

Figure 1

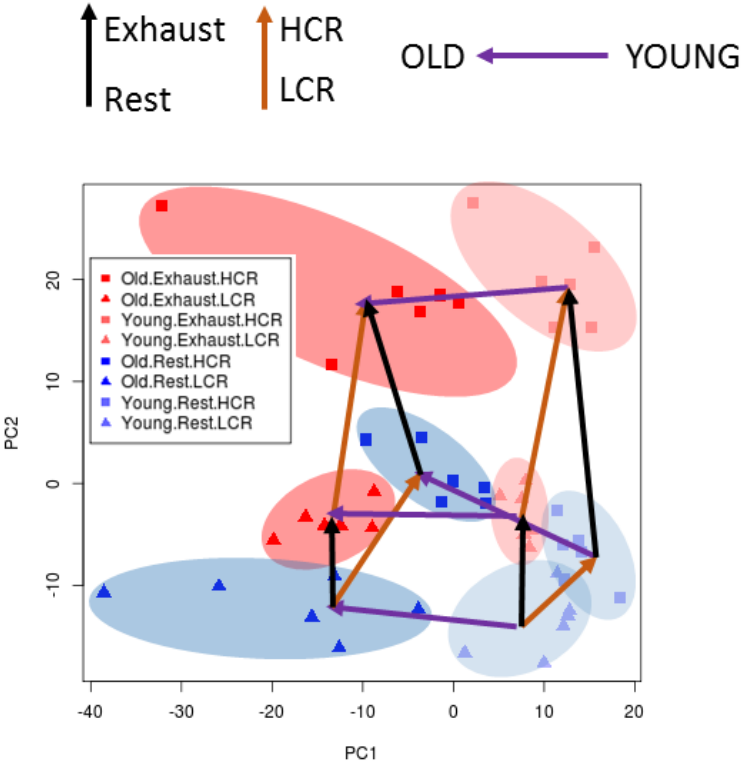


Figure 2

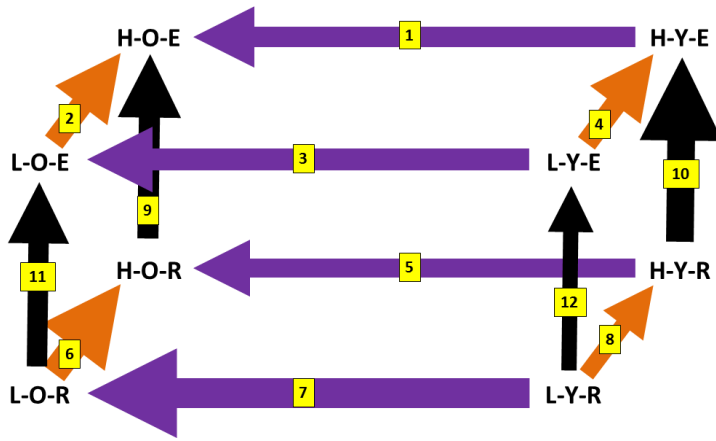


Figure 3

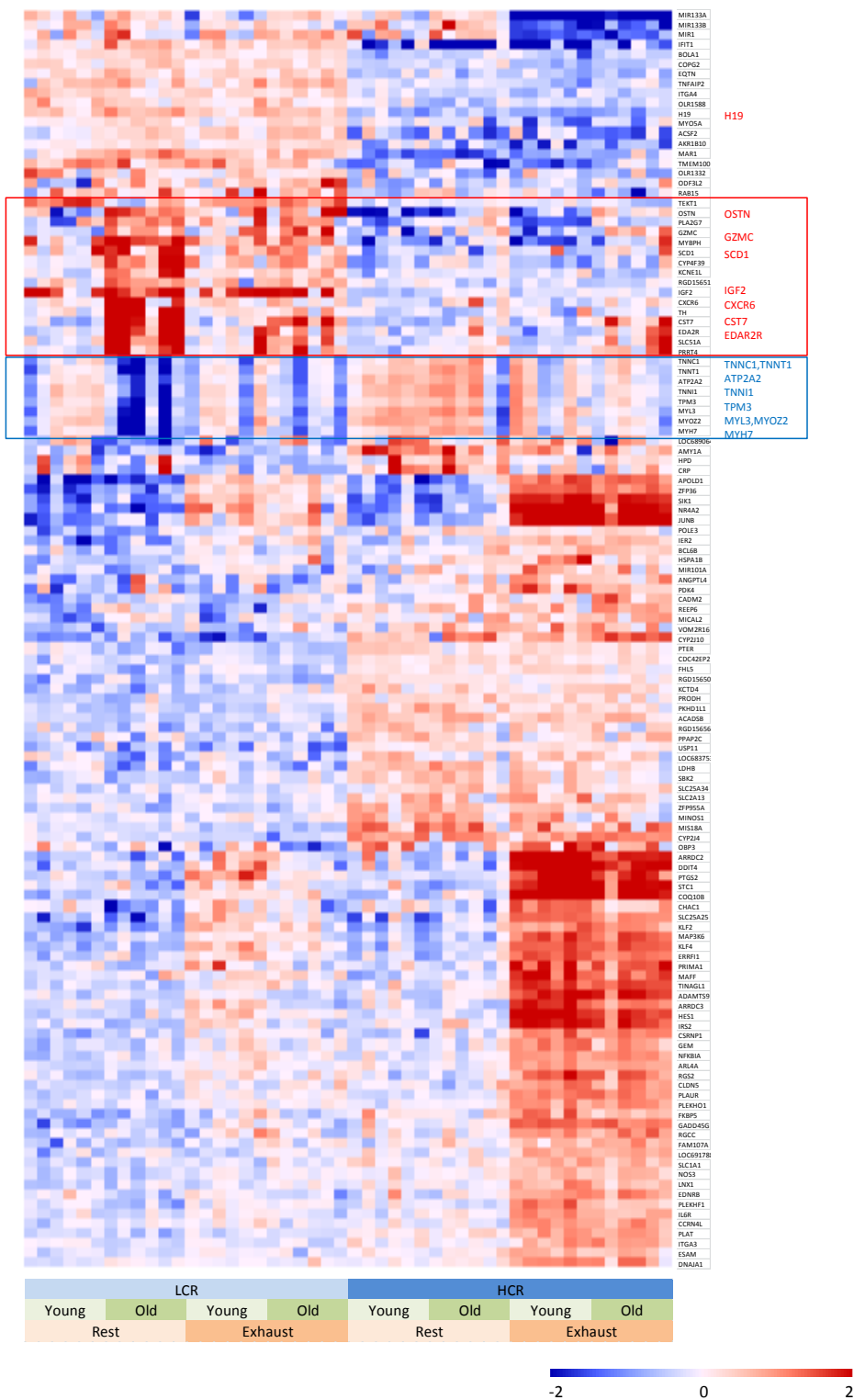
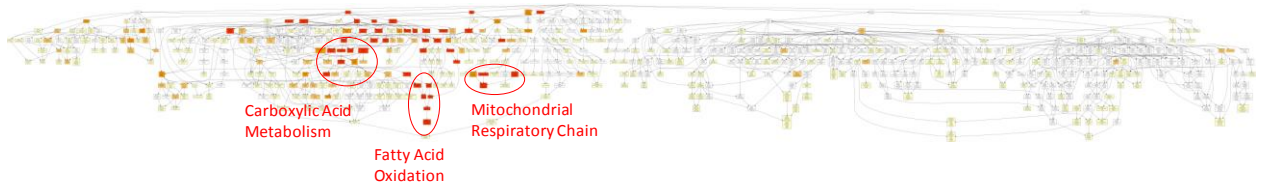


Figure 4

Line genes, GO Biological Processes



Age genes, GO Biological Processes



Exercise genes, GO Biological Processes

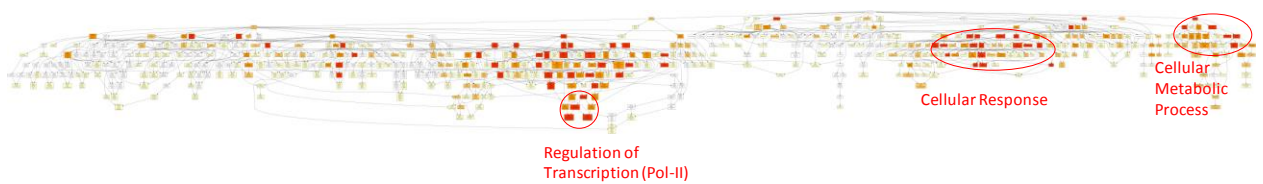
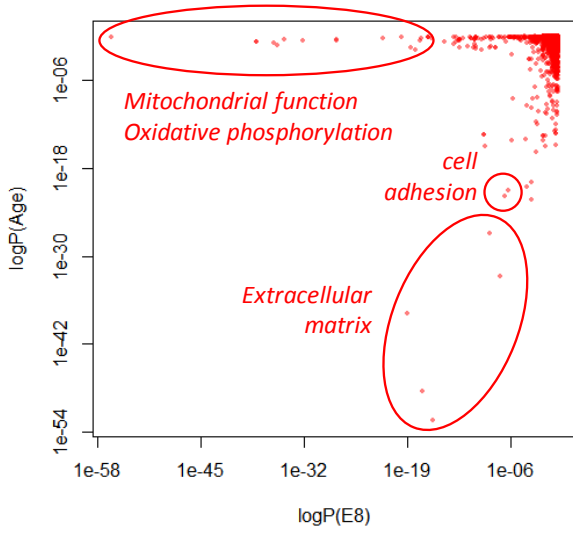
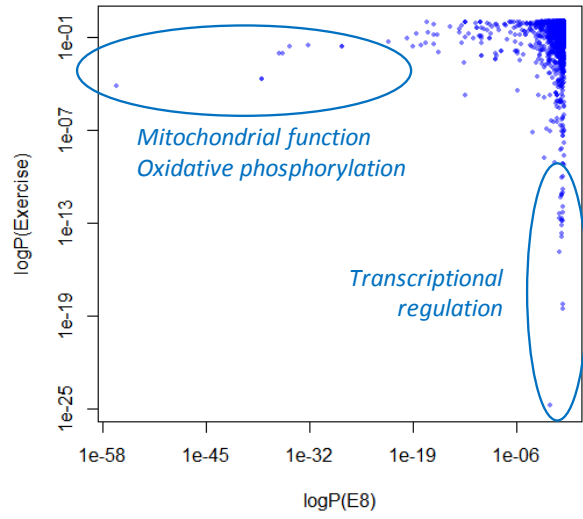


Figure 5

a



b



Name		fatty acid oxidation	carboxylic acid catabolic process	carboxylic acid metabolic process	mitochondrial respiratory chain	cell migration	cell adhesion	extracellular matrix	collagen	regulation of transcription from RNA polymerase II promoter	cellular response to chemical stimulus	positive regulation of cellular metabolic process	negative regulation of cellular metabolic process
# Genes		59	110	535	59	388	628	298	25	624	371	850	651
log(P,10)													
line	HCR-LCR	8.4	15.0	17.4	19.0	0.1	3.4	0.9	1.4	0.1	0.3	0.2	0.2
E2	HCR-LCR Old,Exhausted	1.7	4.6	5.9	1.3	5.2	2.0	6.1	0.2	0.9	2.2	0.8	1.1
E4	HCR-LCR Young,Exhausted	4.6	8.0	11.0	5.7	4.3	7.4	1.3	2.2	0.4	0.0	1.1	1.3
E6	HCR-LCR Old,Rest	2.3	4.7	3.4	15.7	0.5	0.7	0.8	0.2	0.7	0.4	0.1	0.1
E8	HCR-LCR Young,Rest	6.4	9.5	10.0	17.7	2.6	11.5	17.2	7.5	0.3	2.4	0.9	0.1
age	Old-Young	0.2	0.4	2.4	0.3	5.4	16.0	55.1	23.0	7.0	1.2	2.0	6.2
E1	Old-Young HCR,Exhausted	2.6	1.0	3.3	0.0	0.1	1.7	27.1	12.2	1.7	1.0	1.7	1.4
E3	Old-Young LCR,Exhausted	0.1	0.5	0.3	2.4	13.6	22.2	50.5	19.1	1.0	2.4	0.6	1.3
E5	Old-Young HCR,Rest	0.1	0.9	4.1	0.1	0.8	4.0	18.0	8.9	11.6	0.6	3.5	7.1
E7	Old-Young LCR,Rest	0.2	0.3	2.0	0.6	4.3	10.3	33.9	17.7	5.5	1.7	1.9	4.3
exercise	Exhausted-Rest	0.3	0.5	3.0	0.5	3.1	1.8	3.2	0.0	21.4	8.4	8.6	9.0
E9	Exhausted-Rest HCR,Old	3.5	1.4	2.0	5.8	3.0	2.7	4.2	0.1	5.5	3.6	2.8	2.9
E10	Exhausted-Rest HCR,Young	0.1	0.2	1.0	3.0	0.6	1.2	7.7	0.7	13.4	6.4	3.5	7.1
E11	Exhausted-Rest LCR,Old	0.4	0.4	0.8	6.2	0.1	0.7	1.7	0.6	6.1	2.0	1.7	1.3
E12	Exhausted-Rest LCR,Young	0.4	0.8	5.5	0.2	4.1	1.9	0.6	0.1	25.2	3.9	12.2	9.6

Name		fatty acid oxidation	carboxylic acid catabolic process	carboxylic acid metabolic process	mitochondrial respiratory chain	cell migration	cell adhesion	extracellular matrix	collagen	regulation of transcription from RNA polymerase II promoter	cellular response to chemical stimulus	positive regulation of cellular metabolic process	negative regulation of cellular metabolic process
# Genes		59	110	535	59	388	628	298	25	624	371	850	651
Odds Ratio													
line	HCR-LCR	1.98	2.01	1.56	2.54	0.97	0.80	0.87	0.54	1.02	1.04	0.98	1.03
E2	HCR-LCR Old,Exhausted	2.07	2.54	1.75	1.90	1.82	1.34	2.06	1.25	1.19	1.47	1.15	1.22
E4	HCR-LCR Young,Exhausted	2.90	2.94	1.99	3.24	0.57	0.55	0.74	0.26	1.10	1.01	0.85	1.22
E6	HCR-LCR Old,Rest	2.35	2.55	1.49	7.68	1.14	0.86	0.81	0.80	1.15	1.11	1.02	1.04
E8	HCR-LCR Young,Rest	4.59	4.20	2.20	10.47	0.63	0.42	0.23	0.08	0.91	0.63	0.85	0.97
age	Old-Young	0.93	0.91	0.86	1.15	0.78	0.70	0.48	0.37	1.37	0.89	1.13	1.34
E1	Old-Young HCR,Exhausted	0.41	0.66	0.65	0.96	1.04	0.76	0.24	0.14	1.33	0.78	1.28	1.29
E3	Old-Young LCR,Exhausted	0.93	1.31	0.94	2.76	0.42	0.40	0.19	0.08	1.20	0.69	0.91	1.24
E5	Old-Young HCR,Rest	1.13	0.67	0.62	0.94	0.82	0.65	0.28	0.10	2.18	1.18	1.42	1.80
E7	Old-Young LCR,Rest	1.19	0.86	0.75	0.68	0.60	0.52	0.22	0.07	1.67	0.73	1.27	1.55
exercise	Exhausted-Rest	0.86	0.85	0.77	0.80	1.28	1.17	1.33	1.03	1.67	1.49	1.36	1.41
E9	Exhausted-Rest HCR,Old	0.29	0.57	0.71	0.21	1.60	1.43	1.90	1.09	1.70	1.70	1.38	1.45
E10	Exhausted-Rest HCR,Young	1.06	0.90	0.85	0.39	1.15	1.18	1.91	1.70	1.87	1.71	1.32	1.57
E11	Exhausted-Rest LCR,Old	0.71	1.32	0.81	5.65	1.05	0.84	0.63	0.47	1.92	1.55	1.31	1.30
E12	Exhausted-Rest LCR,Young	1.42	0.64	0.51	0.84	1.85	1.37	1.22	0.87	3.45	1.83	2.16	2.15

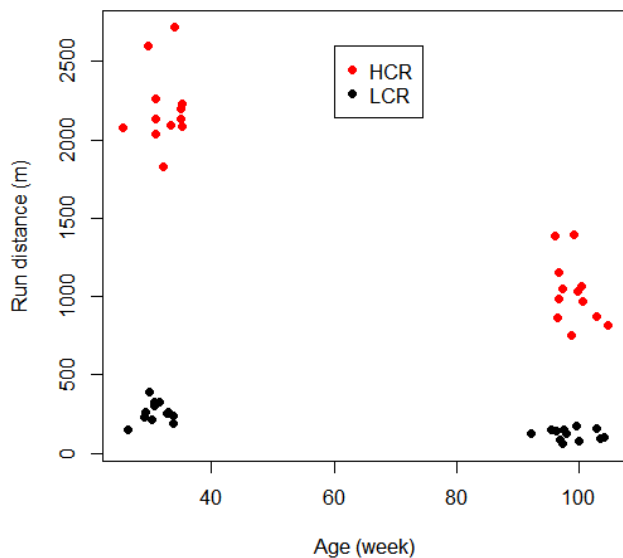
Supplementary Table 1

LogP and odds ratio of the pathways highlighted in Figure 4 for the 3 overall and 12 stratified main effect analysis.

geneSymbol	line.pval	line.FC	age.pval	age.FC	exercise.pval	exercise.FC
CPT1A	0.0038	0.33	0.190	0.14	0.201	0.14
CPT1B	9.1E-07	0.21	0.124	0.06	0.685	0.02
SIRT2	0.091	0.06	0.028	-0.08	0.374	0.03
SIRT3	0.0085	0.18	0.0061	0.18	0.558	0.04
SIRT4	0.0009	0.25	0.853	0.01	0.848	0.01
SIRT5	1.1E-05	0.20	0.408	0.03	0.0092	-0.11
SIRT6	0.282	0.05	0.481	-0.03	0.323	0.04
SIRT7	0.025	0.15	0.453	-0.05	0.899	0.01
UTRN	2.5E-07	0.26	1.6E-04	-0.18	0.539	-0.03
DMD	0.403	-0.03	3.7E-12	0.38	0.622	-0.02
PPARA	4.4E-07	0.38	2.9E-04	-0.26	0.161	-0.09
PPARD	0.0034	0.19	3.6E-05	-0.28	0.045	0.13
PPARGC1A	0.077	0.13	0.086	-0.12	0.814	-0.02
PPARGC1B	1.3E-06	0.24	0.198	0.06	0.344	0.04
NDUFA1	0.0006	0.18	0.423	0.04	0.544	-0.03
NDUFA10	0.024	0.20	0.0022	-0.28	0.136	-0.13
NDUFA10	9.3E-07	0.18	0.053	-0.06	0.0037	-0.10
NDUFA11	1.5E-04	0.19	0.895	0.01	0.456	0.03
NDUFA12	0.0017	0.17	0.365	0.05	0.547	-0.03
NDUFA13	8.7E-06	0.34	0.053	0.14	0.022	0.16
NDUFA2	0.041	0.25	0.411	-0.10	0.380	-0.10
NDUFA3	0.279	0.06	0.034	0.12	0.920	0.01
NDUFA4	0.067	0.05	0.949	0.00	0.767	-0.01
NDUFA4L2	0.071	0.17	3.28E-06	-0.49	0.521	0.06
NDUFA5	3.3E-07	0.21	0.724	0.01	0.196	0.05
NDUFA6	2.4E-04	0.25	5.91E-05	0.27	0.017	0.15
NDUFA7	0.011	0.12	0.119	0.07	0.0077	0.13
NDUFA8	0.049	0.08	4.5E-04	-0.14	0.027	-0.09
NDUFA9	6.1E-05	0.17	0.028	-0.09	0.058	-0.07
NDUFAB1	0.065	0.10	0.562	-0.03	0.509	-0.04
NDUFAB1	0.151	0.08	0.501	-0.04	0.048	-0.11
NDUFAB2	0.101	0.11	0.0006	0.25	0.683	-0.03
NDUFAB3	2.7E-05	0.17	0.017	0.09	0.321	0.04
NDUFAB4	2.3E-04	0.26	0.083	0.11	0.656	-0.03
NDUFAB5	1.5E-04	0.27	0.031	-0.14	0.156	-0.09
NDUFAB6	7.0E-06	0.24	0.089	0.08	0.0084	-0.13
NDUFAB7	0.198	0.10	0.024	-0.17	0.135	-0.11
NDUFB10	9.8E-05	0.20	0.412	0.04	0.375	0.04
NDUFB11	9.8E-06	0.20	0.711	-0.01	0.064	0.08
NDUFB2	3.7E-05	0.21	0.859	0.01	0.376	0.04
NDUFB3	0.086	0.07	0.136	0.06	0.173	-0.06
NDUFB3	0.376	0.03	0.641	0.01	0.002	-0.10
NDUFB3L	0.0013	0.13	0.123	0.06	0.504	0.03
NDUFB3L	0.0013	0.13	0.123	0.06	0.504	0.03
NDUFB4	0.411	0.03	0.218	-0.05	0.732	-0.01
NDUFB4L1	0.007	0.34	0.556	0.07	0.360	-0.11
NDUFB5	0.001	0.15	0.257	-0.05	0.203	-0.05
NDUFB6	0.002	0.18	0.874	0.01	0.974	0.00
NDUFB7	6.7E-05	0.27	4.9E-04	0.23	0.206	0.08
NDUFB8	2.0E-10	0.36	0.355	-0.04	0.969	0.00
NDUFB9	0.019	0.08	0.062	-0.06	0.780	0.01
NDUFC1	0.070	0.08	0.277	-0.05	0.407	-0.04
NDUFC2	0.0053	0.09	0.620	-0.01	0.0013	-0.10
NDUFS1	1.6E-06	0.18	0.427	-0.03	0.035	-0.07
NDUFS3	1.1E-04	0.22	0.797	0.01	0.605	-0.03
NDUFS4	9.3E-06	0.15	0.834	-0.01	0.032	-0.07
NDUFS5	0.0093	0.21	0.515	0.05	0.553	-0.05
NDUFS5	2.0E-05	0.34	0.608	-0.04	0.042	-0.15
NDUFS6	0.122	0.09	0.548	-0.04	0.295	0.06
NDUFS7	1.2E-11	0.30	0.246	-0.04	0.728	-0.01
NDUFS8	3.5E-06	0.21	0.128	-0.06	0.592	-0.02
NDUFV1	3.3E-05	0.19	0.457	-0.03	0.941	0.00
NDUFV2	0.0011	0.13	0.706	-0.01	0.363	0.03
NDUFV3	0.088	0.09	0.0011	0.18	1.1E-06	0.29
NDUFV3	0.494	-0.05	0.398	-0.06	0.485	-0.05
TFAM	3.9E-03	0.11	1.9E-03	0.12	0.888	-0.01
NFE2L2	9.6E-04	0.16	0.064	0.08	0.233	0.05
MAP1LC3B	7.5E-05	0.21	0.813	-0.01	0.190	0.06
MAP1LC3A	4.3E-06	0.36	0.011	0.18	0.0084	0.19
LAMP1	2.7E-05	0.10	0.0011	0.08	0.171	0.03
BECN1	0.044	-0.09	0.373	-0.04	0.763	-0.01
ATG7	0.651	0.02	0.980	0.00	0.796	0.01
MMP14	0.468	0.07	6.4E-07	-0.52	0.343	-0.09
MMP2	0.956	0.01	8.9E-11	-0.79	0.531	-0.06
TLR3	0.089	0.12	4.7E-04	-0.25	0.199	-0.09
TLR4	0.053	-0.14	1.1E-04	-0.29	0.213	0.09
TLR5	0.0084	-0.27	2.0E-04	-0.40	0.942	-0.01
TLR6	2.3E-04	0.37	0.067	-0.17	0.691	-0.04

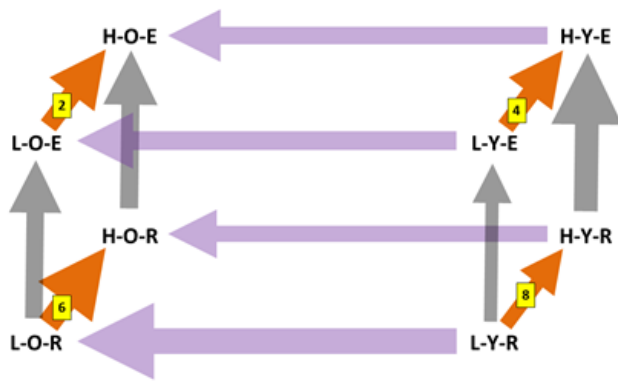
Supplementary Table 2

P-value and fold-change results for select genes that have been reported in literature for their line-, age-, or exercise-effects. Values are extracted from **Supplementary File 1**.

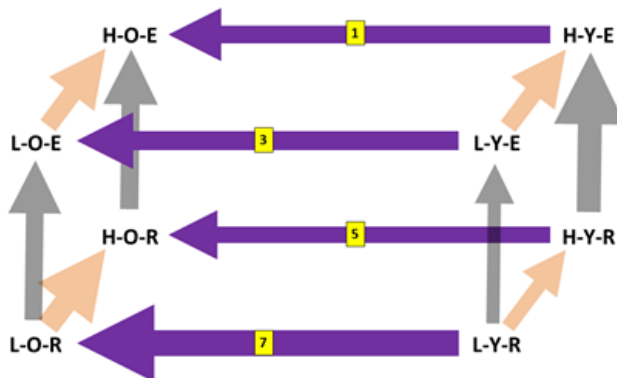


Supplementary Figure 1.

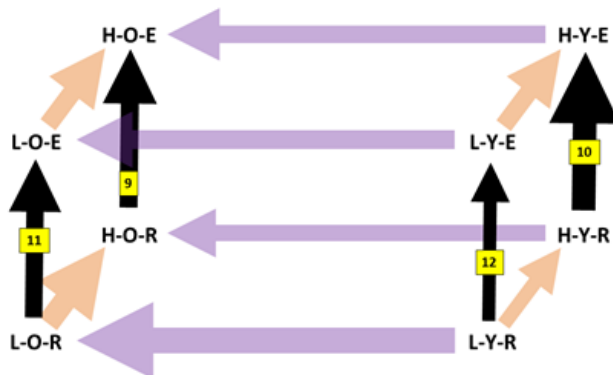
Distribution of age and running distance at the time of experiment for the 12 old and 12 young animals in each of the two lines.

a

Side	Comparison	Euclidean Distance
2	HCR-LCR Old,Exhausted	33.4
4	HCR-LCR Young,Exhausted	32.9
6	HCR-LCR Old,Rest	36.6
8	HCR-LCR Young,Rest	29.2

b

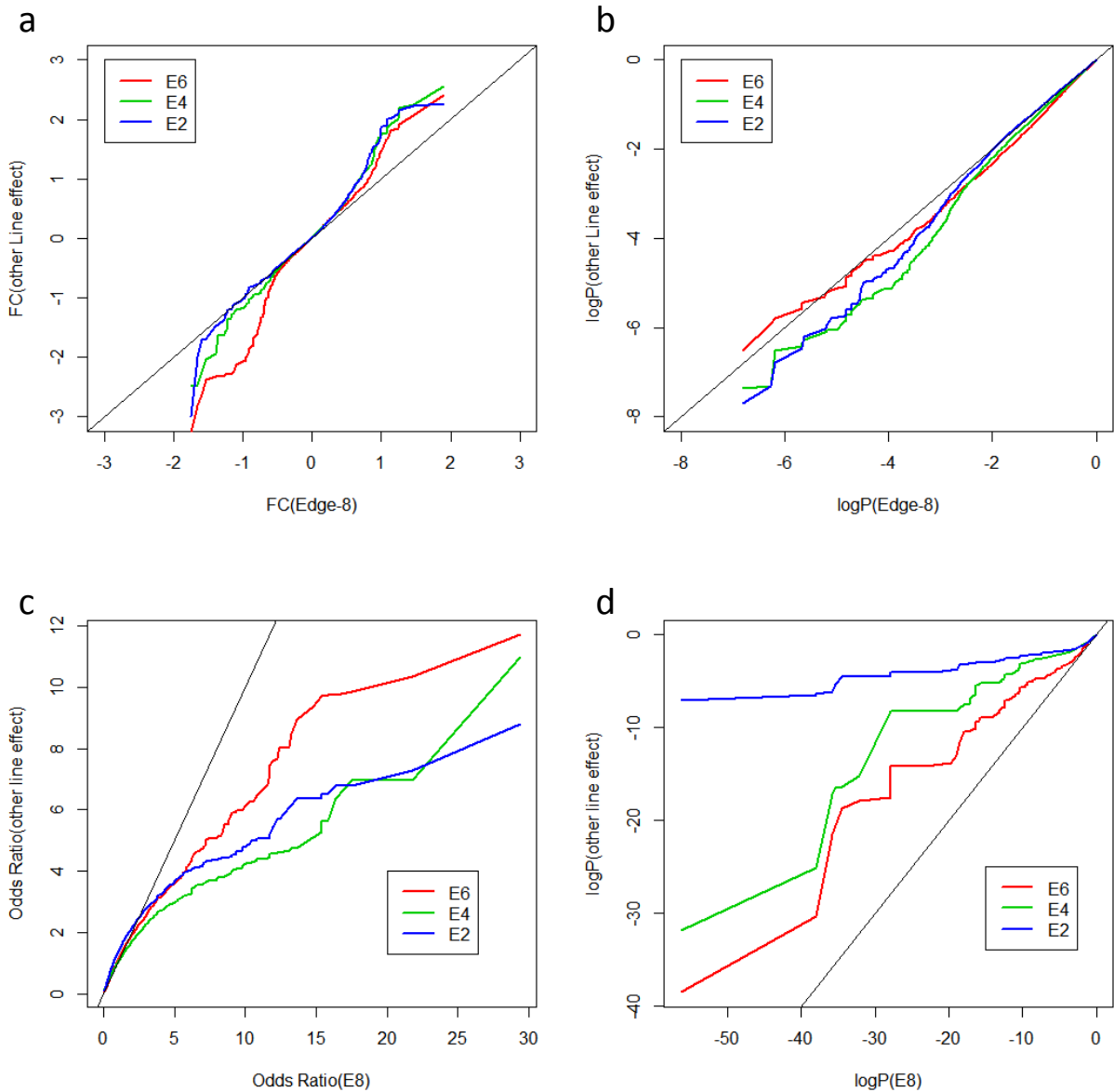
Side	Comparison	Euclidean Distance
1	Old-Young HCR,Exhausted	32.4
3	Old-Young LCR,Exhausted	33.8
5	Old-Young HCR,Rest	31.0
7	Old-Young LCR,Rest	39.1

c

Side	Comparison	Euclidean Distance
9	Exhausted-Rest HCR,Old	33.1
10	Exhausted-Rest HCR,Young	38.1
11	Exhausted-Rest LCR,Old	32.5
12	Exhausted-Rest LCR,Young	28.4

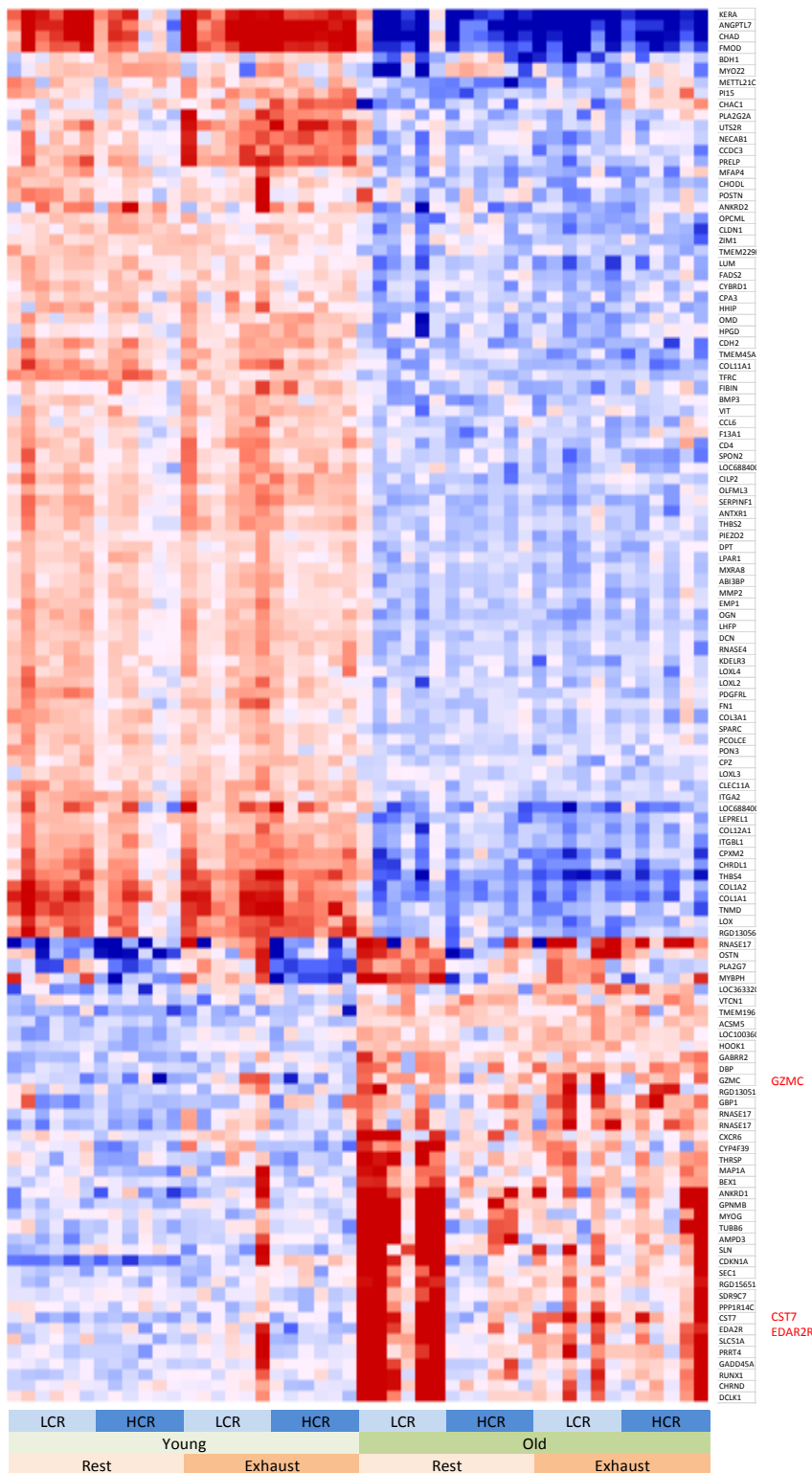
Supplementary Figure 2. Euclidean distances between groups.

Left panels highlight individual comparisons in the cube depiction. (a) Effects of genetic background: HCR vs. LCR (sides 2, 4, 6, and 8); (b) Effects of aging: old vs young (sides 1, 3, 5, and 7); (c) Effects of exercise: exhaustion vs. rest (sides 9, 10, 11, and 12). In expression such as (HCR-LCR|Old, Exhausted), "|" is the mathematical notation of "conditional on", indicating the specific strata in which the contrast is defined.



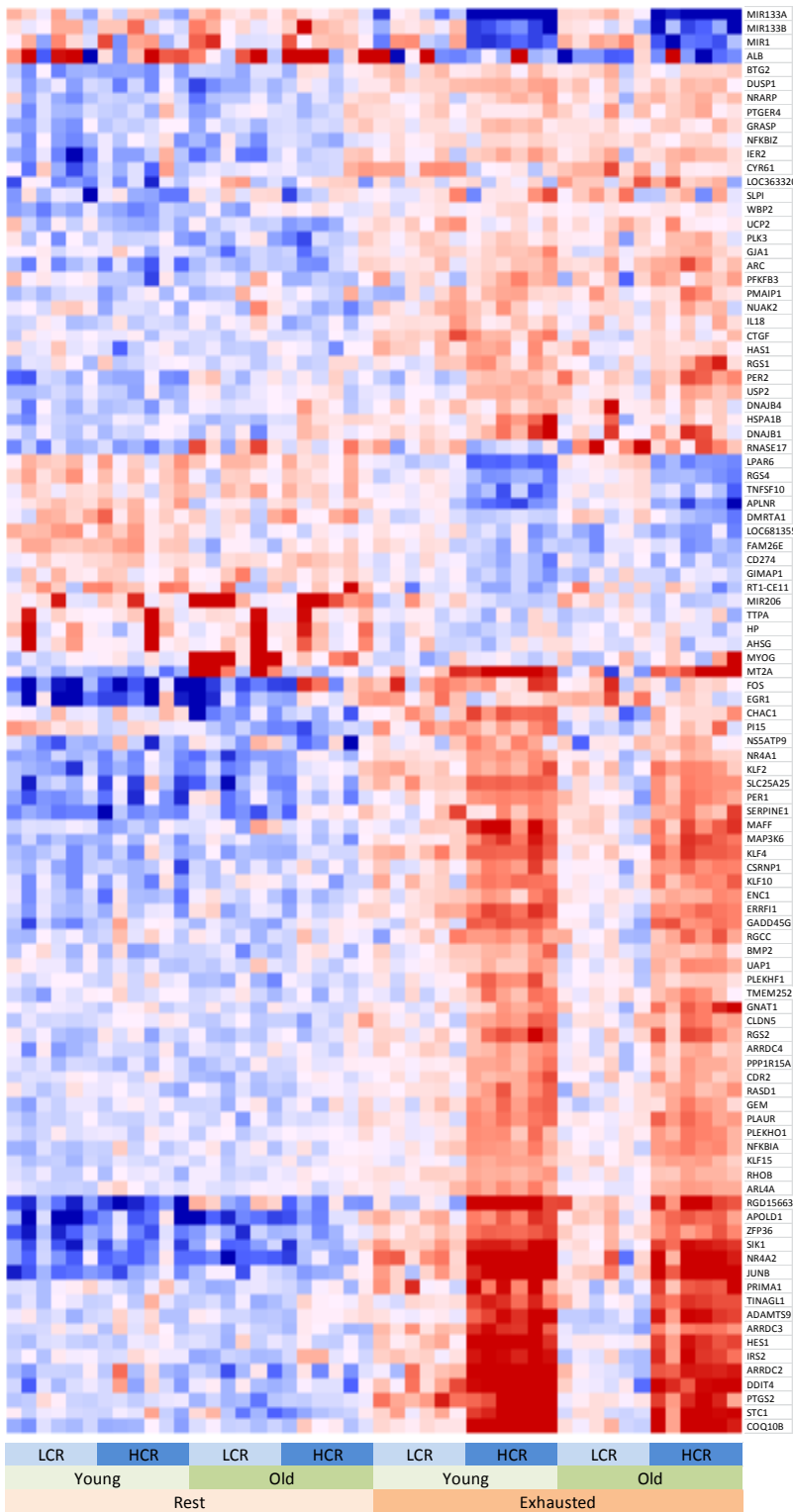
Supplementary Figure 3. Comparison between E8 and the other three line effects (E6, E4, E2).

qq-plots for fold-change (a) and logP (b) in 19,607 genes showing that E8 tends to have smaller effect and less significance at the gene level. qq-plots for odds ratio (c) and logP (d) for 4,146 pathways, showing that E8 tends to have stronger and more significant pathway-level signals.



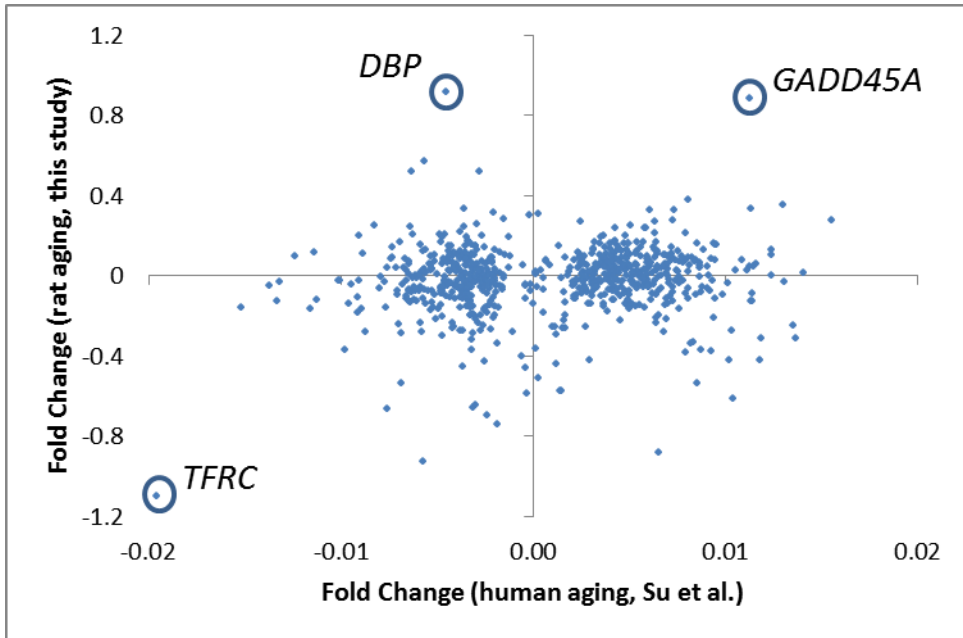
Supplementary Figure 4.

Similar to Figure 3, shown are 123 genes with the largest "Age" effect, satisfying $FDR < 0.05$ and greater than 60% fold change in either direction.



Supplementary Figure 5.

Similar to Figure 3, shown are 102 genes with the largest "Exercise" effect, satisfying FDR < 0.05 and greater than 50% fold change in either direction.



Supplementary Figure 6.

Comparison of fold change of aging effect between a human skeletal muscle meta-analysis (Su et al. 2015) and our study of HCR-LCR rats.