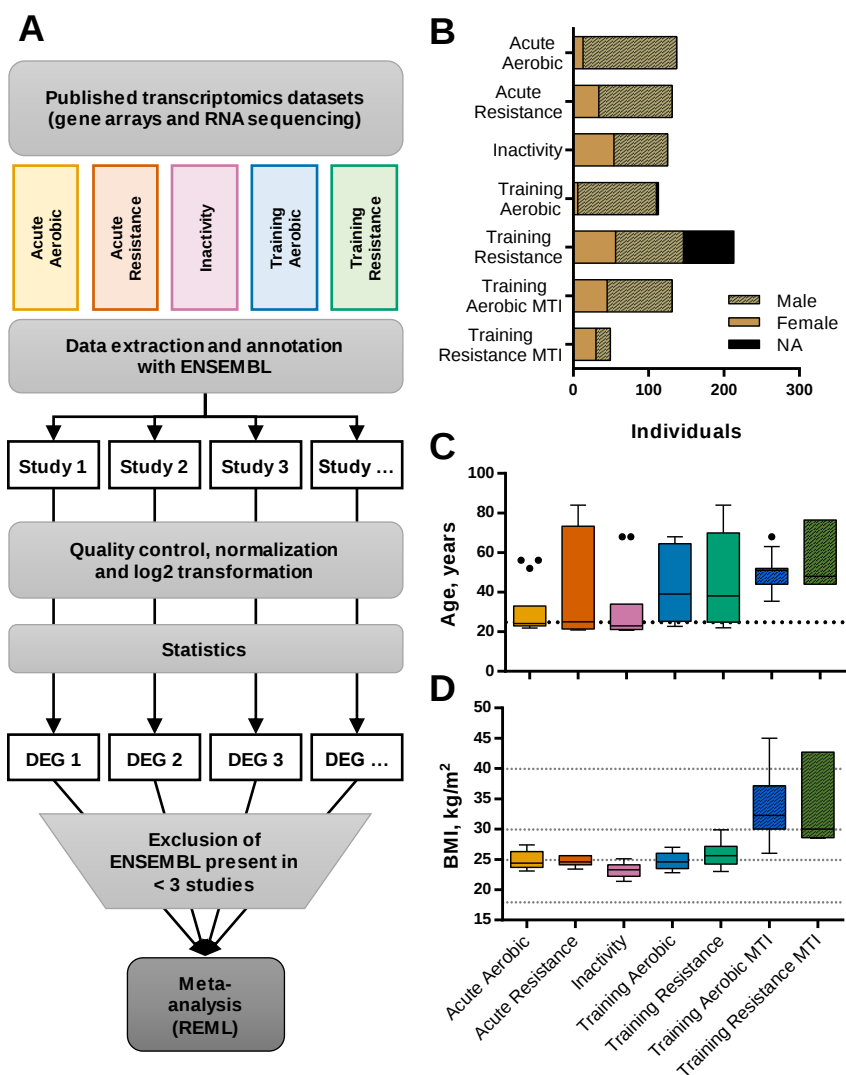


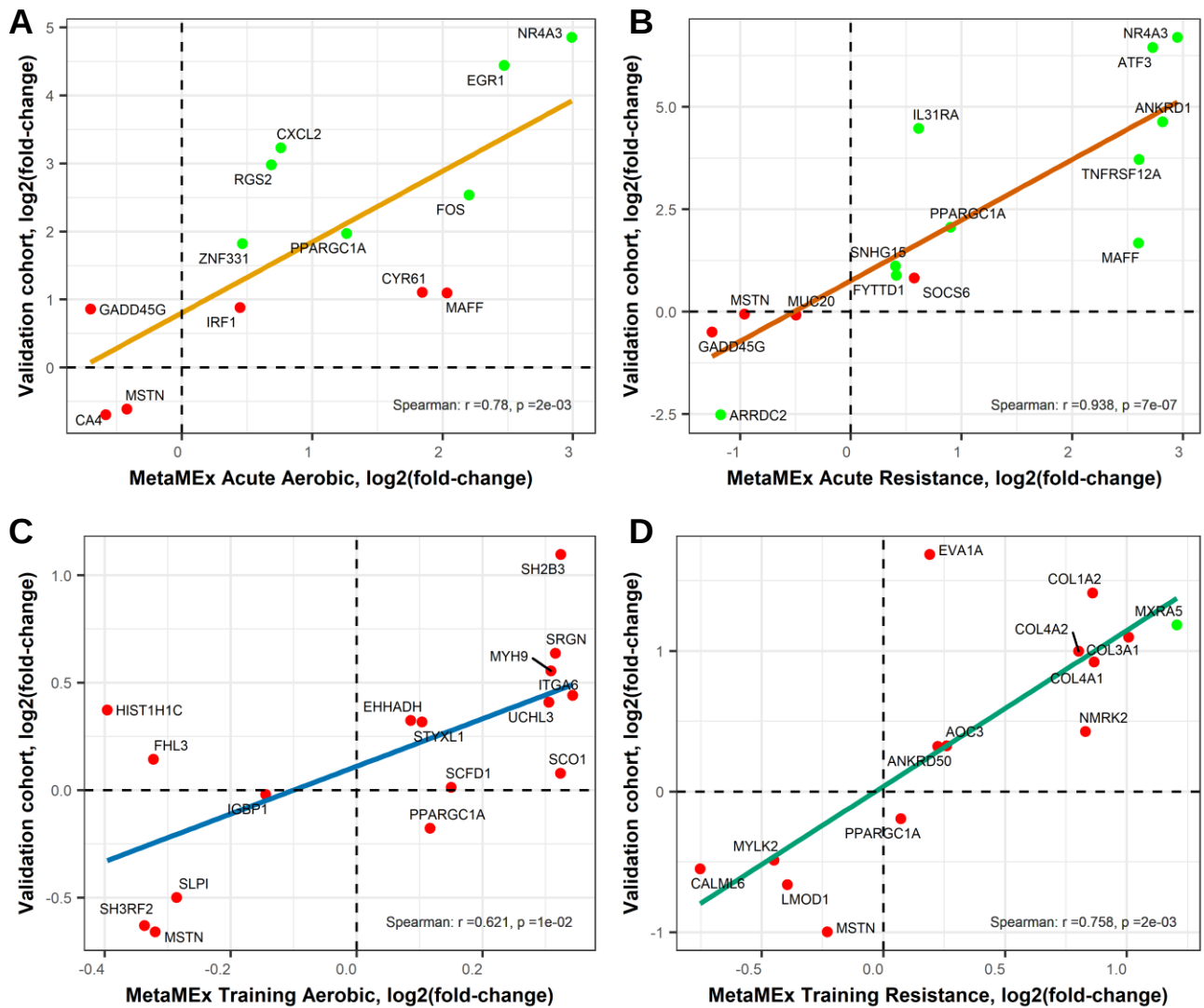
Transcriptomic Profiling of Skeletal Muscle Adaptations to Exercise and Inactivity

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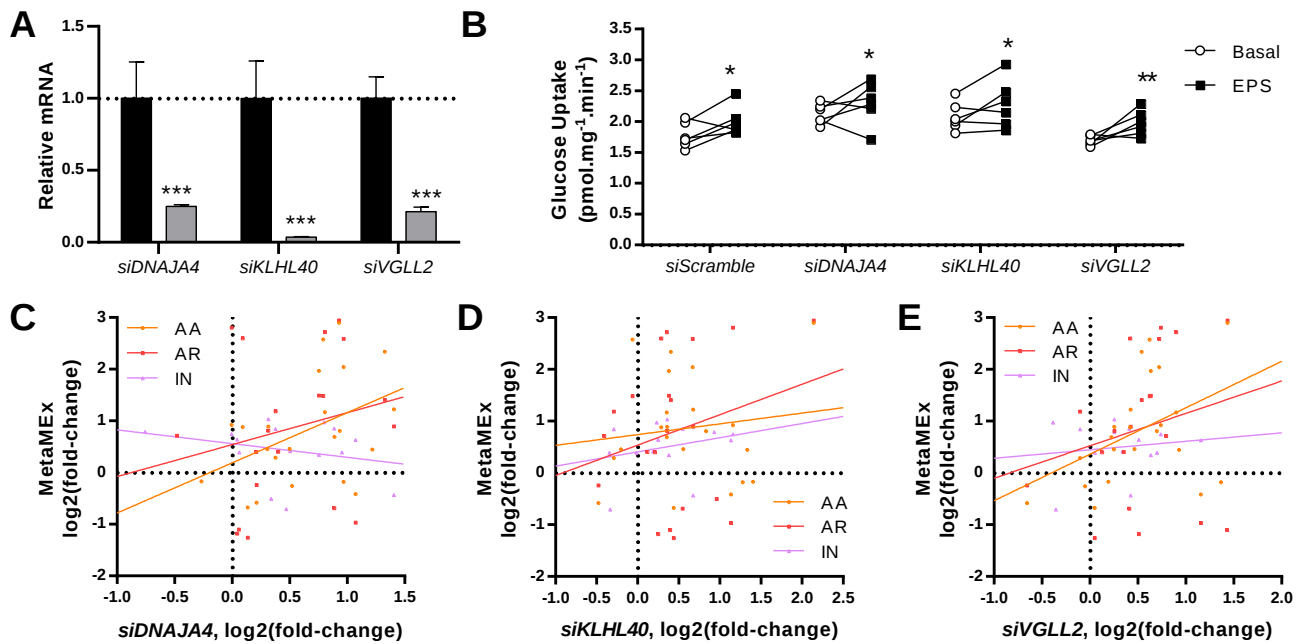
Supplementary information



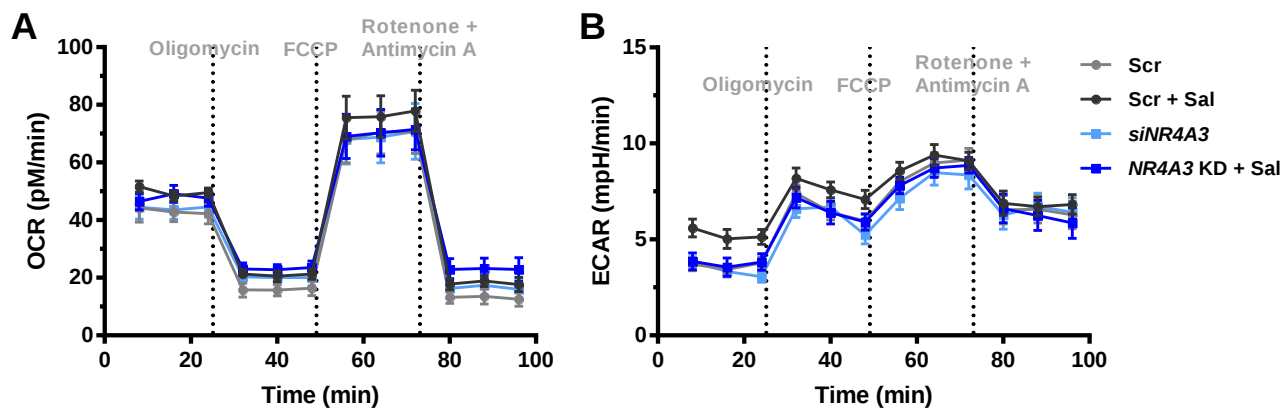
Supplementary Figure 1. Workflow and clinical characteristics. The study design is presented for all 5 categories of acute, training and inactivity studies (A). The same methodology was applied to all studies: collection of raw data when available, quality control, annotation, normalization and calculation of statistics (fold-change, FDR). The meta-analysis was then calculated using the restricted maximum-likelihood method taking into account the average, standard deviation and sample size for each study. Studies had a minority of female participants (B) and various age (C). Body mass index (D) was similar for studies of healthy individuals, but significantly higher in studies that included metabolically impaired (MTI) individuals. Tukey box and whiskers plots. DEG: Differentially Expressed Genes.



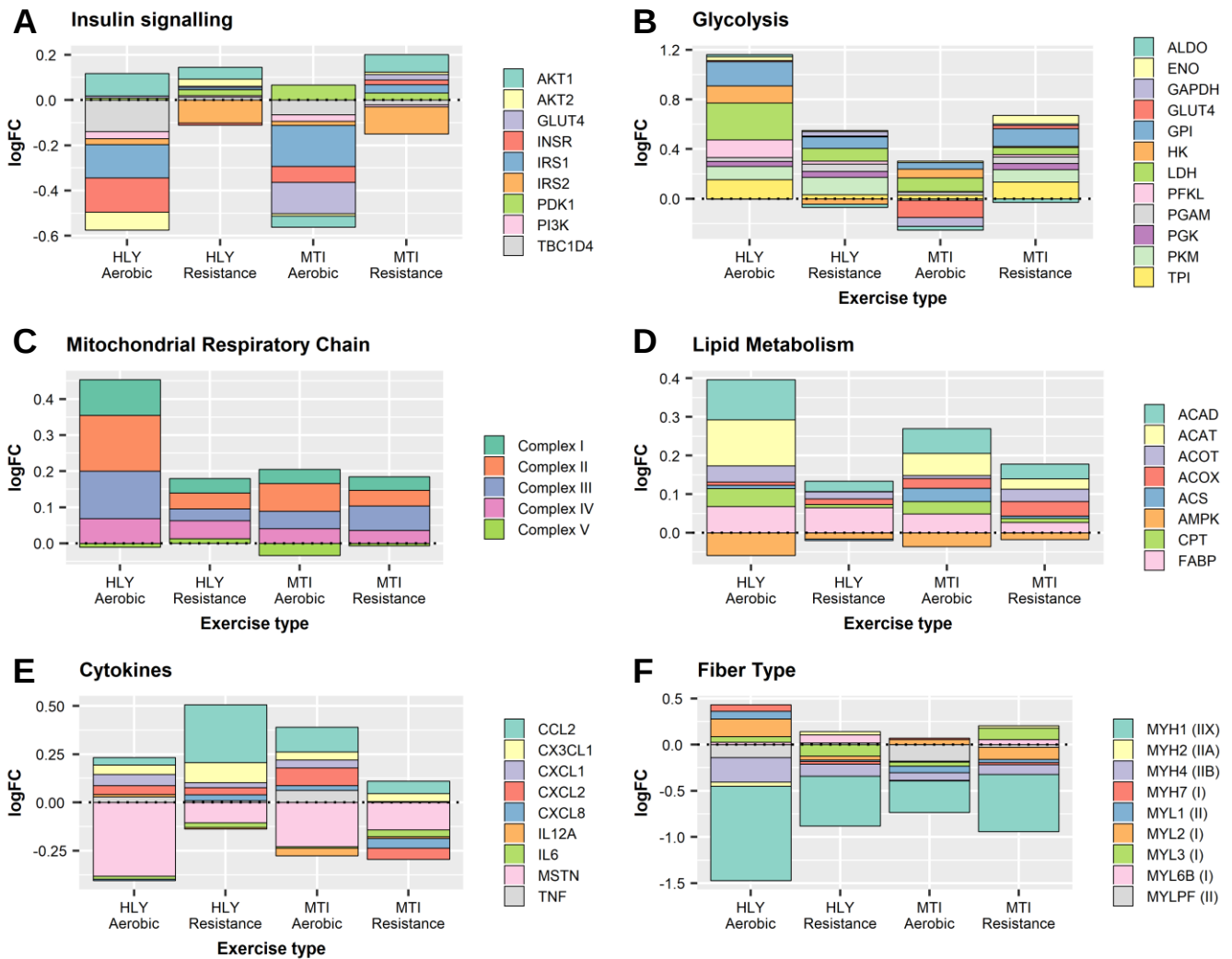
Supplementary Figure 2. Validation of the meta-analysis using independent exercise cohorts. Correlation of the top genes found significantly changed in exercise in MetaMEx with mRNA expression, as assessed by qPCR, in biopsy samples obtained from independent cohorts of acute aerobic (A), acute resistance (B), aerobic training (C) and resistance training (D). Red dots represent genes that do not reach significance in the validation cohorts ($n=8$, $p<0.05$).



Supplementary Figure 3. Selection pipeline of exercise and inactivity responsive genes. A) Silencing efficiency using siRNA against *DNAJA4*, *KLHL40* and *VGLL2*. Data are mean $\pm$ SEM, individual paired t-test vs scramble, ***p < 0.001 B) Electrical pulse stimulation-induced glucose uptake after silencing of *DNAJA4*, *KLHL40* and *VGLL2*. 2-way ANOVA (siRNA, EPS), $n=6$, *p < 0.05, **p < 0.01. C-E) Exercise and inactivity responsive genes selected in MetaMEx were correlated with their expression level in primary human muscle cells after silencing of *DNAJA4*, *KLHL40* or *VGLL2*.



Supplementary Figure 4. Seahorse XF analysis of primary skeletal muscle cells exposed to the beta-adrenergic stimulator salbutamol and *NR4A3* silencing. *NR4A3* was silenced using siRNA. Cells were exposed to 20 μ M of salbutamol for 3h before analyzing oxygen consumption and extracellular acidification rate using the seahorse technology.



Supplementary Figure 5. Pathways differentially regulated by exercise in metabolically impaired individuals. Genes corresponding to the proteins of interest were collected from the KEGG database and fold-changes were added to present the overall modification of enzymes involved in pathways. The behavior of insulin signaling (A), glycolysis (B), mitochondrial respiration (C), lipid metabolism signaling (D), inflammation (E) and muscle fiber composition (F) are presented.

Supplementary Table 1. TaqMan primers.

Gene Symbol(s)	Assay ID	Gene Name(s)	Gene Alias(es)
18S	Hs99999901_s1	Eukaryotic 18S rRNA	-
ADAM12	Hs01106101_m1	ADAM metallopeptidase domain 12	ADAM12-OT1;CAR10;MCMP;MCMPMltna;MLTN;MLTNA
ADH1C	Hs02383872_s1	alcohol dehydrogenase 1C (class I), gamma polypeptide	ADH3
AMOTL2	Hs01048101_m1	angiomotin like 2	LCCP
ANKRD1	Hs00173317_m1	ankyrin repeat domain 1	ALRP;C-193;CARP;CVARP;MCARP;bA320F15.2
ANKRD50	Hs00379454_m1	ankyrin repeat domain 50	-
AOC3	Hs02560271_s1	amine oxidase, copper containing 3	HPAO;SSAO;VAP-1;VAP1
ARRDC2	Hs00367526_g1	arrestin domain containing 2	CLONE24945;PP2703
ATF3	Hs00231069_m1	activating transcription factor 3	-
AVIL	Hs00198114_m1	advillin	ADVIL;DOC6;p92
B2M	Hs00187842_m1	beta-2-microglobulin	IMD43
BGN	Hs00959143_m1	biglycan	DSPG1;PG-S1;PGI;SLRR1A
BRSK2	Hs00908871_m1	BR serine/threonine kinase 2	C11orf7;PEN11B;SAD1;SADA;STK29
C2	Hs00918862_m1	complement component 2	ARMD14;CO2
CA14	Hs01077605_g1	carbonic anhydrase 14	CAXiV
CA4	Hs00426343_m1	carbonic anhydrase 4	CAiV;Car4;RP17
CALML6	Hs00758338_g1	calmodulin like 6	CAGLP
CAPN6	Hs00560073_m1	calpain 6	CANPX;CAPNX;CalpM;DJ914P14.1
CARD10	Hs00367225_m1	caspase recruitment domain family member 10	BIMP1;CARMA3
CDC25B	Hs01582335_m1	cell division cycle 25B	-
CDK2	Hs01548894_m1	cyclin dependent kinase 2	CDKN2;p33(CDK2)
CHAF1B	Hs01123302_m1	chromatin assembly factor 1 subunit B	CAF-1;CAF-IP60;CAF1;CAF1A;CAF1P60;MPHOSPH7;MPP7
CHRD	Hs01060234_m1	chordin like 2	BNF1;CHL2
CHRNA1	Hs00909664_m1	cholinergic receptor nicotinic alpha 1 subunit	ACHRA;ACHRD;CHRNA;CMS1A;CMS1B;CMS2A;FCCMS;SCCMS
CHRNA4	Hs00897937_m1	cholinergic receptor nicotinic delta subunit	ACHRD;CMS2A;CMS3A;CMS3B;CMS3C;FCCMS;SCCMS
CIART	Hs00328968_m1	circadian associated repressor of transcription	C1orf51;CHRONO;GM129
COL1A2	Hs01028956_m1	collagen type I alpha 2 chain	OI4
COL25A1	Hs00930851_m1	collagen type XXV alpha 1	AMY;CFEOM5;CLAC;CLAC-P;CLACP
COL3A1	Hs00943809_m1	collagen type III alpha 1 chain	EDS4A
COL4A1	Hs00266237_m1	collagen type IV alpha 1 chain	BSVD;RATOR
COL4A2	Hs05006309_m1	collagen type IV alpha 2	ICH;POREN2
COL6A3	Hs00915125_m1	collagen type VI alpha 3 chain	BTHLM1;DYT27;UCMD1
CXCL2	Hs00601975_m1	C-X-C motif chemokine ligand 2	CINC-2a;GRO2;GROb;MGSA-b;MIP-2a;MIP2;MIP2A;SCYB2
CYP1B1	Hs00164383_m1	cytochrome P450 family 1 subfamily B member 1	CP1B;CYP1B1;GLC3A;P4501B1
CYP4B1	Hs01086311_m1	cytochrome P450 family 4 subfamily B member 1	CYP1VB1;P-450HP
CYR61	Hs00155479_m1	cysteine rich angiogenic inducer 61	CCN1;GIG1;IGFBP10
DDIT4	Hs01111686_g1	DNA damage inducible transcript 4	Dig2;REDD-1;REDD1
DNAJA4	Hs00388055_m1	DnaJ heat shock protein family (Hsp40) member A4	MST104;MSTP104;PRO1472
DTL	Hs00978565_m1	denticless E3 ubiquitin protein ligase homolog	CDT2;DCAF2;L2DTL;RAMP
EGR1	Hs00152928_m1	early growth response 1	AT225;GOS30;KROX-24;NGFI-A;TIS8;ZIF-268;ZNF225
EHHADH	Hs00157347_m1	enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase	ECHD;FRTS3;L-PBE;LBFP;LBP;PBFE
EMCN	Hs01038204_m1	endomucin	EMCN2;MUC14
EVA1A	Hs00259924_m1	eva-1 homolog A, regulator of programmed cell death	FAM176A;TMEM166
EXTL1	Hs00184929_m1	exostosin like glycosyltransferase 1	EXTL
FABP4	Hs01086177_m1	fatty acid binding protein 4	A-FABP;AFABP;ALBP;HEL-S-104;aP2
FHL3	Hs00916408_g1	four and a half LIM domains 3	SLIM2
FLRT3	Hs01922255_s1	fibronectin leucine rich transmembrane protein 3	HH21
FMO2	Hs01025544_m1	flavin containing monooxygenase 2	FMO1B1
FOS	Hs04194186_s1	Fos proto-oncogene, AP-1 transcription factor subunit	AP-1;C-FOS;p55
FSIP1	Hs00401705_m1	fibrous sheath interacting protein 1	HSD10
FYTD1	Hs00260265_m1	forty-two-three domain containing 1	UIF
GADD45A	Hs00169255_m1	growth arrest and DNA damage inducible alpha	DDIT1;GADD45
GADD45G	Hs02566147_s1	growth arrest and DNA damage inducible gamma	CR6;DDIT2;GADD45gamma;GRP17
GAPDH	Hs99999905_m1	glyceraldehyde-3-phosphate dehydrogenase	G3PD;GAPD;HEL-S-162eP
GLDC	Hs01580591_m1	glycine decarboxylase	GCE;GCSP;HYGN1
GNRHR2	Hs00977373_g1	gonadotropin releasing hormone receptor 2 (pseudogene)	GnRH-II-R
HIST1H1C	Hs00271185_s1	histone cluster 1, H1c	H1.2;H1C;H1F2;H1s-1
HPRT1	Hs02800695_m1	hypoxanthine phosphoribosyltransferase 1	HGPRT;HPRT
IGBP1	Hs00426831_mH	immunoglobulin (CD79A) binding protein 1	ALPHA-4;IBP1
IL31RA	Hs00371172_m1	interleukin 31 receptor A	CRL;CRL3;GLM-R;GLMR;GPL;IL-31RA;PLCA2;PRO21384;hGLM-R
IRF1	Hs00971965_m1	interferon regulatory factor 1	IRF-1;MAR
ITGA6	Hs01041011_m1	integrin subunit alpha 6	CD49f;ITGA6B;VLA-6
KCNV2	Hs00377936_m1	potassium voltage-gated channel modifier subfamily V member 2	KV11.1;Kv8.2;RCD3B
KDR	Hs00911700_m1	kinase insert domain receptor	CD309;FLK1;VEGFR;VEGFR2
KLHL40	Hs00328078_m1	kelch like family member 40	KBTBD5;NEM8;SRYP;SYRP
LAMB1	Hs01055960_m1	laminin subunit beta 1	CLM;LIS5
LMOD1	Hs00201704_m1	leiomodlin 1	1D;64kD;D1;SM-LMOD;SMLMOD
LRRC66	Hs02386735_m1	leucine rich repeat containing 66	-
LYG2	Hs00545618_m1	lysozyme g2	LYGH;LYSG2
MAFF	Hs05026540_g1	MAF bZIP transcription factor F	U-MAF;hMafF
METTL7B	Hs00378551_m1	methyltransferase like 7B	ALDI
MSTN	Hs00976237_m1	myostatin	GDF8;MSLHP
MTFP1	Hs01062596_m1	mitochondrial fission process 1	HSPC242;MTP18
MUC20	Hs00416321_m1	mucin 20, cell surface associated	MUC-20
MXRA5	Hs01019147_m1	matrix remodeling associated 5	-
MYH8	Hs00267293_m1	myosin heavy chain 8	DA7;MyHC-peri;MyHC-pn;gtMHC-F
MYH9	Hs00159522_m1	myosin, heavy chain 9, non-muscle	BDPLT6;DFNA17;EPSTS;FTNS;MHA;

			NMHC-II-A;NMMHC-IIA;NMMHCA
MYLK2	Hs00263888_m1	myosin light chain kinase 2	KMLC;MLCK;MLCK2;skMLCK
NMRK2	Hs01043681_m1	nicotinamide riboside kinase 2	ITGB1BP3;MIBP;NRK2
NR4A3	Hs00545009_g1	nuclear receptor subfamily 4 group A member 3	CHN;CSMF;MINOR;NOR1;TEC
NRAP	Hs00328987_m1	nebulin related anchoring protein	N-RAP
PAIP2B	Hs04965774_m1	poly(A) binding protein interacting protein 2B	-
PER1	Hs00242988_m1	period circadian clock 1	PER;RIGUI;hPER
PFKFB3	Hs00998698_m1	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	IPFK2;PFK2;iPFK-2
PPARGC1A	Hs00173304_m1	PPARG coactivator 1 alpha	LEM6;PGC-1(alpha);PGC-1alpha;PGC-1v;PGC1;PGC1A;PPARGC1
PPP6C	Hs00254827_m1	protein phosphatase 6 catalytic subunit	PP6;PP6C
PRSS50	Hs00203179_m1	protease, serine 50	CT20;TSP50
RASA4	Hs04992021_m1	RAS p21 protein activator 4	CAPRI;GAPL
RGS2	Hs01009070_g1	regulator of G-protein signaling 2	G0S8
RORA	Hs00536545_m1	RAR related orphan receptor A	NR1F1;ROR1;ROR2;ROR3;RZR-ALPHA;RZRA
RYR3	Hs00168821_m1	ryanodine receptor 3	RYR-3
SCFD1	Hs00910148_m1	sec1 family domain containing 1	C14orf163;RA410;SLY1;SLY1P;STXBP1L2
SCN1B	Hs00962350_m1	sodium voltage-gated channel beta subunit 1	ATFB13;BRGDA5;GEFSP1
SCO1	Hs01552201_m1	SCO1 cytochrome c oxidase assembly protein	SCOD1
SH2B3	Hs01081959_g1	SH2B adaptor protein 3	IDDM20;LNK
SH3RF2	Hs00400148_m1	SH3 domain containing ring finger 2	HEPP1;POSHER;PPP1R39;RNF158
SLC16A3	Hs00358829_m1	solute carrier family 16 member 3	MCT 3;MCT 4;MCT-3;MCT-4;MCT3;MCT4
SLC38A4	Hs00394339_m1	solute carrier family 38 member 4	ATA3;NAT3;PAAT;SNAT4
SLC5A1	Hs01573793_m1	solute carrier family 5 member 1	D22S675;NAGT;SGLT1
SLPI	Hs00268204_m1	secretory leukocyte peptidase inhibitor	ALK1;ALP;BLPI;HUSI;HUSI-I;MPI;WAP4;WFDC4
SMCO1	Hs03004796_m1	single-pass membrane protein with coiled-coil domains 1	C3orf43
SMTNL1	Hs00418171_m1	smoothelin like 1	CHASM
SNHG15	Hs05031784_s1	small nucleolar RNA host gene 15	C7orf40;Linc-Myo1g;MYO1GUT
SOCS6	Hs04986635_s1	suppressor of cytokine signaling 6	CIS-4;CIS4;HSPC060;SOCS-4;SOCS-6;SOCS4;SSI4;STAI4;STATI4
SRGN	Hs01004159_m1	serglycin	PPG;PRG;PRG1
ST7-OT4	Hs04989394_g1	ST7 overlapping transcript 4	NCRNA00042;ST7OT4
STYXL1	Hs01553273_m1	serine/threonine/tyrosine interacting-like 1	DUSP24;MK-STYX;MKSTYX
TBP	Hs00427620_m1	TATA-box binding protein	GTF2D;GTF2D1;HDL4;SCA17;TFIID
THAP12	Hs01566400_g1	THAP domain containing 12	DAP4;P52rPK;PRKRIR;THAP0
THBS4	Hs00170261_m1	thrombospondin 4	TSP-4;TSP4
TMEM120A	Hs00230518_m1	transmembrane protein 120A	NET29;TMPIT
TMEM253	Hs04188762_g1	transmembrane protein 253	C14orf176;C14orf95;NCRNA00220
TNFRSF12A	Hs00171993_m1	TNF receptor superfamily member 12A	CD266;FN14;TWEAKR
TPRG1	Hs00415626_m1	tumor protein p63 regulated 1	FAM79B
UCHL3	Hs04334565_m1	ubiquitin C-terminal hydrolase L3	UCH-L3
UCK2	Hs00989900_m1	uridine-cytidine kinase 2	TSA903;UK;UMPK
VAMP5	Hs05042428_s1	vesicle associated membrane protein 5	-
VGLL2	Hs00403461_m1	vestigial like family member 2	VGL2;VITO1
ZNF331	Hs00367929_m1	zinc finger protein 331	RITA;ZNF361;ZNF463
ZNF784	Hs01385515_mH	zinc finger protein 784	-

Supplementary Table 2. Description of the studies included in the analysis of healthy (HLY) and metabolically impaired (MTI) individuals.

	Training Aerobic HLY	Training Resistance HLY	Training Aerobic MTI	Training Resistance MTI
Studies	6	8	6	3
Total females	6	30	15	10
Total males	49	64	63	19
Total undefined	0	67	0	0
%females	10.9	31.9	19.2	34.5
Age, mean±Sd	50.7 ± 19.3	54.5 ± 23.2	48 ± 5.9	52.1 ± 13.8
BMI, mean±Sd	24.6 ± 1.7	25.7 ± 1.7	35.5 ± 6	34.8 ± 7.2
GEOs	GSE1786, GSE20319, GSE24215, GSE27543, GSE43760, GSE9103	EMEXP740, GSE106865, GSE16907, GSE28422, GSE47881, GSE8479, GSE97084, GSE117525	GSE1295, GSE40551, GSE43760, GSE48278, GSE58249, GSE72462	GSE48278, GSE58249, GSE117525