

Table S1A							
<i>sir-2.1(ok434) hcf-1(pk924)</i> double mutant analysis in lifespan							
Experiment	Strain	Mean LS + SEM(Days)	Total N	p-value vs. N2	p-value vs. <i>hcf-1(pk924)</i>	p-value vs <i>sir-2.1(ok434)</i>	% effect on N2
#1	N2	14.3 ± 0.2	102		<0.001	0.007	
	<i>hcf-1(pk924)</i>	17.8 ± 0.5	102	<0.001		<0.001	24
	<i>sir-2.1(ok434)</i>	13.3 ± 0.3	100	<0.001	<0.001		-7
	<i>sir-2.1(-) hcf-1(-) (#1)</i>	17.0 ± 0.8	51	<0.001	0.906	<0.001	19
	<i>daf-16(mgDf47)</i>	9.4 ± 0.1	102	<0.001	<0.001	<0.001	-34
	<i>daf-16(-);hcf-1(-)</i>	8.7 ± 0.2	92	<0.001	<0.001	<0.001	-39
#2	N2	13.9 ± 0.2	102		<0.001	0.001	
	<i>hcf-1(pk924)</i>	17.5 ± 0.4	114	<0.001		<0.001	26
	<i>sir-2.1(ok434)</i>	12.8 ± 0.2	99	0.001	<0.001		-8
	<i>sir-2.1(-) hcf-1(-) (#1)</i>	18.0 ± 0.5	104	<0.001	<0.001	<0.001	30
	<i>daf-16(mgDf47)</i>	9.2 ± 0.1	100	<0.001	<0.001	<0.001	-34
	<i>daf-16(-);hcf-1(-)</i>	8.6 ± 0.2	98	<0.001	0.038	<0.001	-38
#3	N2	14.4 ± 0.2	102		<0.001	<0.001	
	<i>hcf-1(pk924)</i>	19.7 ± 0.5	95	<0.001		<0.001	37
	<i>sir-2.1(ok434)</i>	15.6 ± 0.3	100	<0.001	<0.001		8
	<i>sir-2.1(-) hcf-1(-) (#1)</i>	20.6 ± 0.8	89	<0.001	0.002	<0.001	43
	<i>sir-2.1(-) hcf-1(-) (#2)</i>	18.3 ± 0.5	100	<0.001	0.088	<0.001	27
	<i>sir-2.1(-) hcf-1(-) (#3)</i>	21.2 ± 0.7	100	<0.001	0.001	<0.001	47
	<i>sir-2.1(-) hcf-1(-) (#4)</i>	20.4 ± 0.6	101	<0.001	0.015	<0.001	42
	<i>daf-16(mgDf47)</i>	9.1 ± 0.1	99	<0.001	<0.001	<0.001	-37
	<i>daf-16(-);hcf-1(-)</i>	8.9 ± 0.1	97	<0.001	<0.001	<0.001	-38
	#4	N2	14.5 ± 0.2	95		<0.001	<0.001
	<i>hcf-1(pk924)</i>	18.0 ± 0.3	95	<0.001		<0.001	24
	<i>sir-2.1(ok434)</i>	15.3 ± 0.5	92	<0.001	<0.001		6
	<i>sir-2.1(-) hcf-1(-) (#1)</i>	17.4 ± 0.2	92	<0.001	0.859	<0.001	19
	<i>sir-2.1(-) hcf-1(-) (#2)</i>	18.8 ± 0.4	97	<0.001	0.569	<0.001	20
	<i>sir-2.1(-) hcf-1(-) (#3)</i>	19.3 ± 0.3	71	<0.001	0.056	<0.001	30
	<i>sir-2.1(-) hcf-1(-) (#4)</i>	18.2 ± 0.2	105	<0.001	0.002	<0.001	34
	<i>daf-16(mgDf47)</i>	9.2 ± 0.1	106	<0.001	<0.001	<0.001	-37
	<i>daf-16(-);hcf-1(-)</i>	10.0 ± 0.1	94	<0.001	<0.001	<0.001	-31
Kaplan Meier analysis - experiments pooled							
Experiment	Strain	Mean LS + SEM(Days)	Total N	p-value vs. N2	p-value vs. <i>hcf-1(pk924)</i>	p-value vs <i>sir-2.1(ok434)</i>	% effect on N2
#1-4 pooled	N2	14.3 ± 0.1	400		<0.001	0.012	
Figure 1A	<i>hcf-1(pk924)</i>	18.2 ± 0.2	406	<0.001		<0.001	28
	<i>sir-2.1(ok434)</i>	14.2 ± 0.1	390	0.012	<0.001		0
	<i>sir-2.1(-) hcf-1(-) (#1)</i>	18.4 ± 0.3	336	<0.001	0.004	<0.001	28
	<i>sir-2.1(-) hcf-1(-) (#2)*</i>	17.9 ± 0.3	196	<0.001	0.556	<0.001	25
	<i>sir-2.1(-) hcf-1(-) (#3)</i>	20.2 ± 0.5	170	<0.001	<0.001	<0.001	41
	<i>sir-2.1(-) hcf-1(-) (#4)</i>	19.9 ± 0.4	205	<0.001	<0.001	0.001	39
	<i>daf-16(mgDf47)</i>	9.2 ± 0.1	406	<0.001	<0.001	<0.001	-35
	<i>daf-16(-);hcf-1(-)</i>	9.1 ± 0.1	380	<0.001	<0.001	<0.001	-37

Table S1B

***pkIs1642[sir-2.1(O/E)] and hcf-1(pk924)* epistasis analysis in lifespan**

Experiment	Strain	Mean LS + SEM(Days)	Total N	<i>p</i> -value vs. <i>hcf-1(pk924)</i>	<i>p</i> -value vs. <i>pkIs1641</i>	<i>p</i> -value vs. <i>pkIs1642</i>	% effect on <i>pkIs1641</i>
#1	N2	15.4 ± 0.2	94	<0.001	0.008	<0.001	4
	<i>hcf-1(pk924)</i>	18.4 ± 0.4	101		<0.001	0.002	25
	<i>pkIs1641[sir-2.1(wt)]</i>	14.7 ± 0.2	94	<0.001		<0.001	
	<i>pkIs1642[sir-2.1(O/E)]</i>	17.5 ± 0.2	104	0.002	<0.001		19
	<i>hcf-1(pk924);pkIs1642 (#1)</i>	17.5 ± 0.4	88	0.122	<0.001	0.584	19
	<i>hcf-1(pk924);pkIs1642 (#2)</i>	19.1 ± 0.4	69	0.401	<0.001	<0.001	30
	<i>hcf-1(pk924);pkIs1642 (#3)</i>	16.2 ± 0.3	110	<0.001	<0.001	0.014	10
	<i>hcf-1(pk924);pkIs1642 (#4)</i>	17.0 ± 0.4	88	0.004	<0.001	0.899	15
	<i>hcf-1(pk924);pkIs1642 (#5)</i>	17.8 ± 0.3	103	0.058	<0.001	0.087	21
	<i>daf-16(mgDf50);pkIs1642</i>	8.5 ± 0.1	97	<0.001	<0.001	<0.001	-42
#2	N2	15.1 ± 0.1	99	<0.001	0.428	<0.001	1
	<i>hcf-1(pk924)</i>	18.9 ± 0.3	96		<0.001	0.001	26
	<i>pkIs1641[sir-2.1(wt)]</i>	15.0 ± 0.3	98	<0.001		<0.001	
	<i>pkIs1642[sir-2.1(O/E)]</i>	17.3 ± 0.3	101	0.001	<0.001		15
	<i>hcf-1(pk924);pkIs1642 (#1)</i>	16.7 ± 0.6	58	0.007	<0.001	0.971	11
	<i>hcf-1(pk924);pkIs1642 (#2)</i>	19.1 ± 0.4	58	0.427	<0.001	<0.001	27
	<i>hcf-1(pk924);pkIs1642 (#3)</i>	15.9 ± 0.4	104	<0.001	<0.001	0.002	6
	<i>hcf-1(pk924);pkIs1642 (#4)</i>	16.5 ± 0.4	65	<0.001	0.002	0.056	10
	<i>hcf-1(pk924);pkIs1642 (#5)</i>	17.3 ± 0.3	95	<0.001	<0.001	0.982	15
	<i>daf-16(mgDf50);pkIs1642</i>	8.5 ± 0.1	97	<0.001	<0.001	<0.001	-43
#3	N2	15.0 ± 0.2	98	<0.001	0.727	0.007	0
	<i>hcf-1(pk924)</i>	18.9 ± 0.3	100		<0.001	<0.001	28
	<i>pkIs1641[sir-2.1(wt)]</i>	15.4 ± 0.2	102	<0.001		<0.001	
	<i>pkIs1642[sir-2.1(O/E)]</i>	18.1 ± 0.3	94	<0.001	<0.001		17
	<i>hcf-1(pk924);pkIs1642 (#1)</i>	17.1 ± 0.4	80	0.007	<0.001	0.573	13
	<i>hcf-1(pk924);pkIs1642 (#2)</i>	18.4 ± 0.5	80	0.087	<0.001	<0.001	25
	<i>hcf-1(pk924);pkIs1642 (#3)</i>	15.5 ± 0.3	107	<0.001	<0.001	<0.001	5
	<i>hcf-1(pk924);pkIs1642 (#4)</i>	17.5 ± 0.3	96	<0.001	<0.002	<0.001	9
	<i>hcf-1(pk924);pkIs1642 (#5)</i>	17.5 ± 0.3	96	<0.001	<0.001	0.924	16
	<i>daf-16(mgDf50);pkIs1642</i>	9.1 ± 0.1	87	<0.001	<0.001	<0.001	-42

Kaplan Meier analysis - experiments pooled

Experiment	Strain	Mean LS + SEM(Days)	Total N	<i>p</i> -value vs. <i>hcf-1(pk924)</i>	<i>p</i> -value vs. <i>pkIs1641</i>	<i>p</i> -value vs. <i>pkIs1642</i>	% effect on <i>pkIs1641</i>
#1-3 pooled	N2	15.1 ± 0.1	292	<0.001	0.727	0.007	0
Figure 1B	<i>hcf-1(pk924)</i>	19.4 ± 0.2	305		<0.001	<0.001	28
	<i>pkIs1641[sir-2.1(wt)]</i>	15.1 ± 0.1	294	<0.001		<0.001	
	<i>pkIs1642[sir-2.1(O/E)]</i>	17.6 ± 0.2	299	<0.001	<0.001		17
	<i>hcf-1(pk924);pkIs1642 (#1)</i>	17.1 ± 0.3	226	<0.001	<0.001	0.573	13
	<i>hcf-1(pk924);pkIs1642 (#2)*</i>	18.9 ± 0.2	240	0.087	<0.001	<0.001	25
	<i>hcf-1(pk924);pkIs1642 (#3)</i>	15.9 ± 0.2	321	<0.001	<0.001	<0.001	5
	<i>hcf-1(pk924);pkIs1642 (#4)</i>	16.5 ± 0.2	253	<0.001	<0.001	<0.001	9
	<i>hcf-1(pk924);pkIs1642 (#5)</i>	17.5 ± 0.2	294	<0.001	<0.001	<0.001	16
	<i>daf-16(mgDf50);pkIs1642</i>	8.7 ± 0.1	285	<0.001	<0.001	0.924	-42

Table S1C						
<i>sir-2.1(ok434)</i> and <i>hcf-1(pk924)</i> epistasis analysis in <i>t</i>-Butyl hydroperoxide						
Kaplan Meier analysis						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	% effect on N2		
#1	N2	26.2 ± 0.6	127			
	<i>hcf-1(pk924)</i>	41.8 ± 1.2	105	59.8		
	<i>sir-2.1(ok434)</i>	19.0 ± 0.5	109	-27.2		
	<i>sir-2.1(-) hcf-1(-)</i> (#1)	43.4 ± 1.2	105	66.1		
	<i>sir-2.1(-) hcf-1(-)</i> (#2)	40.2 ± 1.3	107	53.5		
#2	N2	24.9 ± 0.9	113			
	<i>hcf-1(pk924)</i>	58.7 ± 2.0	108	136.3		
	<i>sir-2.1(ok434)</i>	23.9 ± 1.1	103	-3.7		
	<i>sir-2.1(-) hcf-1(-)</i> (#1)	73.2 ± 2.7	88	194.5		
	<i>sir-2.1(-) hcf-1(-)</i> (#2)	55.0 ± 2.1	114	121.4		
Linear Mixed model analysis						
#1, 2 pooled	Strain	Averaged % variation compared to wt ± SEM	Total N	p-value vs. <i>sir-2.1(-) hcf1(-)</i>		
Figure S1A	<i>sir-2.1(ok434)</i>	-15.5 ± 43.1	212	0.035		
	<i>hcf-1(pk924)</i>	98.0 ± 48.9	213	0.715		
	<i>sir-2.1(-) hcf-1(-)</i>	108.9 ± 46.3	414			
Kaplan Meier analysis - experiments and double mutants pooled						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	p-value vs. N2	p-value vs. <i>hcf-1(pk924)</i>	% effect on N2
#1, 2 pooled	N2	25.5 ± 0.5	240		<0.001	
Figure 1C	<i>hcf-1(pk924)</i>	50.1 ± 1.3	212	<0.001		96.0
	<i>sir-2.1(ok434)</i>	21.4 ± 0.6	213	<0.001	<0.001	-16.4
	<i>sir-2.1(-) hcf-1(-)</i>	52.2 ± 1.1	414	<0.001	0.193	104.3

Table S1D						
<i>pkls1642[sir-2.1(O/E)]</i> and <i>hcf-1(pk924)</i> epistasis analysis in <i>t</i>-Butyl hydroperoxide						
Kaplan Meier analysis						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	% effect on N2	% effect on <i>pkls1641</i>	
#1	N2	26.2 ± 0.6	127		11.4	
	<i>pkls1641[sir-2.1(wt)]</i>	23.5 ± 0.6	100	-10.2		
	<i>hcf-1(pk924)</i>	41.8 ± 1.2	105	59.8	32.0	
	<i>pkls1642[sir-2.1(O/E)]</i>	31.0 ± 0.4	118	18.5	78.0	
	<i>hcf-1(pk924);pkls1642 (#1)</i>	32.3 ± 0.6	115	23.4	37.5	
	<i>hcf-1(pk924);pkls1642 (#2)</i>	43.0 ± 1.1	108	64.3	83.0	
#2	N2	24.9 ± 0.9	113		13.3	
	<i>pkls1641[sir-2.1(wt)]</i>	21.9 ± 0.7	101	-11.8		
	<i>hcf-1(pk924)</i>	58.7 ± 2.0	108	136.3	167.7	
	<i>pkls1642[sir-2.1(O/E)]</i>	52.3 ± 1.2	109	110.4	138.4	
	<i>hcf-1(pk924);pkls1642 (#1)</i>	46.2 ± 1.2	103	86.1	110.8	
	<i>hcf-1(pk924);pkls1642 (#2)</i>	68.6 ± 1.7	102	176.0	212.7	
Linear Mixed model analysis						
#1, 2 pooled	Strain	Averaged % variation compared to wt ± SEM	Averaged % variation compared to <i>pkls1641</i> ± SEM	Total N	<i>p</i>-value vs. <i>hcf-1(pk924);pkls1642 (wt / pkls1641)</i>	
Figure S1B	<i>pkls1642[sir-2.1(O/E)]</i>	64.4 ± 50.1	85.2 ± 57.9	227	0.557 / 0.560	
	<i>hcf-1(pk924)</i>	98.0 ± 47.9	122.9 ± 55.5	213	0.782 / 0.784	
	<i>hcf-1(pk924);pkls1642</i>	87.4 ± 43.4	111.0 ± 50.4	428		
Kaplan Meier analysis - experiments and double mutants pooled						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	<i>p</i>-value vs. N2	<i>p</i>-value vs. <i>hcf-1(pk924)</i>	% effect on N2
#1, 2 pooled	N2	25.5 ± 0.5	240		<0.001	
Figure 1D	<i>pkls1641[sir-2.1(wt)]</i>	22.7 ± 0.5	201	<0.001	<0.001	-11.1
	<i>hcf-1(pk924)</i>	50.1 ± 1.3	213	<0.001		96.0
	<i>pkls1642[sir-2.1(O/E)]</i>	41.3 ± 1.0	227	<0.001	<0.001	61.5
	<i>hcf-1(pk924);pkls1642</i>	47.0 ± 0.9	428	<0.001	0.093	83.9

Table S1E						
<i>sir-2.1(ok434)</i> and <i>hcf-1(pk924)</i> epistasis analysis in paraquat						
Kaplan Meier analysis						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	% effect on N2		
#1	N2	21.0 ± 1.2	156			
	<i>hcf-1(pk924)</i>	35.9 ± 1.4	177	71.0		
	<i>sir-2.1(ok434)</i>	18.6 ± 1.3	193	-11.1		
	<i>sir-2.1(-) hcf-1(-)</i> (#1)	37.3 ± 1.8	152	77.8		
	<i>sir-2.1(-) hcf-1(-)</i> (#2)	29.3 ± 2.0	135	39.8		
	<i>sir-2.1(-) hcf-1(-)</i> (#3)	34.9 ± 1.7	157	66.2		
#2	<i>sir-2.1(-) hcf-1(-)</i> (#4)	36.5 ± 1.5	183	74.0		
	N2	33.5 ± 1.1	281			
	<i>hcf-1(pk924)</i>	44.6 ± 1.0	277	33.2		
	<i>sir-2.1(ok434)</i>	26.9 ± 1.1	295	-19.7		
	<i>sir-2.1(-) hcf-1(-)</i> (#1)	30.4 ± 1.9	116	-9.2		
	<i>sir-2.1(-) hcf-1(-)</i> (#2)	39.4 ± 1.3	303	17.6		
	<i>sir-2.1(-) hcf-1(-)</i> (#3)	40.9 ± 2.0	129	22.0		
	<i>sir-2.1(-) hcf-1(-)</i> (#4)	40.3 ± 0.8	549	20.3		
Linear Mixed model analysis						
#1, 2 pooled	Strain	Averaged % variation compared to wt ± SEM	Total N	p-value vs. <i>sir-2.1(-) hcf1(-)</i>		
Figure S1C	<i>sir-2.1(ok434)</i>	-15.4 ± 24.4	488	0.007		
	<i>hcf-1(pk924)</i>	52.1 ± 26.3	454	0.296		
	<i>sir-2.1(-) hcf-1(-)</i>	38.6 ± 22.1	1725			
Kaplan Meier analysis - experiments and double mutants pooled						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	p-value vs. N2	p-value vs. <i>hcf-1(pk924)</i>	% effect on N2
#1,2 pooled	N2	21.0 ± 1.2	295		<0.001	
	<i>hcf-1(pk924)</i>	35.9 ± 1.4	314	0.017		47.5
	<i>sir-2.1(ok434)</i>	18.6 ± 1.3	339	<0.001	<0.001	-17.4
	<i>sir-2.1(-) hcf-1(-)</i>	37.3 ± 1.8	1079	<0.001	0.686	36.7

Table S1F						
<i>pkls1642[sir-2.1(O/E)]</i> and <i>hcf-1(pk924)</i> epistasis analysis in paraquat						
Kaplan Meier analysis						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	% effect on N2	% effect on <i>pkls1641</i>	
#1	N2	4.8 ± 0.1	114		-8.4	
	<i>pkls1641[sir-2.1(wt)]</i>	5.2 ± 0.2	109	9.2		
	<i>hcf-1(pk924)</i>	12.3 ± 0.7	109	157.8	136.1	
	<i>pkls1642[sir-2.1(O/E)]</i>	13.0 ± 0.5	115	171.5	148.6	
	<i>hcf-1(pk924); pkls1642 (#1)</i>	9.2 ± 0.6	98	93.7	77.4	
	<i>hcf-1(pk924);pkls1642 (#2)</i>	18.8 ± 0.7	109	294.7	261.4	
#2	N2	5.5 ± 0.2	116		-12.3	
	<i>pkls1641[sir-2.1(wt)]</i>	6.3 ± 0.3	117	14.1		
	<i>hcf-1(pk924)</i>	9.5 ± 0.4	120	71.0	49.9	
	<i>pkls1642[sir-2.1(O/E)]</i>	10.3 ± 0.5	115	84.8	62.0	
	<i>hcf-1(pk924);pkls1642 (#1)</i>	8.5 ± 0.5	110	53.3	34.4	
	<i>hcf-1(pk924);pkls1642 (#2)</i>	18.9 ± 0.6	115	240.3	198.4	
Linear Mixed model analysis						
#1,2 pooled	Strain	Averaged % variation compared to wt ± SEM	Averaged % variation compared to <i>pkls1641</i> ± SEM	Total N	<i>p</i>-value vs. <i>hcf-1(pk924); pkls1642 (wt / <i>pkls1641</i>)</i>	
Figure S1D	<i>pkls1642[sir-2.1(O/E)]</i>	128.2 ± 73.9	105.3 ± 68.0	230	0.664 / 0.581	
	<i>hcf-1(pk924)</i>	114.4 ± 73.9	93.0 ± 67.9	229	0.569 / 0.675	
	<i>hcf-1(pk924);pkls1642</i>	170.5 ± 52.3	142.9 ± 48.1	432		
Kaplan Meier analysis - experiments and double mutants pooled						
Experiment	Strain	Mean survival + SEM(Hrs)	Total N	<i>p</i>-value vs. N2	<i>p</i>-value vs. <i>hcf-1(pk924)</i>	% effect on N2
#1, 2 pooled	N2	4.8 ± 0.1	114		<0.001	
Figure 1F	<i>pkls1641[sir-2.1(wt)]</i>	5.2 ± 0.2	109	0.105	<0.001	9.2
	<i>hcf-1(pk924)</i>	12.3 ± 0.7	109	<0.001		157.8
	<i>pkls1642[sir-2.1(O/E)]</i>	13.0 ± 0.5	115	<0.001	0.831	171.5
	<i>hcf-1(pk924); pkls1642</i>	14.3 ± 0.6	207	<0.001	0.116	199.6

Table S1G**Non-outcrossed and outcrossed *pkIs1642 [sir-2.1(O/E)]* lifespan analysis**

Strain	Mean LS + SEM(Days)	Total N	<i>p</i> -value vs. N2	<i>p</i> -value vs. <i>sir-2.1(wt)</i>	<i>p</i> -value vs <i>sir-2.1(wt)-1X</i>	% effect on N2
N2	14.9 ± 0.1	97		0.832	0.003	
<i>pkIs1641[sir-2.1(wt)]</i>	14.7 ± 0.2	93	0.832		0.004	-2
<i>pkIs1642[sir-2.1(O/E)]</i>	17.1 ± 0.3	97	<0.001	<0.001	<0.001	14
<i>sir-2.1(wt)-1X</i>	14.3 ± 0.1	100	0.003	0.004		-4
<i>sir-2.1(O/E)-1X</i>	17.2 ± 0.2	95	<0.001	<0.001	<0.001	16

Table S1H***sir-2.1* RNAi knockdown lifespan analysis**

Strain + RNAi	Mean LS + SEM(Days)	Total N	<i>p</i> -value vs. N2	<i>p</i> -value vs. <i>sir-2.1(wt) + ctrl</i> RNAi	<i>p</i> -value vs <i>sir-2.1(wt) + sir-2.1</i> RNAi	% effect on N2+ <i>ctrl</i>
N2 + <i>ctrl</i>	13.8 ± 0.3	95		0.200	0.314	
N2 + <i>sir-2.1</i>	13.7 ± 0.2	96	0.144	0.897	0.669	-1
<i>sir-2.1(wt) + ctrl</i>	13.7 ± 0.2	94	0.200		0.767	-1
<i>sir-2.1(wt) + sir-2.1</i>	13.8 ± 0.2	87	0.314	0.767		0
<i>sir-2.1(O/E) + ctrl</i>	16.1 ± 0.3	96	<0.001	<0.001	<0.001	16
<i>sir-2.1(O/E) + sir-2.1</i>	14.3 ± 0.3	94	0.192	0.009	0.020	3