 2005), are reduced in *daf-2* mutants. MsrA is an important antioxidant enzyme that repairs oxidatively damaged methionine residues and is well-conserved from prokaryotes to eukaryotes (Cabreiro *et al.* 2006; Kim & Gladyshev 2007). The *C. elegans* genome encodes a single MsrA gene (*msra-1*) with biochemically confirmed methionine sulfoxide reductase activity (Lee *et al.* 2005). Similar to other species, mutation in *msra-1* renders *C. elegans* hypersensitive to oxidative stress, reducing both wild-type and *daf-2* lifespan (Minniti *et al.* 2009). Remarkably, Minniti *et al*. report increased *daf-16*-dependent MSRA-1 enzyme activity in adult *daf-2* mutants that increases even further with advancing age. This is unexpected in light of our own finding that total MSRA-1 protein levels in *daf-2* mutants are robustly and consistently decreased. This could imply strong post-translational regulation of MSRA-1 enzyme activity.

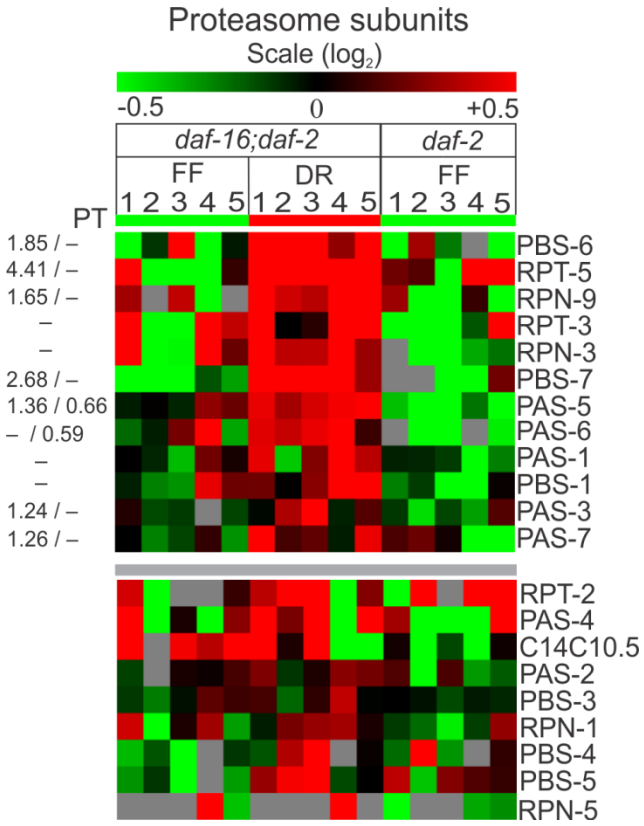
Increased expression of antioxidant enzymes is thought to be an essential part of the worms' innate immunity. In response to pathogenic bacteria *C. elegans* generates ROS at the site of infection in order to kill off the offending pathogens (Chavez *et al.* 2007; Chavez *et al.* 2009). Since this is detrimental to

117 the local endogenous tissue as well as proteins, the worm protects itself from excessive damage by
118 concurrently activating antioxidant enzymes and heat-shock proteins through DAF-16 and SKN-1 (Chavez
119 *et al.* 2007; Mohri-Shiomi & Garsin 2008; Chavez *et al.* 2009; Hoeven *et al.* 2011). Therefore, the over-
120 expression of anti-oxidant enzymes in IIS mutants explains their increased resistance to various bacterial
121 pathogens (Garsin *et al.* 2003; Troemel *et al.* 2006; Wang *et al.* 2011). In addition to anti-oxidant
122 enzymes, whole-genome transcript profiling studies have revealed DAF-16-dependent gene regulation
123 of other known antimicrobial proteins, including C-type lectins (CLECs), lysozymes and saposins
124 (McElwee *et al.* 2003; Murphy *et al.* 2003; Halaschek-Wiener *et al.* 2005). CLECs and lysozymes are an
125 important part of the innate immune response in many animals, including *C. elegans* (Mallo *et al.* 2002;
126 O'Rourke *et al.* 2006; Troemel *et al.* 2006; Alper *et al.* 2007; Wong *et al.* 2007; Schulenburg *et al.* 2008;
127 Irazoqui *et al.* 2010; Boehnisch *et al.* 2011)**.** Consistent with these studies, we found extensive DAF-16-
128 dependent regulation of several CLECs and protist-type lysozymes (**Supplemental figure 2D**).
129 Interestingly, the abundance of several lysozymes and CLECs is actually decreased in *daf-2* and/or DR
130 animals. McElwee *et al.* have reported the downregulation of 7 CLEC domain containing genes in *daf-2*
131 (McElwee *et al.* 2004). Boehnisch *et al.* have reported reduced expression of five out of eight protist-like
132 lysozymes upon infection with the pathogenic *B. thuringiensis,* notwithstanding the requirement of
133 these genes for a full host defense (Boehnisch *et al.* 2011). It therefore remains possible that these
134 genes could have other functions and, perhaps, only indirectly influence *C. elegans* survival upon
135 pathogen infection.

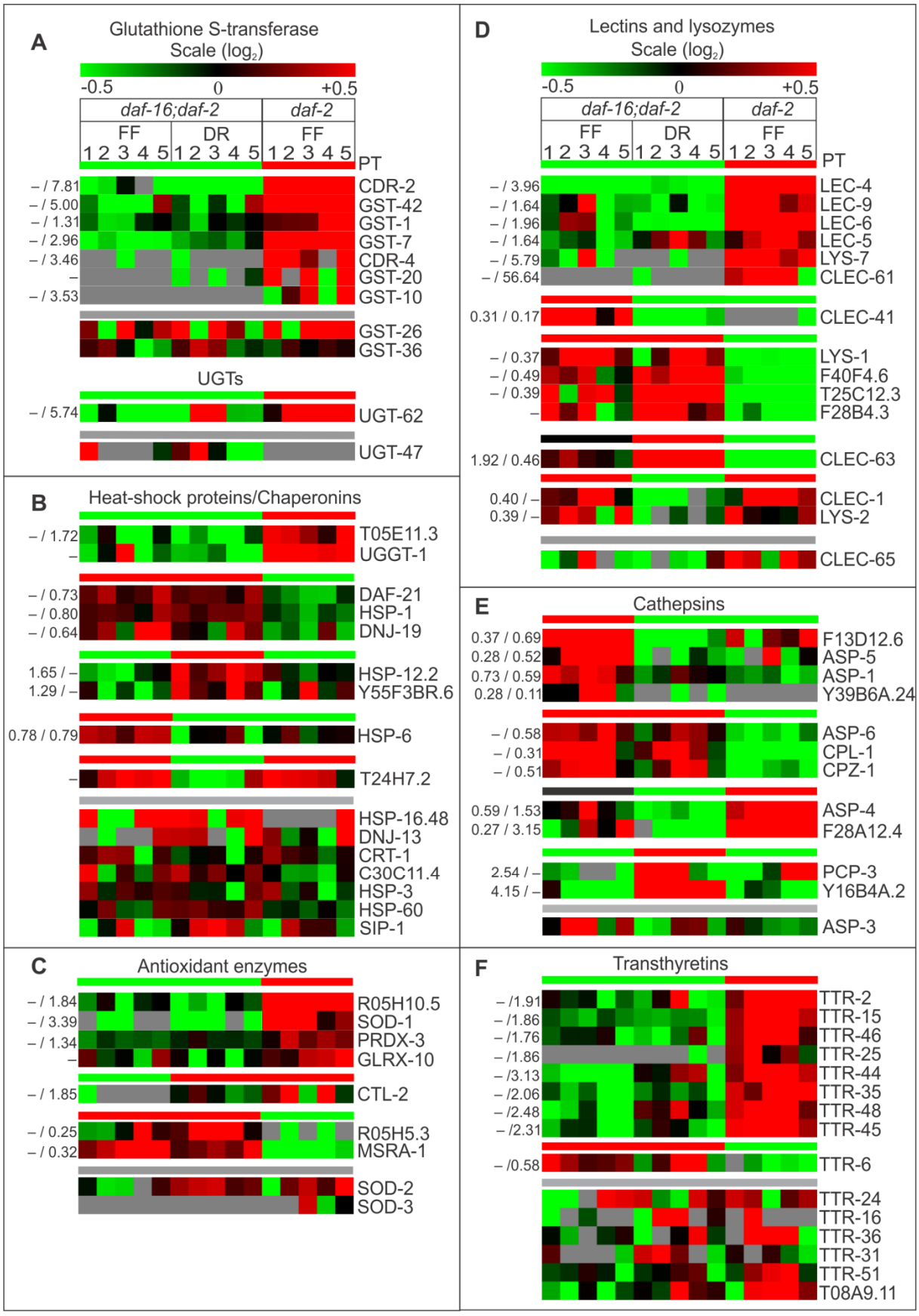
136 DR and IIS deficiency leads to differential expression of different aspartyl proteases (ASP-1,-3,-4,-5,-6,
137 Y39B6A.24 and F28A12.4), Serine carboxypeptidases (F13D12.6, PCP-3 and Y16B4A.2), and cysteine
138 proteases (CPL-1 and CPZ-1) **(Supplemental figure 2E)**. Several groups have reported increased
139 expression of aspartyl proteases upon pathogen infection, suggesting a role for cathepsins in worm
140 innate immunity (O'Rourke *et al.* 2006; Wong *et al.* 2007; Simonsen *et al.* 2011). The exact role of

autophagy and cathepsins in the immune response is not entirely clear and can have either remediating (Jia *et al.* 2009) or detrimental (Syntichaki *et al.* 2002; Wong *et al.* 2007) effects upon infection, depending on the pathogen source.

Supplemental Figures



Supplemental figure 1: Upregulation of the proteasome complex in diet-restricted worms.


A
Glutathione S-transferase
Scale (log2)
-0.5
0
+0.5
daf-16;daf-2
daf-2
FF
DR
FF
1 2 3 4 5 1 2 3 4 5 1 2 3 4 5
PT
– / 7.81 CDR-2
– / 5.00 GST-42
– / 1.31 GST-1
– / 2.96 GST-7
– / 3.46 CDR-4
– GST-20
– / 3.53 GST-10
GST-26
GST-36
UGTs
– / 5.74 UGT-62
UGT-47
B
Heat-shock proteins/Chaperonins
– / 1.72 T05E11.3
– UGGT-1
– / 0.73 DAF-21
– / 0.80 HSP-1
– / 0.64 DNJ-19
1.65 / – HSP-12.2
1.29 / – Y55F3BR.6
0.78 / 0.79 HSP-6
– T24H7.2
HSP-16.48
DNJ-13
CRT-1
C30C11.4
HSP-3
HSP-60
SIP-1
C
Antioxidant enzymes
– / 1.84 R05H10.5
– / 3.39 SOD-1
– / 1.34 PRDX-3
– GLRX-10
– / 1.85 CTL-2
– / 0.25 R05H5.3
– / 0.32 MSRA-1
SOD-2
SOD-3
D
Lectins and lysozymes
Scale (log2)
-0.5
0
+0.5
daf-16;daf-2
daf-2
FF
DR
FF
1 2 3 4 5 1 2 3 4 5 1 2 3 4 5
PT
– / 3.96 LEC-4
– / 1.64 LEC-9
– / 1.96 LEC-6
– / 1.64 LEC-5
– / 5.79 LYS-7
– / 56.64 CLEC-61
0.31 / 0.17 CLEC-41
– / 0.37 LYS-1
– / 0.49 F40F4.6
– / 0.39 T25C12.3
– F28B4.3
1.92 / 0.46 CLEC-63
0.40 / – CLEC-1
0.39 / – LYS-2
CLEC-65
E
Cathepsins
0.37 / 0.69 F13D12.6
0.28 / 0.52 ASP-5
0.73 / 0.59 ASP-1
0.28 / 0.11 Y39B6A.24
– / 0.58 ASP-6
– / 0.31 CPL-1
– / 0.51 CPZ-1
0.59 / 1.53 ASP-4
0.27 / 3.15 F28A12.4
2.54 / – PCP-3
4.15 / – Y16B4A.2
ASP-3
F
Transthyretins
– /1.91 TTR-2
– /1.86 TTR-15
– /1.76 TTR-46
– /1.86 TTR-25
– /3.13 TTR-44
– /2.06 TTR-35
– /2.48 TTR-48
– /2.31 TTR-45
– /0.58 TTR-6
TTR-24
TTR-16
TTR-36
TTR-31
TTR-51
T08A9.11

Supplemental Figure 2: Differential expression of enzymes in cellular stress defensive systems **(A-E)** and DAF-16 specific activation of transthyretin **(F)**.

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