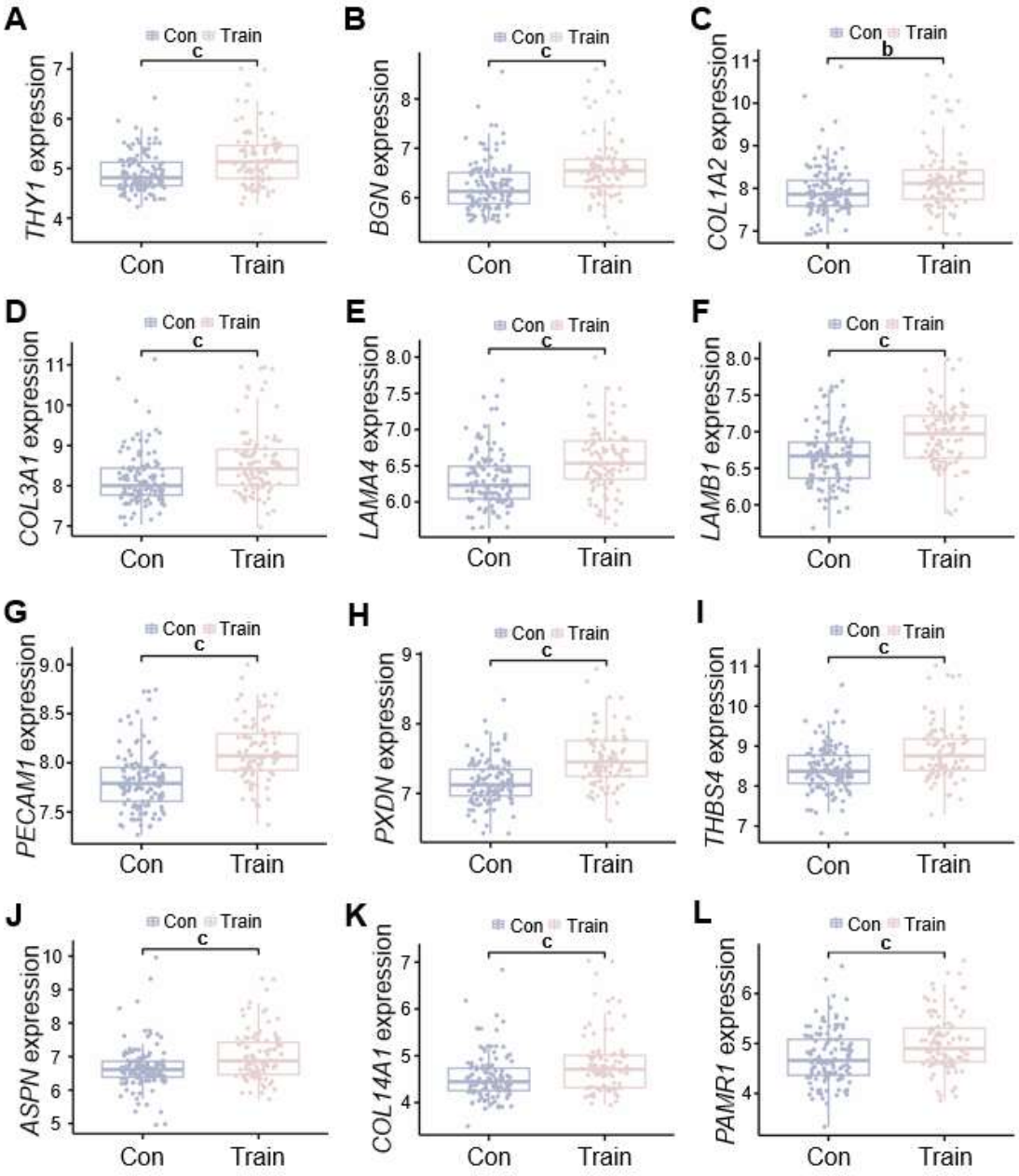
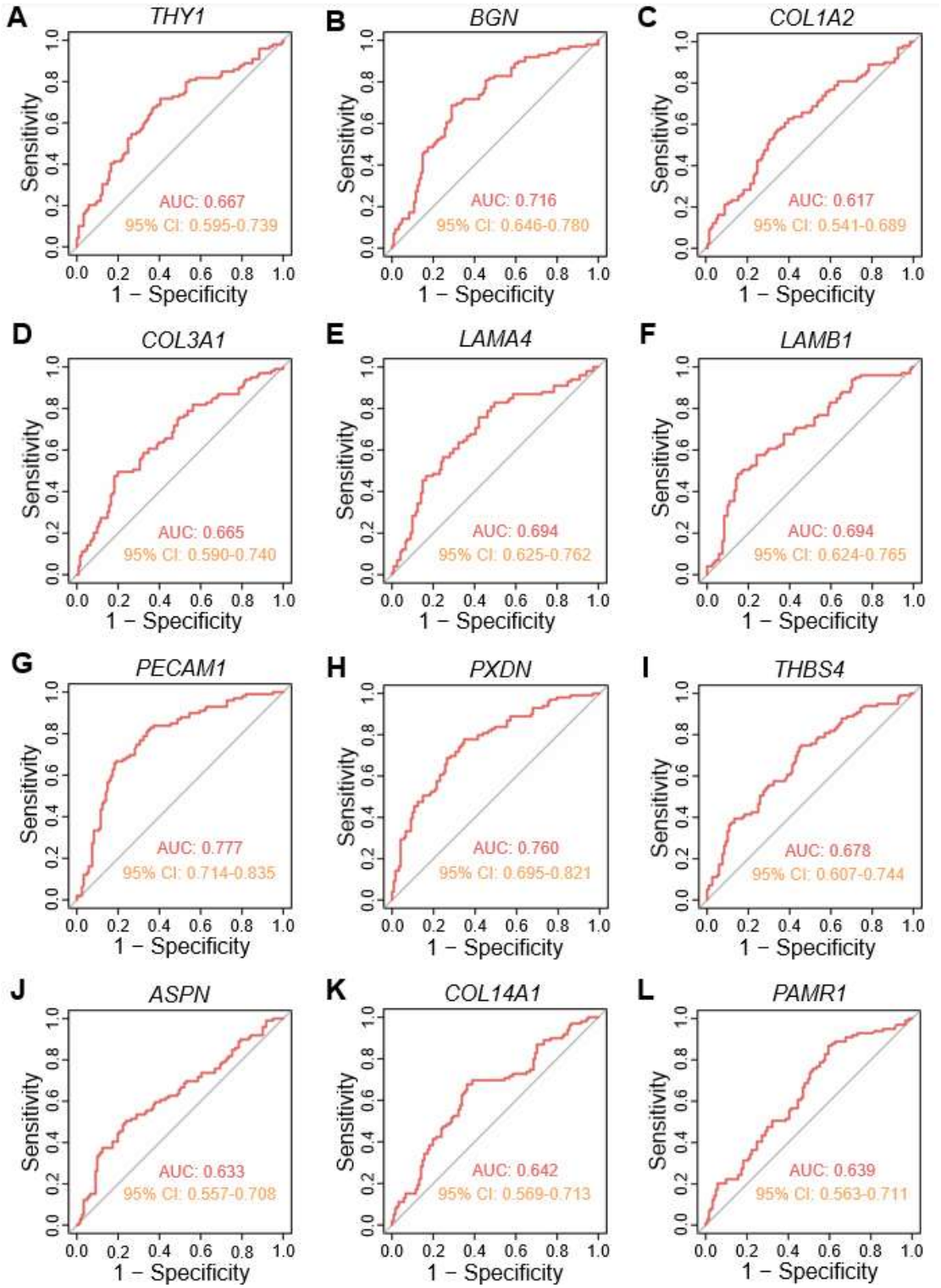


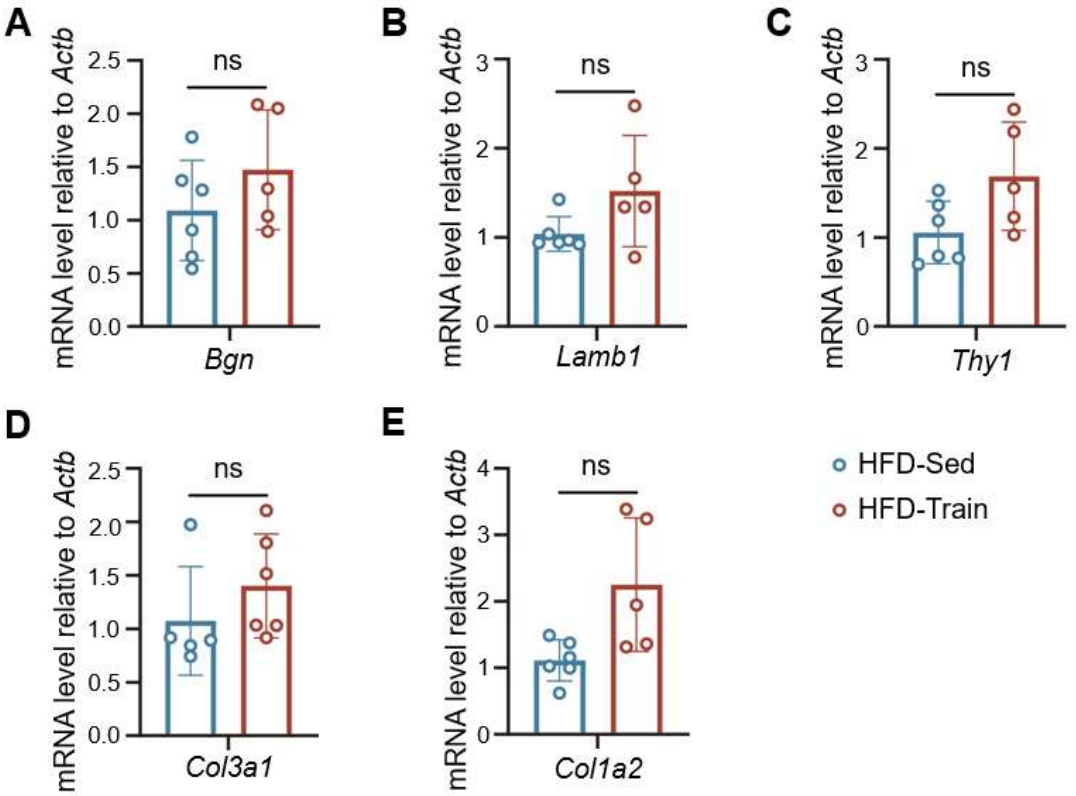
Supplementary Figure 1 Expression of key hub genes and in the discovery groups. A-L: Box plots depicting the expression levels of genetic biomarkers in the discovery cohorts (GSE161749, GSE48278, GSE156247, and GSE53598). $^{b}P < 0.01$; $^{c}P < 0.001$. "Con" means pre-exercise, "Train" means post-exercise. *THY1*: Thy-1 cell surface antigen; *BGN*: Biglycan; *COL1A2*: Collagen α 2 (I) chain; *COL3A1*: Collagen α 1 (III) chain; *LAMA4*: Laminin subunit α 4; *LAMB1*: Laminin subunit β 1; *PECAM1*: Platelet endothelial cell adhesion molecule 1; *PXDN*: Peroxidasin; *THBS4*: Thrombospondin 4; *ASPN*: Asporin; *COL14A1*:

Collagen α 1 (XIV) chain; *PAMR1*: Peptidase domain containing associated with muscle regeneration 1.



Supplementary Figure 2 Diagnostic prediction efficacy analysis of key hub genes in the discovery groups. A-L: ROC curve analysis for the discovery

cohorts (GSE161749, GSE48278, GSE156247, and GSE53598). AUC: Area under the curve; CI: Confidence interval; *THY1*: Thy-1 cell surface antigen; *BGN*: Biglycan; *COL1A2*: Collagen α 2 (I) chain; *COL3A1*: Collagen α 1 (III) chain; *LAMA4*: Laminin subunit α 4; *LAMB1*: Laminin subunit β 1; *PECAM1*: Platelet endothelial cell adhesion molecule 1; *PXDN*: Peroxidasin; *THBS4*: Thrombospondin 4; *ASPN*: Asporin; *COL14A1*: Collagen α 1 (XIV) chain; *PAMR1*: Peptidase domain containing associated with muscle regeneration 1.



Supplementary Figure 3 Expression of key hub genes in high-fat diet-induced metabolic dysfunction-associated steatotic liver disease combined with endurance exercise. A-E: The mRNA levels of biglycan (*Bgn*) (A), laminin subunit β 1 (*Lamb1*) (B), thy-1 cell surface antigen (*Thy1*) (C), collagen α 1 (III) chain (*Col3a1*) (D) and collagen α 2 (I) chain *(Col1a2)* (E) in gastrocnemius muscle of HFD-Sed and HFD-Train mice were measured by quantitative polymerase chain reaction (qPCR), *Actb* was used as an internal control, $n \geq 5$. ns, not significant. HFD: High-fat diet; HFD-Sed: High-fat diet, sedentary;

HFD-Train: High-fat diet, training; *Actb*: β-actin; *Bgn*: Biglycan; *Lamb1*: Laminin subunit β 1; *Thy1*: Thy-1 cell surface antigen; *Col3a1*: Collagen α 1 (III) chain; *Col1a2*: Collagen α 2 (I) chain.

Supplementary Table 1 Basic characteristics of the induced datasets

Datasets	GSE161749	GSE48278	GSE156247	GSE53598	GSE58249
Age, years	29.8 ± 8.4	51.8 ± 11	59 ± 4	59.4 ± 1.1	49 ± 5
Gender, female/male	16/9	23/24	0/18	0/18	13/5
BMI, kg/m^2	31.5 ± 4.3	30.3 ± 3.1	29.7 ± 3.6	30.0 ± 0.8	43.8 ± 9.5
Metabolic status	T2DM, Overweight, Obesity	Overweight, Obesity	Overweight	T2DM	Obesity with T2DM
Sample source	Skeletal muscle	Skeletal muscle	Skeletal muscle	Vastus lateralis	Skeletal muscle
No. of pre-exercise	25	47	18	18	18
No. of post-exercise	24	47	18	18	18
Exercise modality	Endurance training	Aerobic exercise	Combined exercise	Combined exercise	Combined exercise
Exercise frequency	3 sessions/week	3 sessions/week	3 sessions/week	3 sessions/week	3 sessions/week
Exercise duration	8 weeks	24 weeks	12 weeks	12 weeks	16 weeks

BMI: Body mass index; T2DM: Type 2 diabetes mellitus.

Supplementary Table 2 Primer sequences for qPCR

Gene	Sequences (5′–3′)
Mouse *Actb*	F: GTGACGTTGACATCCGTAAAGA
	R: GCCGGACTCATCGTACTCC

Mouse *Lamb1*	F: GAAAGGAAGACCCGAAGAAAAGA
	R: CCATAGGGCTAGGACACCAAA
Mouse *Lama4*	F: ATGAGCTGCAAGGAAAACTATCC
	R: CTGTTTCGTTGGCTTCACTGA
Mouse *Cola1*	F: CTGTAACATGGAAACTGGGGAAA
	R: CCATAGCTGAACTGAAAACCACC
Mouse *Col1a2*	F: GGTGAATCTGGACGTGAGGG
	R: AAGGTCATAACCGCCACTGGG
Mouse *Thy1*	F: TGCTCTCAGTCTTGCAGGTG
	R: TGGATGGAGTTATCCTTGGTGTT
Mouse *Thbs4*	F: GCTTGTGGTCCTCTCAGCTT
	R: CATGGGTTCTGCTCTGGGTT
Mouse *Bgn*	F: TGCCATGTGTCCTTTCGGTT
	R: CAGGTCTAGCAGTGTGGTGTC
Mouse *Pxdn*	ATTGACAGGCAAGCATTTAAGGG
	CAGGGTCCAGCGTTTCTATCT
Mouse *Pecam1*	F: CTGCCAGTCCGAAAATGGAAC
	R: CTTCATCCACCGGGGCTATC

qPCR: Quantitative polymerase chain reaction; *Actb*: β-actin; *Lamb1*: Laminin subunit β 1; *Lama4*: Laminin subunit α 4; *Col3a1*: Collagen α 1 (III) chain; *Col1a2*: Collagen α 1 (II) chain; *Thy1*: Thy-1 cell surface antigen; *Thbs4*: Thrombospondin 4; *Bgn*: Biglycan; *Pxdn*: Peroxidasin; *Pecam1*: Platelet endothelial cell adhesion molecular 1; F: Forward; R: Reverse.

Supplementary Table 3 Differentially expressed genes identified by limma analysis

Gene ID	log2FC	AveExpr	t	*P*.Value	adj.*P*.Val	B
MYBPH	0.59487	4.72069	2.61274	0.0096	0.0929	-2.9881
MXRA5	0.5091	6.68364	4.61961	6.5E-06	0.00068	3.5957
COL4A1	0.45053	7.87417	7.88024	1.5E-13	1.2E-09	20.0963
IGFN1	0.43286	6.31441	2.01361	0.04526	0.22833	-4.2947
COL3A1	0.4171	8.3577	4.14164	4.9E-05	0.00276	1.7390
THBS4	0.40596	8.60904	4.76072	3.5E-06	0.00042	4.1756
BGN	0.37916	6.40371	5.05939	8.8E-07	0.00016	5.4491
COL4A2	0.36893	7.13742	7.62605	7.0E-13	3.6E-09	18.6125
COL1A1	0.36866	7.05119	3.59353	0.0004	0.01193	-0.1755
SLC26A9	0.36446	4.2389	4.07002	6.5E-05	0.00337	1.4756
ACTC1	0.34834	9.35738	2.6615	0.00835	0.08417	-2.8677
PXDN	0.3377	7.30863	7.16089	1.2E-11	2.7E-08	15.9699
ASPN	0.33733	6.82771	3.55969	0.00045	0.01293	-0.2859
DLL4	0.33318	5.23091	2.67138	0.00811	0.08263	-2.8431

HECW2	0.32984	5.46272	7.0883	1.8E-11	3.6E-08	15.5665
ELMO1	0.32596	4.79815	4.20063	3.9E-05	0.00235	1.9590
SLC38A1	0.32404	6.60993	3.03914	0.00266	0.04092	-1.8654
KDR	0.32188	6.10134	7.58922	8.8E-13	3.6E-09	18.3997
EDNRB	0.31952	5.71198	5.97973	8.9E-09	5.9E-06	9.7418
KIT	0.31766	5.50306	5.32912	2.4E-07	6.7E-05	6.6511
NID2	0.30238	6.54408	6.07951	5.2E-09	4.4E-06	10.2385
SIPA1 L2	0.30085	6.31175	5.81824	2.1E-08	1.2E-05	8.9504
PECAM1	0.29701	7.95479	7.2183	8.3E-12	2.2E-08	16.2907
OLIG1	0.29509	4.97567	3.20399	0.00156	0.02919	-1.3896
HLA-DPA1	0.29271	7.99002	2.52243	0.01235	0.10856	-3.2056
LOC284379	0.29021	4.03728	3.17883	0.00169	0.03093	-1.4637
MIA2	0.28903	3.33117	2.26172	0.02468	0.16218	-3.7927
THY1	0.28576	5.04043	4.47588	1.2E-05	0.00109	3.0196
A2M	0.28489	9.48629	8.06657	4.5E-14	7.26E-1	21.2007
NSAP11	0.28283	2.26849	2.88791	0.00426	0.05562	-2.2815
KCNB1	0.28083	5.63610	3.48016	0.0006	0.01553	-0.5417
TM4SF18	0.28032	6.40294	5.85811	1.6E-08	1.1E-05	9.1443
LAMB1	0.27965	6.7864	5.1273	6.4E-07	0.00013	5.7472
SH3KBP1	0.27728	8.58104	6.30507	1.5E-09	1.6E-06	11.3823

PAMR1	0.27658	4.864	3.70863	0.00026	0.00917	0.2069
COL1A2	0.27539	8.0686	3.04747	0.00259	0.04036	-1.8419
COL14A1	0.27158	4.67938	3.62079	0.00036	0.01129	-0.0859
LGSN	0.26984	2.96297	2.18645	0.02983	0.18098	-3.9509
LAMA4	0.26478	6.43942	4.80778	2.8E-06	0.00036	4.3721
CCDC102B	0.26332	2.60939	2.50812	0.01285	0.11088	-3.2394
TPRG1 L	-0.0235	8.76198	-0.97046	0.33288	0.64952	-5.7821
HIST1H2BO	-0.2647	2.939	-3.45627	0.00066	0.01658	-0.6175
RLN3	-0.2684	2.59813	-2.35259	0.01952	0.14159	-3.595
TAL2	-0.2688	5.50636	-5.21755	4.2E-07	9.4E-05	6.14807
GGT7	-0.271	6.29624	-3.00001	0.003	0.04441	-1.9749
C16orf89	-0.2744	2.93177	-2.56597	0.01095	0.10072	-3.1016
EYA2	-0.2745	4.00891	-2.32991	0.02071	0.14686	-3.645
LMNB2	-0.2759	5.70684	-3.65834	0.00032	0.01048	0.0385
TMEM159	-0.2789	8.2118	-4.17214	4.3E-05	0.00252	1.8524
PRKAG3	-0.2946	8.00384	-4.51537	1.0E-05	0.00096	3.17642
MLF1	-0.2976	8.84256	-4.20831	3.E-05	0.00231	1.98778
SH2D1B	-0.3003	5.80002	-2.39142	0.01762	0.1333	-3.5082
NPTX1	-0.301	4.05529	-2.50028	0.01313	0.1122	-3.2578
S100B	-0.3115	2.89424	-2.7721	0.00604	0.06881	-2.5869

TSPAN8	-0.3882	8.2631	-4.35566	2.0E-05	0.00151	2.54946
MYLK2	-0.3943	9.7312	-6.80289	9.4E-11	1.7E-07	14.0052
ADIPOQ	-0.408	6.36624	-2.16549	0.03142	0.18633	-3.994
MSTN	-0.4324	7.05135	-5.44079	1.4E-07	4.6E-05	7.16273
CALML6	-0.4387	5.92522	-3.79535	0.00019	0.0073	0.50196
LRRC3B	-0.4466	6.61625	-3.52156	0.00052	0.01411	-0.4092
C1orf158	-0.6727	3.62312	-5.18078	4.96E-07	0.00011	5.98405

Gene ID: Gene or transcript identifier; log2FC: Log2 fold change; AveExpr: Average expression across all samples; t: Moderated t-statistic; *P*. Value: Raw *P*-value; adj.*P*.Val: Adjusted *P*-value after multiple testing correction (false discovery rate, FDR); B: B-statistic (log-odds that the gene is differentially expressed).

Supplementary Table 4 A complete list of enriched gene ontology analysis of 61 differentially expressed genes

ONTOLOGY	**ID**	**Description**	**GeneRatio**	**FoldEnric-hment**	**p.adjust**	**qvalue**	**Gene ID**	**Count**
BP	GO:0071711	basement membrane organization	5/50	49.70526	7.57E-05	5.80E-05	COL4A1/PXDN/NID2/LAMB1/COL3A1	5
BP	GO:0030198	extracellular matrix organization	9/50	10.24048	7.65E-05	5.86E-05	COL4A1/COL4A2/PXDN/NID2/LAMB1/COL3A1/COL14A1/COL1A1/	9

							COL1A2	
BP	GO:0043062	extracellular structure organization	9/50	10.20973	7.65E-05	5.86E-05	COL4A1/COL4A2/PXDN/ NID2/LAMB1/COL3A1/ COL14A1/COL1A1/COL1A2	9
BP	GO:0045229	external encapsulating structure organization	9/50	10.17916	7.65E-05	5.86E-05	COL4A1/COL4A2/PXDN/ NID2/LAMB1/COL3A1/ COL14A1/COL1A1/COL1A2	9
BP	GO:0030199	collagen fibril organization	5/50	28.61818	0.000255	0.000195	PXDN/COL3A1/COL14A1/ COL1A1/COL1A2	5
BP	GO:0038063	collagen-activated tyrosine kinase receptor signaling pathway	3/50	113.328	0.000524	0.000402	COL4A1/COL4A2/COL1A1	3
CC	GO:0062023	collagen-containing extracellular matrix	16/56	13.28037	3.60E-12	2.83E-12	A2M/COL4A1/COL4A2/PXDN/ NID2/LAMB1/BGN/LAMA4/ THBS4/MXRA5/COL3A1/ COL14A1/COL1A1/ASPN/	16

							COL1A2/ADIPOQ	
CC	GO:0098644	complex of collagen trimers	5/56	84.58333	1.71E-07	1.34E-07	COL4A1/COL4A2/COL3A1/COL1A1/COL1A2	5
CC	GO:0005581	collagen trimer	7/56	28.9157	1.71E-07	1.34E-07	COL4A1/COL4A2/COL3A1/COL14A1/COL1A1/COL1A2/ADIPOQ	7
CC	GO:0005604	basement membrane	7/56	27.02989	2.06E-07	1.62E-07	COL4A1/COL4A2/PXDN/NID2/LAMB1/LAMA4/THBS4	7
CC	GO:0005583	fibrillar collagen trimer	3/56	88.8125	9.05E-05	7.13E-05	COL3A1/COL1A1/COL1A2	3
CC	GO:0098643	banded collagen fibril	3/56	88.8125	9.05E-05	7.13E-05	COL3A1/COL1A1/COL1A2	3
MF	GO:0005201	extracellular matrix structural constituent	14/55	28.40175	5.76E-15	4.99E-15	COL4A1/COL4A2/PXDN/NID2/LAMB1/BGN/LAMA4/MXRA5/COL3A1/COL14A1/COL1A1/	14

							ASPN/COL1A2/ADIPOQ	
MF	GO:0030020	extracellular matrix structural constituent conferring tensile strength	6/55	44.90182	2.83E-07	2.46E-07	COL4A1/COL4A2/COL3A1/COL14A1/COL1A1/COL1A2	6
MF	GO:0019838	growth factor binding	8/55	19.95636	2.89E-07	2.50E-07	A2M/COL4A1/KDR/PXDN/KIT/COL3A1/COL1A1/COL1A2	8
MF	GO:0048407	platelet-derived growth factor binding	4/55	122.4595	8.31E-07	7.20E-07	COL4A1/COL3A1/COL1A1/COL1A2	4
MF	GO:0002020	protease binding	5/55	12.02727	0.001734	0.00150 2	A2M/KIT/COL3A1/COL1A1/COL1A2	5
MF	GO:0005178	integrin binding	5/55	10.72496	0.002486	0.00215 4	KDR/THBS4/THY1/TSPAN8/COL3A1	5

Gene ID: Gene or transcript identifier; GO: Gene ontology; BP: Biological process; CC: Cellular components; MF: Molecular functions.

Supplementary Table 5 A complete list of kyoto encyclopedia of genes and genome enrichment analyses of 61 differentially expressed genes

Category	Subcategory	ID	Description	GeneRatio	FoldEnrichment	zScore	p.adjust	qvalue	Gene ID	Count
NA	NA	hsa04820	Cytoskeleton in muscle cells	11/36	12.3717	10.8779	7.5E-08	6.29E-08	COL4A1/COL4A2/NID2/BGN/THBS4/COL3A1/LMNB2/COL1A1/COL1A2/ACTC1/MYBPH	11
Environmental Information Processing	Signaling molecules and interaction	hsa04512	ECM-receptor interaction	7/36	20.6111	11.5045	2.1E-06	1.72E-06	COL4A1/COL4A2/LAMB1/LAMA4/THBS4/COL1A1/COL1A2	7
Cellular Processes	Cellular community-eukaryotes	hsa04510	Focal adhesion	9/36	11.6182	9.46529	2.1E-06	1.72E-06	COL4A1/COL4A2/KDR/MYLK2/LAMB1/LAMA4/	9

									THBS4/COL1A1/COL1A2	
Human Diseases	Infectious disease: Parasitic	hsa05146	Amoebiasis	7/36	17.8096	10.6162	3.2E-06	2.65E-06	COL4A1/COL4A2/LAMB1/ LAMA4/COL3A1/COL1A1/ COL1A2	7
Organismal Systems	Endocrine system	hsa04926	Relaxin signaling pathway	7/36	14.1107	9.31581	1.3E-05	1.05E-05	COL4A1/COL4A2/EDNRB/ COL3A1/COL1A1/COL1A2/ RLN3	7
Organismal Systems	Digestive system	hsa04974	Protein digestion and absorption	6/36	14.9746	8.912	5.3E-05	4.46E-05	COL4A1/COL4A2/COL3A1/ COL14A1/COL1A1/ COL1A2	6
Environmental Informatio	Signal transduction	hsa04151	PI3K-Akt signaling pathway	9/36	6.51519	6.6225	0.00011	9.59E-05	COL4A1/COL4A2/KDR/ KIT/LAMB1/LAMA4/	9

n Processing									THBS4/COL1A1/COL1A2	
Human Diseases	Endocrine and metabolic disease	hsa04933	AGE-RAGE signaling pathway in diabetic complications	5/36	12.9731	7.4871	0.0006	0.000505	COL4A1/COL4A2/COL3A1/ COL1A1/COL1A2	5
Human Diseases	Infectious disease: Viral	hsa05165	Human papillomavirus infection	7/36	5.50868	5.18424	0.0032	0.002689	COL4A1/COL4A2/LAMB1/ LAMA4/THBS4/COL1A1/ COL1A2	7
Human Diseases	Cancer: Specific types	hsa05222	Small cell lung cancer	4/36	11.2712	6.16062	0.0053	0.004483	COL4A1/COL4A2/LAMB1/ LAMA4	4
Organismal Systems	Immune system	hsa04611	Platelet activation	4/36	8.31922	5.11895	0.015171	0.012776	MYLK2/COL3A1/COL1A1/ COL1A2	4

Organismal Systems	Endocrine system	hsa04916	Melanogenesis	3/36	7.78383	4.24212	0.07131	0.06005	EDNRB/KIT/CALML6	3
Environmental Information Processing	Signal transduction	hsa04015	Rap1 signaling pathway	4/36	4.94444	3.59501	0.08237	0.06841	KDR/SIPA1 L2/KIT/CALML6	4
Human Diseases	Infectious disease: Parasitic	hsa05145	Toxoplasmosis	3/36	7.01934	3.96609	0.08237	0.06841	LAMB1/LAMA4/HLA-DPA1	3
Environmental Information Processing	Signal transduction	hsa04020	Calcium signaling pathway	4/36	4.12686	3.12653	0.11981	0.10089	KDR/MYLK2/EDNRB/CALML6	4
Human Diseases	Infectious disease: Parasitic	hsa05144	Malaria	2/36	10.4822	4.16064	0.11981	0.10089	PECAM1/THBS4	2

Environmental Information Processing	Signal transduction	hsa04371	Apelin signaling pathway	3/36	5.61548	3.40516	0.119812	0.100894	MYLK2/PRKAG3/CALML6	3
Human Diseases	Cardiovascular disease	hsa05418	Fluid shear stress and atherosclerosis	3/36	5.53639	3.371	0.119812	0.100894	KDR/PECAM1/CALML6	3
Organismal Systems	Endocrine system	hsa04921	Oxytocin signaling pathway	3/36	5.07204	3.16363	0.142992	0.120415	MYLK2/PRKAG3/CALML6	3
Environmental Information Processing	Signal transduction	hsa04022	cGMP-PKG signaling pathway	3/36	4.73594	3.00552	0.162398	0.136756	MYLK2/EDNRB/CALML6	3
Organismal Systems	Endocrine system	hsa04920	Adipocytokine signaling pathway	2/36	7.4873	3.37164	0.17995	0.151537	PRKAG3/ADIPOQ	2

Organismal Systems	Digestive system	hsa04971	Gastric acid secretion	2/36	6.8962	3.19408	0.199852	0.168296	MYLK2/CALML6	2
Human Diseases	Cancer: Overview	hsa05205	Proteoglycans in cancer	3/36	3.85376	2.55029	0.23131	0.194787	KDR/COL1A1/COL1A2	3
Human Diseases	Cardiovascular disease	hsa05415	Diabetic cardiomyopathy	3/36	3.83496	2.53983	0.23131	0.194787	COL3A1/COL1A1/COL1A2	3
Organismal Systems	Aging	hsa04211	Longevity regulating pathway	2/36	5.82346	2.84559	0.239107	0.201353	PRKAG3/ADIPOQ	2
Organismal Systems	Immune system	hsa04658	Th1 and Th2 cell differentiation	2/36	5.6356	2.78041	0.243853	0.205349	DLL4/HLA-DPA1	2

Gene ID: Gene or transcript identifier; KEGG: Kyoto encyclopedia of gene and genomes.