

Supplementary Table 1

Effects of age and sex on mtDNA copy number in striatum, cortex and skeletal muscle of YAC128 and WT mice

Tissue	Variables	Spline ³	Coef.	Std.Err.	DF	t-value	p-value	95% CI ⁴
Striatum WT ¹	Age		22.1	6.21	52	3.56	0.001	9.63 – 34.6
	Sex		-71.5	86.1	52	-0.83	0.411	-244.5 – 101.6
YAC128 ²	Age Spline 1	1-6	75.9	62.8	69	1.21	0.231	-49.4 – 201.4
	Age Spline 2	6-12	-565.0	334.3	69	-1.69	0.096	-1,232.8 – 102.8
	Age Spline 3	12-18	1,938	888.4	69	2.18	0.033	163.0 – 3,713
	Age Spline 4	18-21	-3,568	1,196.7	69	-2.98	0.004	5,958 – 1,177
	Sex		6.31	108.6	69	0.06	0.954	-210.6 – 223.2
Cortex WT ²	Age Spline 1	1-6	67.6	31.7	60	2.13	0.037	4.16 – 131.1
	Age Spline 2	6-21	-150.2	78.0	60	-1.94	0.058	-307.4 – 5.00
	Sex		-100.5	135.4	60	-0.74	0.461	-371.7 – 170.6
YAC128 ²	Age Spline 1	1-6	86.7	44.8	81	1.94	0.057	-2.51 – 175.8
	Age Spline 2	6-12	-574.5	251.9	81	-2.28	0.025	-1,076 – 72.6
	Age Spline 3	12-18	1,868	693.8	81	2.69	0.009	485.7 – 3,249
	Age Spline 4	18-21	-3,459	1,001	81	-3.45	0.001	-5,453 – -1,465
	Sex		65.5	91.1	81	0.72	0.474	-115.8 – 246.9
Skeletal muscle WT ¹	Age		448.6	139.5	64	3.21	0.002	169.7 – 727.5
	Sex		904.2	2,024.7	64	0.45	0.657	-3,143 – 4,942
YAC128 ²	Age Spline 1	1-9	1,104	355.0	78	3.11	0.003	397.8 – 1,812
	Age Spline 2	9-21	-1,473	533.3	78	-2.76	0.007	-2,535 – -410.5
	Sex		370.7	1,611	78	0.23	0.819	-2,839 – 3,580

1) Linear regression was used for analysis of mtDNA copy number in striatum and skeletal muscle of WT mice.

2) Cubic spline regression was used for analysis of mtDNA copy number in striatum of YAC128, cortex of WT and YAC128 mice, and skeletal muscle of YAC128 mice, respectively.

3) Spline indicates the knots in the cubic spline regression.

4) 95% confidence interval

Supplementary Table 2¹

Significant differences in mtDNA copy number in YAC128 compared to WT mice at specific ages

Tissue	Age (months)	Mean difference ²	Std.Err.	DF	t-value	p-value
Striatum	12	-342.8	135.2	18	-2.54	0.021
Cortex	6	-506.9	228.7	14	-2.22	0.044
	9	-365.7	161.4	9	-2.27	0.049
	12	-648.8	220	18	-2.95	0.008
Skeletal muscle	3	-6,120	2,784	18	-2.20	0.041
	21	-7,158	3,048	20	-2.35	0.029

1) This table shows the statistical results for the age comparisons that were statistically significant using pooled t-test ($p < 0.05$).

2) Negative values reflect lower mean mtDNA copy number in YAC128 compared to WT mice.

Supplementary Table 3

Average mtDNA copy number (mtDNAcn) in striatum, cortex and skeletal muscle of YAC128 and WT mice

Age (months)	Average mtDNAcn in striatum					
	WT	n ¹	Sex ² (M/F)	YAC128	n ¹	Sex ² (M/F)
1	1,197	14	4/10	1,297	9	2/7
3	1,272	9	3/6	1,214	11	6/5
6	1,172	1	0/1	1,436	5	3/2
9	1,335	5	2/3	1,449	6	1/5
12	1,372	10	5/5	1,029	10	4/6
15	1,459	5	3/2	1,818	10	4/6
18	1,651	5	4/1	1,896	7	4/3
21	1,721	4	1/3	1,609	12	5/7

Age (months)	Average mtDNAcn in cortex					
	WT	n ¹	Sex ² (M/F)	YAC128	n ¹	Sex ² (M/F)
1	1,623	18	7/11	1,378	15	7/8
3	1,335	8	2/6	1,442	11	6/5
6	2,236	6	3/3	1,730	10	6/4
9	1,673	5	2/3	1,308	6	1/5
12	1,996	10	5/5	1,348	10	4/6
15	1,641	5	3/2	2,006	10	4/6
18	1,947	5	4/1	1,769	8	5/3
21	1,492	4	1/3	1,425	12	5/7

Age (months)	Average mtDNAcn in skeletal muscle					
	WT	n ¹	Sex ² (M/F)	YAC128	n ¹	Sex ² (M/F)
1	10,487	17	7/10	8,215	14	7/7
3	15,882	9	3/6	9,762	11	6/5
6	16,349	6	3/3	18,963	10	6/4
9	18,511	5	2/3	18,996	6	1/5
12	14,580	10	5/5	14,138	10	4/6
15	20,748	4	3/1	13,839	8	4/4
18	15,893	5	4/1	10,160	7	4/3
21	21,880	9	8/1	14,722	13	6/7

1) Total number of mice analyzed.

2) Number of male mice (M) and female mice (F)

Supplementary Table 4

Effects of age, genotype and sex on gene expression in striatum and skeletal muscle of YAC128 and WT mice

Gene/ Tissue ³	Variables	Spline	Coef.	Std.Err.	t-value	DF	p-value	95% CI
<i>Pgc-1α</i> STR ¹	Age		-1.49	6.92	-0.22	88	0.830	-15.3 – 12.3
	Sex		-68.6	109.4	-0.63	88	0.532	-286.1 – 148.9
	Genotype		-120.7	109.3	-1.10	88	0.273	-338.1 – 96.6
SKM ²	Age Spline 1	1-3	183.1	79.6	2.30	104	0.024	25.1 – 341.0
	Age Spline 2	3-21	-842.2	417.6	-2.02	104	0.046	-1,671 – -13.7
	Sex		-241.5	281.0	-0.86	104	0.392	-799.1 – 316.0
	Genotype		219.9	272.8	0.81	104	0.422	-321.3 – 761.0
<i>Pparδ</i> STR ¹	Age		-3.85	7.72	-0.50	89	0.619	-19.2 – 11.5
	Sex		13.9	122.3	0.11	89	0.910	-229.2 – 256.9
	Genotype		-34.7	122.6	-0.28	89	0.778	-278.4 – 208.9
SKM ²	Age Spline 1	1-3	168.4	129.6	1.30	109	0.197	-88.6 – 425.4
	Age Spline 2	3-12	-1,782	1,449	-1.23	109	0.222	-4,656 – 1,091
	Age Spline 3	12-21	2,323	1,893	1.23	109	0.223	-1,431 – 6,077
	Sex		-82.4	179.9	-0.46	109	0.648	-439.1 – 274.3
<i>p62</i> STR ²	Genotype		118.1	178.3	0.66	109	0.509	-235.5 – 471.8
	Age Spline 1 ^d	1-12	409.9	103.3	3.97	88	<0.0001	204.5 – 615.4
	Age Spline 2 ^e	12-21	-467.7	160.0	-2.92	88	0.004	-785.9 – -149.5
SKM ²	Sex		-317.5	464.7	-0.68	88	0.496	-1,242 – 606.6
	Genotype		526.6	464.5	1.13	88	0.260	-397.1 – 1,450.3
SKM ²	Age Spline 1	1-3	3,217	570.5	5.64	109	<0.0001	2,085 – 4,348
	Age Spline 2	3-9	-43,854	8,466	-5.18	109	<0.0001	-60,644 – -27,063
	Age Spline 3	9-18	65,123	12,449	5.23	109	<0.0001	40,432 – 89,814
	Age Spline 4	18-21	-30,455	5,737	-5.31	109	<0.0001	-41,838 – 19,078
<i>LC3b</i> STR ²	Sex		-1,883	681.2	-2.76	109	0.007	-3,234 – 531.8
	Genotype		-1,076	668.7	-1.61	109	0.110	-2,402 – 249.6
SKM ²	Age Spline 1	1-9	-349.4	84.0	-4.16	89	<0.0001	-516.4 – -182.4
	Age Spline 2	9-21	461.3	129.6	3.56	89	0.001	203.6 – 719
	Sex		-224.8	376.5	-0.60	89	0.552	-973.3 – 523.7
	Genotype		-495.4	378.0	-1.31	89	0.194	-1247 – 256.1
SKM ²								
	Age Spline 1	1-3	2,466	522.2	4.72	107	<0.0001	1,430.5 – 3,502
	Age Spline 2	3-9	-29,170	6,980.2	-4.18	107	<0.0001	43,015 – 15,325
	Age Spline 3	9-21	40,765	9,829.9	4.15	107	<0.0001	21,268 – 60,263
<i>Bax</i> STR ²	Sex		100.6	652.9	0.15	107	0.878	-1,194 – 1,396
	Genotype		-234.9	638.7	-0.37	107	0.714	-1,502 – 1,032
SKM ²	Age Spline 1	1-9	-36.2	6.87	-5.26	89	<0.0001	-49.8 – 22.5
	Age Spline 2	9-18	92.2	19.6	4.70	89	<0.0001	53.2 – 131.2
	Age Spline 3	18-21	-308.1	68.8	-4.48	89	<0.0001	-444.9 – 171.3
	Sex		52.3	22.4	2.33	89	0.022	7.70 – 96.9
<i>Bcl-XL</i> STR ²	Genotype		4.26	22.1	0.19	89	0.848	-39.6 – 48.2
SKM ²	Age Spline 1	1-3	40.5	11.24	3.60	104	<0.0001	18.2 – 62.8
	Age Spline 2	3-9	-639.9	149.9	-4.27	104	<0.0001	-937.4 – -342.5
	Age Spline 3	9-21	914.9	211.0	4.34	104	<0.0001	496.2 – 1,334
	Sex		-7.24	13.96	-0.52	104	0.605	-34.9 – 20.5
<i>Bcl-XL</i> STR ²	Genotype		29.7	13.60	2.18	104	0.031	2.69 – 56.7
SKM ¹	Age Spline 1	1-3	-320.8	122.8	-2.61	89	0.011	12.1 – 70.7
	Age Spline 2	3-18	3,143	1,198	2.62	89	0.010	-1,160 – -231.2
	Age Spline 3	18-21	-3,848	1,500	-2.56	89	0.012	-741.7 – 189.2
	Sex		-639.8	227.3	-2.81	89	0.006	-1,091 – -187.7
SKM ¹	Genotype		-251.1	226.5	-1.11	89	0.271	-701.6 – 199.4
SKM ¹	Age	107	-0.549	4.57	-0.12	107	0.904	-9.61 – 8.51
	Sex	107	-130.8	71.7	-1.82	107	0.071	-272.9 – 11.5
	Genotype	107	78.6	70.4	1.12	107	0.266	-60.9 – 218.2

<i>Drp1</i> STR ²	Age Spline 1	1-3	-1,344	436.7	-3.08	89	0.003	-2,213 – -475.7
	Age Spline 2	3-12	17,257	5,060	3.41	89	0.001	7,195 – 27,319
	Age Spline 3	12-21	-22,839	6,656	-3.43	89	0.001	-36,075 – 9,602
	Sex		-881.9	629.2	-1.40	89	0.165	-2,133 – 369.2
	Genotype		-192.9	633.6	-0.30	89	0.761	-1,453 – 1,067
SKM ²	Age Spline 1	1-3	703.2	156.5	4.49	109	<0.0001	392.8 – 101.4
	Age Spline 2	3-9	-14,694	2,323	-6.33	109	<0.0001	-19,300 – 10,087
	Age Spline 3	9-18	22,789	3,416	6.67	109	<0.0001	16,015 – 29,563
	Age Spline 4	18-21	-12,206	1,574	-7.76	109	<0.0001	-15,327 – 9,085
	Sex		-485.5	186.9	-2.60	109	0.011	-856.2 – -114.9
<i>Mfn1</i> STR ¹	Genotype		138.4	183.4	0.75	109	0.452	-225.4 – 502.3
	Age	87	10.6	4.01	2.63	87	0.010	2.6 – 18.5
	Sex	87	-60.5	63.5	-0.95	87	0.343	-186.9 – 65.8
	Genotype	87	-16.3	63.2	-0.26	87	0.797	-142.0 – 109.5
SKM ²	Age Spline 1	1-3	1102.8	259.2	4.26	109	<0.0001	588.9 – 1,617
	Age Spline 2	3-12	-12,184	2,898	-4.20	109	<0.0001	-17,932 – -6,438
	Age Spline 3	12-21	15,876	3,786	4.19	109	<0.0001	8,369 – 23,383
	Sex		-644.1	359.7	-1.79	109	0.076	-1,357 – 69.1
	Genotype		-124.0	356.6	-0.35	109	0.729	-831.1 – 583.1
<i>Mfn2</i> STR ¹	Age	89	-172.9	38.8	-4.45	89	<0.0001	-250.0 – -95.7
	Sex	89	-111.3	614.9	-0.18	89	0.857	-1,334 – 1111
	Genotype	89	-710.9	616.5	-1.15	89	0.252	1,937 – 514.7
SKM ²	Age Spline 1	1-3	2,253	908.7	2.48	109	0.015	451.0 – 4,055
	Age Spline 2	3-9	-27,706	12,086	-2.29	109	0.024	-51,674 – 3,737
	Age Spline 3	9-21	38,990	17,001	2.29	109	0.024	5,276 – 72,705
	Sex		-1,588	1,119	-1.42	109	0.159	-3,807 – 631.4
	Genotype		-576.9	1,111	-0.52	109	0.605	-2,781 – 1,627
<i>Opa1</i> STR ²	Age Spline 1	1-9	-384.0	117.7	-3.26	89	0.002	-618.1 – -149.9
	Age Spline 2	9-12	1,372	438.5	3.13	89	0.002	500.4 – 2,245
	Age Spline 3	12-21	-8,519	2,668	-3.19	89	0.002	-13,826 – -3,213
	Sex		130.6	286.0	0.46	89	0.649	-438.1 – 699.4
	Genotype		-120.0	284.2	-0.42	89	0.674	-685.2 – 445.2
SKM ²	Age Spline 1	1-3	641.9	237.1	2.71	109	0.008	171.7 – 1,112
	Age Spline 2	3-9	-9,680	3,154	-3.07	109	0.003	-15,935 – -3,425
	Age Spline 3	9-21	13,729	4,437	3.09	109	0.003	4,931 – 22,527
	Sex		-361.1	292.0	-1.24	109	0.219	-940.2 – 217.9
	Genotype		-287.7	290.0	-0.99	109	0.324	-862.9 – 287.4
<i>mt-Co1</i> STR ¹	Age	88	299.7	173.8	1.72	88	0.088	-45.9 – 645.3
	Sex	88	-5,935.2	2,766.1	-2.15	88	0.035	-11,435 – -435.4
	Genotype	88	200.7	2,774.1	0.07	88	0.942	-5,316 – 5,717
SKM ²	Age Spline 1	1-3	12,585	6,149	2.05	109	0.043	392.0 – 24,788
	Age Spline 2	3-9	-168,417	81,782	-2.06	109	0.042	-330,595 – -6,239
	Age Spline 3	9-21	237,198	115,035	2.06	109	0.042	9,078 – 465,317
	Sex		-24,646	7,571	-3.26	109	0.002	-39,661 – -9,631
	Genotype		-531.7	7,520	-0.07	109	0.944	-15,444 – 14,380
<i>Actn2</i> STR ¹	Age	89	-273.4	45.7	-5.98	89	<0.0001	-364.3 – -182.5
	Sex	89	1,122.6	724.6	1.55	89	0.125	-317.8 – 2,563
	Genotype	89	-9,154.9	726.5	-12.6	89	<0.0001	-10,599 – -7,711
SKM ²	Age Spline 1	1-3	18,602	7,049	2.64	109	0.010	4,623 – 32,581
	Age Spline 2	3-12	-258,235	78,832	-3.28	109	0.001	-414,563 – -101,907
	Age Spline 3	12-21	343,408	102,980	3.33	109	0.001	139,194 – 547,622
	Sex		-10,499	9,784	-1.07	109	0.286	-29,900 – 8,903
	Genotype		12,132	9,700	1.25	109	0.214	-7,103 – 31,366

1) Linear regression was used for analysis.

2) Cubic spline regression was used for analysis.

3) Genes are indicated in italics and bold text. Tissue: STR=Striatum; SKM= Skeletal muscle

Supplementary Table 5¹

Difference in gene expression levels in YAC128 compared to WT mice at specific ages

Gene ²	Tissue ³	Age (months)	Mean difference ⁴	Std.Err.	DF	t-value	p-value
<i>p62</i>	STR	21	-2,941	878.5	13	-3.34	0.0053
	SKM	21	-2,826	1,321	18	-2.14	0.046
<i>Bax</i>	SKM	1	47.9	17.8	26	2.69	0.012
	SKM	9	66.0	28.6	8	2.31	0.049
	SKM	21	66.9	27.2	18	2.46	0.024
<i>mt-Co1</i>	STR	9	8,865	3,373	8	2.63	0.030
<i>Actn2</i>	STR	1	-8,930	1,395	22	-6.40	<0.0001
	STR	3	-9,774	1,168	17	-8.37	<0.0001
	STR	9	-9,576	2,167	9	-4.41	0.017
	STR	12	-7,557	1,791	5	-4.21	0.0083
	STR	18	-7,478	1,914	11	-3.91	0.0024
	STR	21	-10,818	2,721	14	-3.98	0.0014
	SKM	18	52,420	20,269	10	2.59	0.027
	SKM	21	39,981	15,967	18	2.50	0.022

1) Table shows the results for the age comparisons that were statistically significant using pooled t-test (p<0.05).

2) The genes are indicated in italics.

3) STR=Striatum; SKM=Skeletal muscle

4) Negative values reflect lower mean transcript mRNA levels in YAC128 compared to WT.

Supplementary Table 6
Number of mice analyzed in gene expression analysis

Age (months)	STRIATUM				SKELETAL MUSCLE			
	WT	Sex ¹ (M/F)	YAC128	Sex ¹ (M/F)	WT	Sex ¹ (M/F)	YAC128	Sex ¹ (M/F)
1	13	4/9	11	4/7	16	7/9	14	7/7
3	8	2/6	11	6/5	9	3/6	11	6/5
9	5	2/3	6	1/5	4	2/2	6	1/5
12	4	2/2	3	2/1	9	5/4	7	4/3
18	5	4/1	8	5/3	5	4/1	7	4/3
21	4	1/3	12	5/7	9	8/1	13	6/7

1) Number of male mice (M) and female mice (F)

Supplementary Table 7

Primers used in gene expression analysis (quantitative real-time PCR)

Gene target	Forward primer nucleotide sequence	Reverse primer nucleotide sequence	Amplicon size (basepairs)
<i>mt-Co1</i>	TCGTTGATTATTCTCAACCAATCA	GCCTCCAATTATTATTGGTATTACTATGA	220
<i>Pgc-1a</i>	GCGTCATTGCGGGAGCTGG	CGCTACACCACTTCAATCCAC C	190
<i>Pparδ</i>	CGAGTTTGCTGTCAAGTTCAATG	TGGCCGGTCTCCACACA	91
<i>LC3b</i>	CTTTGAACAAAGAGTGGAAGA TGTCCG	ACCATGCTGTGCCCATTCACCA	231
<i>p62</i>	CACAGGAAGGACCCACAGGG	GAGCAGCCCCGATGTCGTAA	174
<i>Bax</i>	TGCACTAAAGTGCCCCGAGCTG	ACACAGTCCAAGGCAGTGGG	229
<i>Bcl-XL</i>	AAACTGGGGTCGCATCGTGG	CTCTCGGCTGCTGCATTGTTCC	204
<i>Drp1</i>	TCAGCCCAAGGACATCGAGC	GGCATCAGTACCCGCATCCA	208
<i>Mfn1</i>	AATGCACAGAGGGTGCTGCT	GGAGTTCTCGACGTGAGGG	171
<i>Mfn2</i>	CCCATGCCCTCCATCAGGAC	AGCGTGGACTCTGAGTTGGC	208
<i>Opa1</i>	CAGGTCACGCCAAAGCACTG	CCAGGCAACCTCGACTGC	195
<i>Actn2</i>	GCGCAGGAGCTCAATGAACT	CTATCCCACTGGTCGCAAATTT	83
<i>Rplp0</i>	TGGGCATCACCACGAAAAT	ATCAGCTGCACATCACTCAGAATT	61
<i>Hprt1</i>	CGTCGTGATTAGCGATGATGA	TCCAAATCCTCGGCATAATGA	78
<i>Actb</i>	CCAGCCTTCCTTCTTGGGTAT	TGTGTTGGCATAGAGGTCTTTACG	106