

Supplementary Table 1: Targeted DNA methylation panel. Genomic coordinates are based on genome assembly GRCh38/hg38.

Target region	Chromosome	Start	End	Length
<i>ATF2 Promoter</i>	chr2	175181611	175182358	747
<i>CAMK2A Enhancer</i>	chr5	150256130	150256868	738
<i>CAMK2A Promoter</i>	chr5	150289630	150290353	723
<i>CAMKIV Promoter</i>	chr5	111223579	111224486	907
<i>CREB1 Promoter</i>	chr2	207529048	207530297	1249
<i>CREB5 Promoter</i>	chr7	28685390	28686760	1370
<i>CREB5 TSS</i>	chr7	28412446	28412669	223
<i>CS Promoter</i>	chr12	56299357	56301150	1793
<i>ESRRA Promoter</i>	chr11	64305030	64306212	1182
<i>FOXO1 Enhancer</i>	chr13	40598208	40599640	1432
<i>FOXO1 Promoter</i>	chr13	40666208	40667577	1369
<i>FOXO3 Enhancer</i>	chr6	108650156	108651861	1705
<i>FOXO3 Promoter</i>	chr6	108558752	108560683	1931
<i>HES1 Promoter</i>	chr3	194135518	194136612	1094
<i>HIF1A Promoter</i>	chr14	61694712	61695621	909
<i>HIF1A Promoter/Enhancer</i>	chr14	61697314	61698034	720
<i>MAPK12 Enhancer</i>	chr22	50248041	50249380	1339
<i>MAPK12 Promoter</i>	chr22	50261277	50262808	1531
<i>MEF2A Enhancer</i>	chr15	99718988	99719684	696
<i>MEF2A Promoter</i>	chr15	99565358	99566091	733
<i>MSTN Promoter/Enhancer</i>	chr2	190062542	190066015	3473
<i>MTOR Enhancer</i>	chr1	11157965	11158698	733
<i>MTOR Promoter</i>	chr1	11261784	11262982	1198
<i>MYC Enhancer</i>	chr8	127898412	127898532	120
<i>MYF5 Promoter</i>	chr12	80716415	80717349	934
<i>MYF6 Promoter</i>	chr12	80706525	80707694	1169
<i>MYH2 Promoter</i>	chr17	10549558	10550157	599
<i>MYH6 Promoter</i>	chr14	23409253	23409513	260
<i>MYH7 Promoter</i>	chr14	23435560	23436160	600
<i>MYL3 Promoter</i>	chr3	46863344	46863943	599
<i>MYOD1 Core Enhancer</i>	chr11	17699561	17699898	337
<i>MYOD1 DRR Enhancer</i>	chr11	17713956	17715330	1374
<i>MYOD1 Promoter</i>	chr11	17718561	17720213	1652
<i>MYOG Promoter</i>	chr1	203085593	203087076	1483
<i>NDUFA4L2_1 Promoter</i>	chr12	57236323	57237603	1280
<i>NDUFA4L2_2&3 Promoter</i>	chr12	57240621	57241360	739
<i>NRF1 Promoter</i>	chr7	129610993	129611946	953
<i>PAX7 Promoter</i>	chr1	18630893	18631726	833
<i>PDK4 Enhancer</i>	chr7	95592725	95592845	120
<i>PDK4 Promoter</i>	chr7	95596415	95597014	599

<i>PPARGC1A alternative Promoter</i>	chr4	23903795	23904977	1182
<i>PPARGC1A Enhancer?</i>	chr4	23880612	23883359	2747
<i>PPARGC1A Enhancer?</i>	chr4	23934209	23935339	1130
<i>PPARGC1A Enhancer?</i>	chr4	23945150	23946601	1451
<i>PPARGC1A proximal Promoter</i>	chr4	23887877	23891221	3344
<i>PRKAA1 Promoter</i>	chr5	40797940	40798913	973
<i>PRKAA2 Promoter</i>	chr1	56644815	56645414	599
<i>SLC2A4 Promoter</i>	chr17	7279539	7283489	3950
<i>SMAD Enhancer</i>	chr15	67165245	67166183	938
<i>SMAD3 Enhancer</i>	chr15	67098033	67098808	775
<i>SMAD3 Enhancer</i>	chr15	67136625	67136886	261
<i>SMAD3 Promoter</i>	chr15	67065343	67065942	599
<i>TBP promoter</i>	chr6	170553777	170554471	694
<i>TFAM Promoter</i>	chr10	58384572	58385550	978
<i>TGFB1 Promoter</i>	chr19	41353376	41354375	999
<i>VEGFA Enhancer</i>	chr6	44057596	44058015	419
<i>VEGFA Promoter</i>	chr6	43769299	43772782	3483

Supplementary Table 2: Proportions of different immune cells estimated by CIBERSORTx (see Methods for details).

CellType	CG	EG	SG	Significant difference
B.cells.memory	0,00085012	0	0,0013107	
B.cells.naive	0,13336205	0,12519107	0,11428227	
Dendritic.cells.activated	0,00637968	0,00181708	0,00585571	
Dendritic.cells.resting	0,00122349	0,00085793	0,00574504	
Eosinophils	0,02522647	0,01423789	0,04422174	
Macrophages.M0	0,00684289	0,00112732	0	
Macrophages.M1	0,06982851	0,05455127	0,06964833	
Macrophages.M2	0,46896146	0,37532914	0,5090656	* EGvsSG
Mast.cells.activated	0,01099842	0,00549446	0,00299834	
Mast.cells.resting	0,26890452	0,24829314	0,27521446	
Monocytes	0,06148975	0,05800037	0,07526069	
Neutrophils	0,06795992	0,01822721	0,03432295	
NK.cells.activated	0,06457682	0,05828663	0,0624323	
NK.cells.resting	0,09553358	0,16741426	0,11907675	*EGvsCG
Plasma.cells	0,05870218	0,01477505	0,01686137	
T.cells.CD4.memory.activated	5,6021E-05	0	0	
T.cells.CD4.memory.resting	0,29569428	0,30169222	0,37713086	
T.cells.CD4.naive	0,00340222	0,01025579	0,01476943	
T.cells.CD8	0,05837374	0,03959892	0,01652016	
T.cells.follicular.helper	0,07121601	0,07461673	0,10550473	
T.cells.gamma.delta	0	0	0	

T.cells.regulatory..Tregs.	0,00217911	0,0010491	0,00491188	
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CG = control group, EG = endurance group, SG = strength group

Supplementary Table 3: Correlations between methylation percentage at baseline and A) Gene expression, B) VO₂peak, C) Leg Strength and D) Type I Fiber percentage

Gene	A) Gene expression		B) VO ₂ peak		C) Leg Strength		D) Type I Fiber %	
	R	FDR	R	FDR	R	FDR	R	FDR
CREB1	0.21	0.43	-0.01	0.94	-0.26	0.66	0.49	0.04
CREB5	-0.38	0.11	0.59	<0.01	-0.10	0.84	0.26	0.31
FOXO1	-0.25	0.36	0.70	<0.01	0.07	0.89	0.46	0.06
FOXO3	-0.30	0.22	0.71	<0.01	-0.12	0.84	0.63	0.01
HIF1A	0.17	0.50	-0.18	0.35	-0.30	0.66	0.30	0.25
MAPK12	-0.39	0.11	0.69	<0.01	0.04	0.89	0.31	0.24
MEF2A	-0.14	0.59	0.23	0.23	-0.19	0.70	0.20	0.42
MTOR	-0.09	0.70	0.43	0.02	-0.04	0.89	0.51	0.05
MYF5	-0.23	0.39	0.32	0.09	-0.27	0.66	0.50	0.04
MYH2	-0.39	0.11	0.54	<0.01	-0.02	0.89	0.09	0.77
MYH7	-0.18	0.50	-0.45	0.02	-0.24	0.66	-0.62	<0.01
MYL3	-0.52	0.04	-0.51	0.01	-0.05	0.89	-0.83	<0.01
MYOD1	0.12	0.62	0.33	0.08	0.66	<0.01	0.001	0.99
MYOG	0.01	0.98	0.42	0.02	0.10	0.84	0.002	0.99
PPARGC1A	-0.43	0.11	0.64	<0.01	0.10	0.84	0.24	0.33
SMAD3	-0.37	0.11	0.45	0.02	-0.14	0.84	0.34	0.20

Supplementary Table 4: Primer Sequences

Amplicon Name	Forward Primer	Reverse Primer
Total PGC-1 α	GTGGTGCAGTGACCAATGAG	CTGCTAGCAAGTTTGCCTCA
PGC-1 α -ex1a	TGTATGGAGTGACATCGAGTGT	GCTGGTCTTCACCAACCAGA
PGC-1 α -ex1b	GACACACATGTTGGGGTTATCA	ACCAACCAGAGCAGCACATTT
B2M	AAGGACTGGTCTTTCTATCTC	GATCCCACTTAACTATCTTGG
TBP	TGTGCTCACCCACCAACAAT	TCTGCTCTGACTTTAGCACCTG
PPIA	ATGGTTCCCAGTTTTTCATC	CTCCACAATATTCATGCCTTC