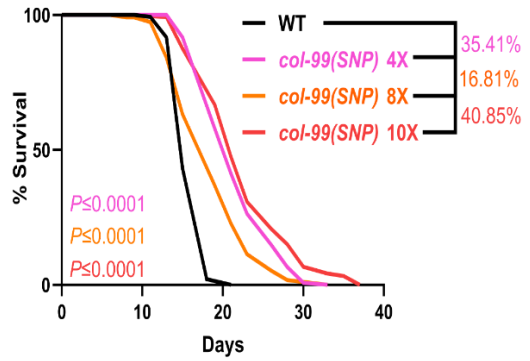
a

Gene Name	Description	SNP centenarian [# of SNPs/ # studies]	Experimental evidence for longevity
TACR3	Tachykinin Receptor 3	1/1	
CXXC4	CXXC Finger Protein 4		
TET2	Tet methylcytosine dioxygenase 2		
PPA2	Pyrophosphatase 2		yeast longevity
ARHGEF38	Rho Guanine Nucleotide Exchange Factor 38		
INTS12	Integrator complex subunit 12		
GSTCD	Glutathione S-Transferase C-Terminal Domain Containing		
NPNT	Nephronectin		
TBCK	Tre-2/Bub2/Cdc16 (TBC) domain kinase		
AIMP1	Arginyl-tRNA synthase		
GIMD1	GIMAP Family P-Loop NTPase Domain Containing 1		
DKK2	Dickkopf WNT Signaling Pathway Inhibitor 2	1/1	
PAPSS1	3'-Phosphoadenosine 5'-Phosphosulfate Synthase 1	1/1	
SGMS2	Sphingomyelin Synthase 2		
CYP2U1	Cytochrome P450 Family 2 Subfamily U Member 1		*C. elegans* longevity
HADH	Hydroxyacyl-CoA Dehydrogenase		
LEF1	Lymphoid Enhancer Binding Factor 1		
RPL34	Ribosomal Protein L34		yeast & *C. elegans* longevity
OSTC	Oligosaccharyltransferase Complex Non-Catalytic Subunit		
ETNPPL	Ethanolamine-Phosphate Phospho-Lyase		
COL25A1	Collagen type XXV alpha 1 chain	9/3	
SEC24B	COPII Coat Complex Component		
MCUB	Mitochondrial Calcium Uniporter Dominant Negative Subunit Beta		
CASP6	Caspase 6		
PLA2G12A	Phospholipase A2 Group XIIA		
CFI	Complement factor I (eye)		
GAR1	Ribonucleoprotein	1/1	
RRH	Retinal Pigment Epithelium-Derived Rhodopsin Homolog		
LRIT3	Leucine Rich Repeat, Ig-Like And Transmembrane Domains 3		
EGF	Epidermal Growth Factor		*C. elegans* longevity
ELOVL6	Fatty acid elongases	1/1	*C. elegans* longevity
ENPEP	Glutamyl Aminopeptidase		
PITX2	Paired-like homeodomain transcription factor 2		

b



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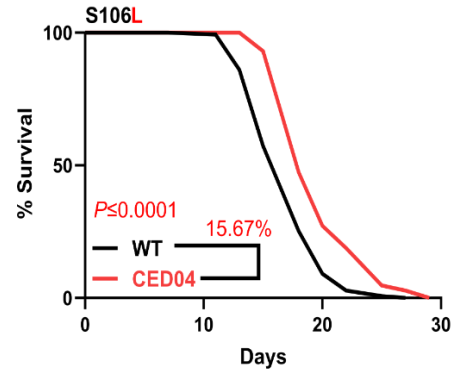

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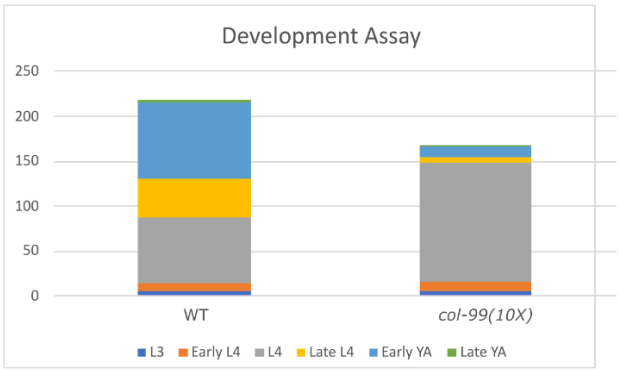

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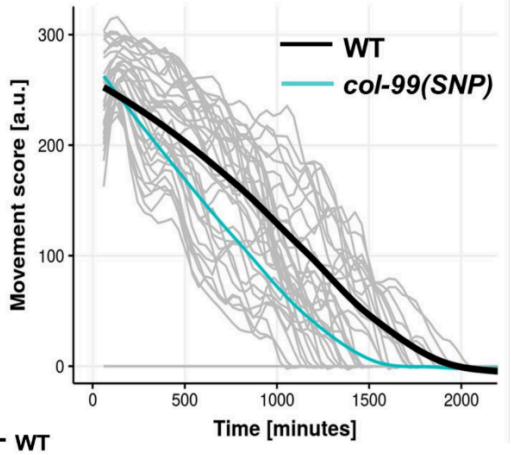

f

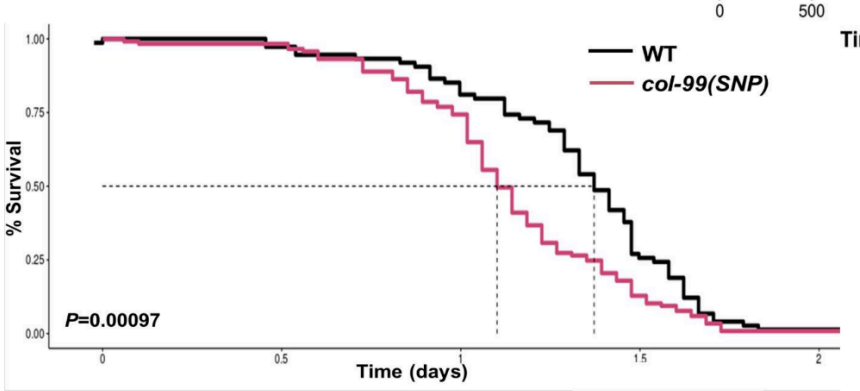

Figure S1:

a) List of the 108 ensemble features annotated in the longevity-associated region on chromosome 4. For details, see Supplementary Table 1. b) Lifespan curve showing the differential increase in lifespan by 4X, 8X, and 10X outcrossed *col-99(gk694263*[S106L]*)* SNP mutant. c) Lifespan curve showing extension of lifespan by CRISPR mutant CED04 *col-99(syb4350*[S106L]*)*. The lifespans were performed in at least two biological replicates at 20 ℃. Kaplan-Meier Log-Rank test was performed for statistical analysis using the online software OASIS. A lifespan summary for individual experiments is provided in Supplementary Table 2. d) A bar graph representing a slight delay in the developmental stages of *col-99(gk694263*[S106L]*)* SNP mutant compared to wild-type. e, f) Survival curves showing susceptibility of *col-99(gk694263*[S106L]*)* SNP mutant to oxidative stress (e; 14 mM Arsenite), and heat stress (f; 32 ℃). The oxidative stress experiment was done in three biological replicates, and the heat stress assay was done in two biological replicates at 32 ℃ and once at 35 ℃. *col-99*(SNP) is *col-99(gk694263*[S106L]*).*

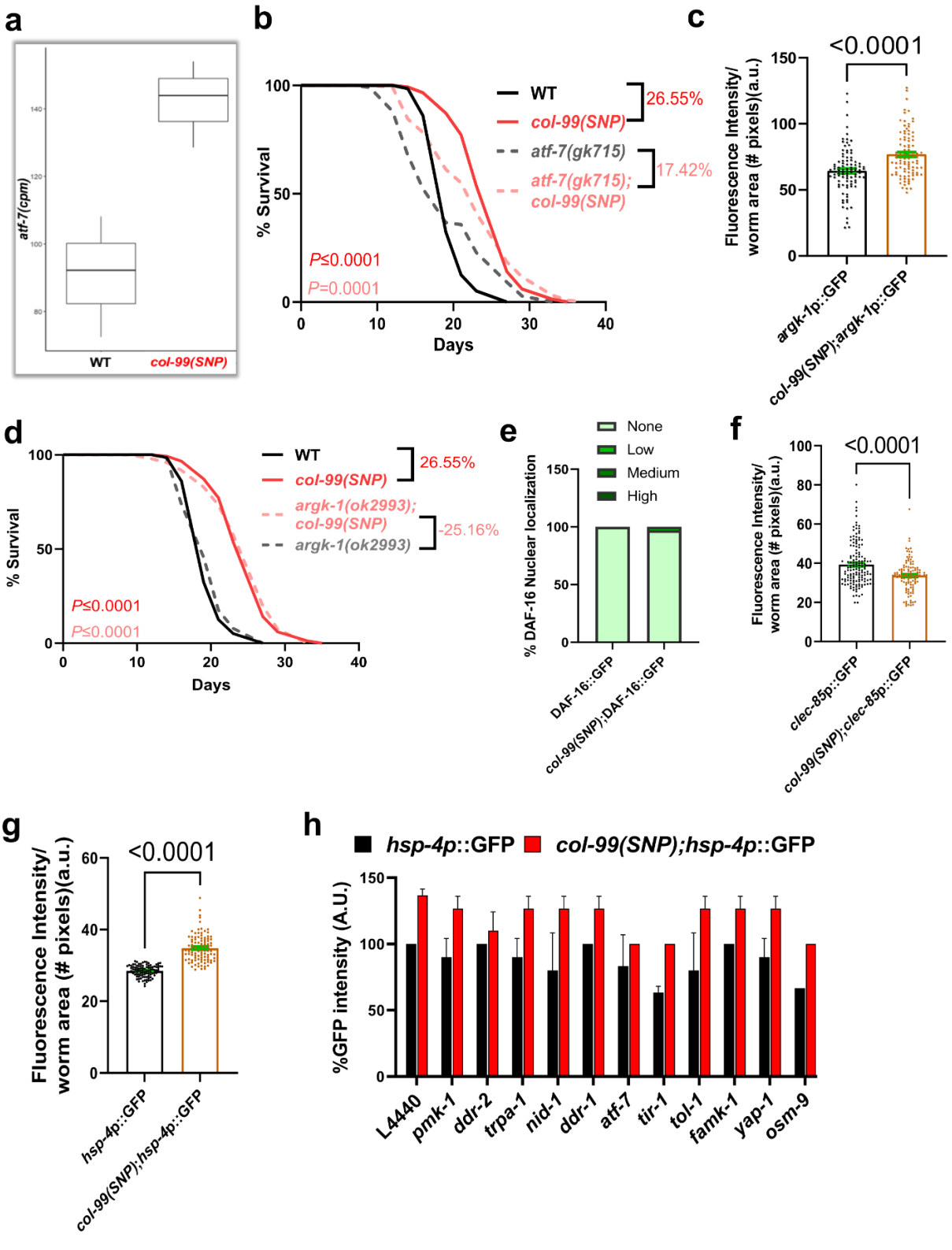
a
atf-7(cpm)
WT
col-99(SNP)
b
% Survival
Days
WT
col-99(SNP)
atf-7(gk715)
atf-7(gk715); col-99(SNP)
26.55%
17.42%
P≤0.0001
P=0.0001
c
Fluorescence Intensity/ worm area (# pixels)(a.u.)
<0.0001
argk-1p::GFP
col-99(SNP);argk-1p::GFP
d
% Survival
Days
WT
col-99(SNP)
argk-1(ok2993); col-99(SNP)
argk-1(ok2993)
26.55%
-25.16%
P≤0.0001
P≤0.0001
e
% DAF-16 Nuclear localization
None
Low
Medium
High
DAF-16::GFP
col-99(SNP);DAF-16::GFP
f
Fluorescence Intensity/ worm area (# pixels)(a.u.)
<0.0001
clec-85p::GFP
col-99(SNP);clec-85p::GFP
g
Fluorescence Intensity/ worm area (# pixels)(a.u.)
<0.0001
hsp-4p::GFP
col-99(SNP);hsp-4p::GFP
h
hsp-4p::GFP
col-99(SNP);hsp-4p::GFP
%GFP intensity (A.U.)
L4440
pmk-1
ddr-2
trpa-1
nid-1
ddr-1
atf-7
tir-1
tol-1
famk-1
yap-1
osm-9

Figure S2:

a) Graph showing an increase in the expression of *atf-7* transcripts in *col-99(gk694263*[S106L]*)* SNP mutant compared to wild-type (in terms of FKPM values). b) Survival curve showing the lifespan of *col-99(gk694263*[S106L]*)* SNP mutant is independent of *atf-7*. The lifespans were performed in at least two biological replicates at 20 °C. Kaplan-Meier Log-Rank test was performed for statistical analysis using the online software OASIS. A lifespan summary for individual experiments is provided in Supplementary Table 2. c) Bar graph showing slightly more fluorescence intensity per pixel number for *argk-1p::*GFP in *col-99(gk694263*[S106L]*)* SNP mutant background. Data is plotted as mean, and error bars represent SEM. Two-tailed Welch's *t*-test statistical analysis. The experiment was performed in three biological batches, with n>80 total animals per condition. d) Survival curve showing extension in the lifespan of *col-99(gk694263*[S106L]*)* SNP mutant is independent of *argk-1* mutation. The lifespans were performed in at least two biological replicates at 20 °C. Kaplan-Meier Log-Rank test was performed for statistical analysis using the online software OASIS. A lifespan summary for individual experiments is provided in Supplementary Table 2. e) Bar graph showing no change in DAF-16 nuclear localization percentage in *col-99(gk694263*[S106L]*)* SNP mutant versus wild-type. f, g) Bar graph showing slightly less fluorescence intensity per pixel number for *clec-85p::*GFP in *col-99(gk694263*[S106L]*)* SNP mutant background compared to wild-type (f), and an increase in the fluorescence intensity per pixel number for *hsp-4p::*GFP; *col-99(gk694263*[S106L]*)* SNP transgenic as compared to wild-type (g). h) Targeted eyeball screening of selected genes to look for the dependence of *hsp-4* in

col-99(gk694263[S106L]*)* SNP mutant background. Data is plotted as mean, and error bars represent SEM. Two-tailed Welch's *t*-test statistical analysis. The experiment was performed in three biological batches, with n>80 total animals per condition. *col-99*(SNP) is *col-99(gk694263*[S106L]*)*.

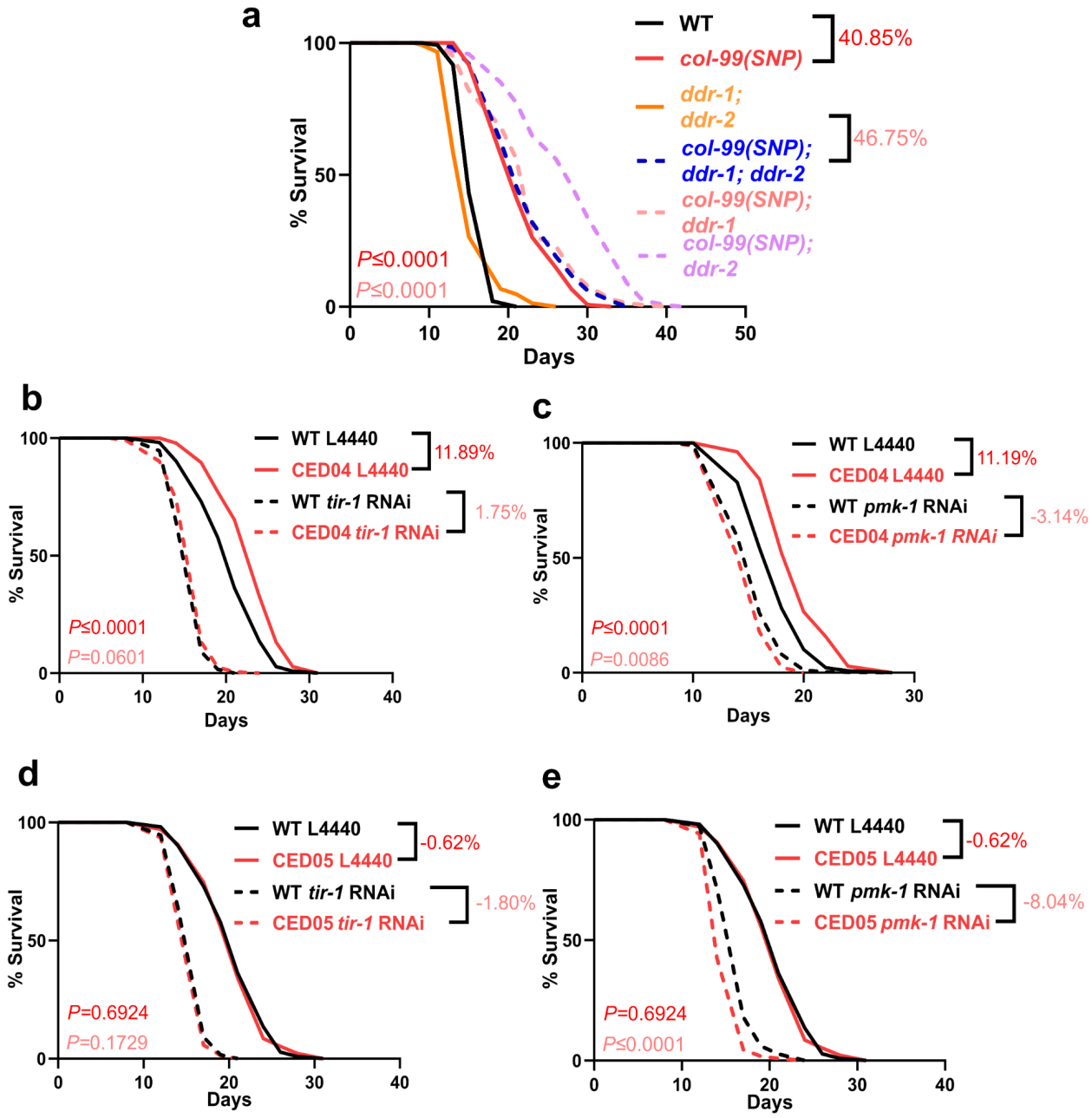

Figure S3:

The survival curve shows that a) *col-99(gk694263*[S106L]*)* SNP still extends lifespan in *ddr-1* and *ddr-2* mutant backgrounds, showing independence from *ddr-1* or *ddr-2*. b, c) extension in lifespan in *col-99(gk694263*[S106L]*)* SNP mutant is dependent on *tir-1* (b) and *pmk-1* (d), as knockdown of these genes does not lead to an increase in lifespan in *col-99(gk694263*[S106L]*)* SNP background. d, e) dependence of CED05 *col-99(syb4352*[S106D]*)* lifespan on *tir-1* (d) and *pmk-1* (e). The lifespans were performed in at least two biological replicates at 20 ℃. Kaplan-Meier Log-Rank test was performed for statistical analysis using the online software OASIS. A lifespan summary for individual experiments is provided in Supplementary Table 2. *col-99*(SNP) is *col-99(gk694263*[S106L]*).*

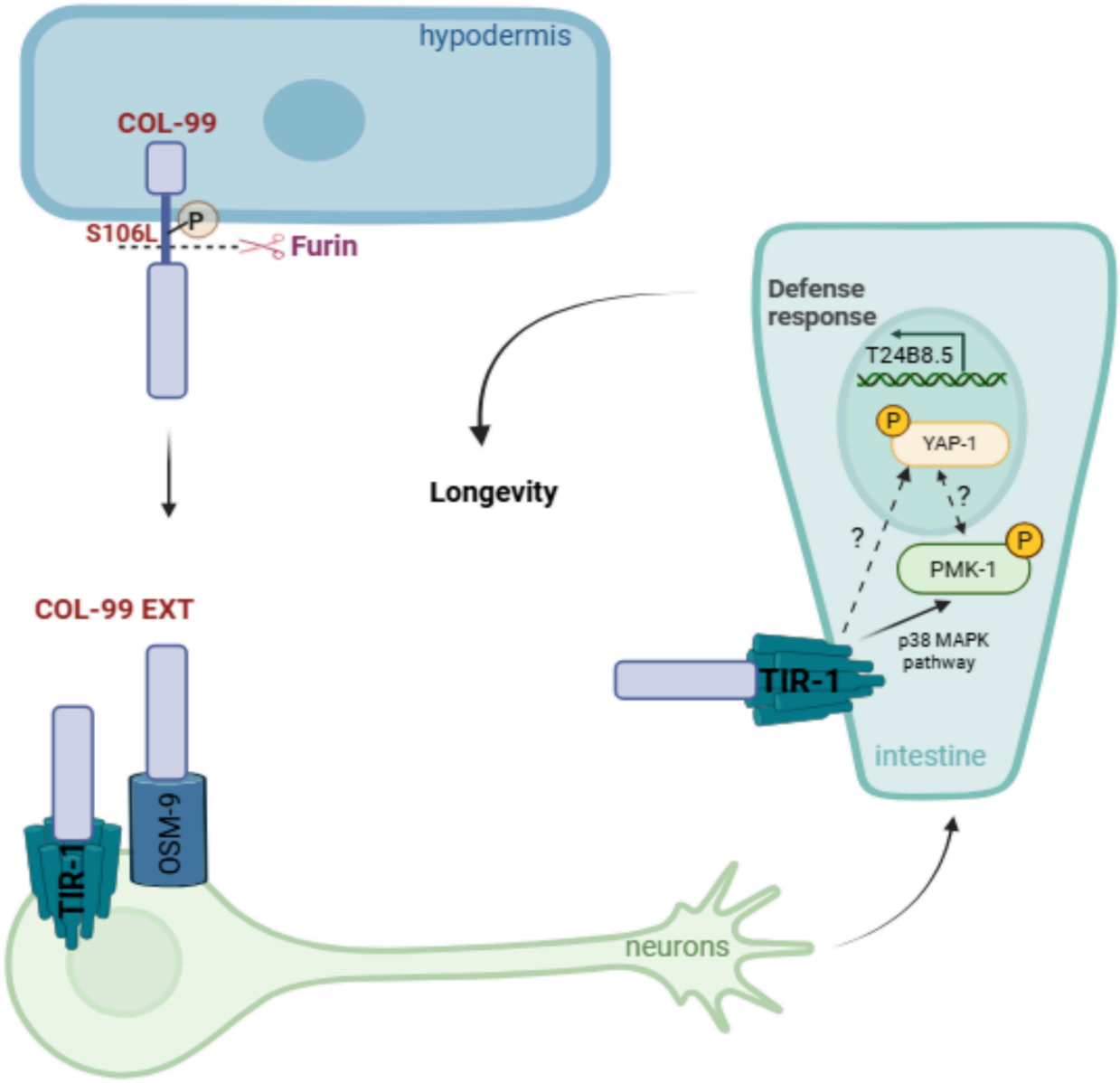

Figure S4: Hypothetical model showing the role of *col-99* in innate immune response and longevity.

We speculate that the S106L SNP in COL-99 alters furin-mediated cleavage, releasing the COL-99 extracellular domain (COL-99 EXT) in the hypodermis. COL-99 EXT traverses to interact with OSM-9/TIR-1 receptors in neurons or TIR-1 in the intestine.

COL-99 EXT interacts with TIR-1 in the intestine or indirectly through binding to OSM-9 in neurons, activating the p38 MAPK pathway. Together with YAP-1, PMK-1 upregulates innate immune responses, leading to longevity.