

Supplementary Information

A Computational Framework for Detecting Inter-tissue Gene-expression Coordination Changes with Aging

Shaked Briller¹, Gil Ben David², Yam amir^{2,3}, Gil Atzmon², Judith Somekh^{1,*}

¹University of Haifa, Department of Information Systems, Haifa, Israel

²University of Haifa, Department of Human Biology, Haifa, Israel

³Tel Aviv University, Faculty of Medicine, Tel-Aviv, Israel

Supplementary Figures

Figure S1: Multi-tissue network's modules composition

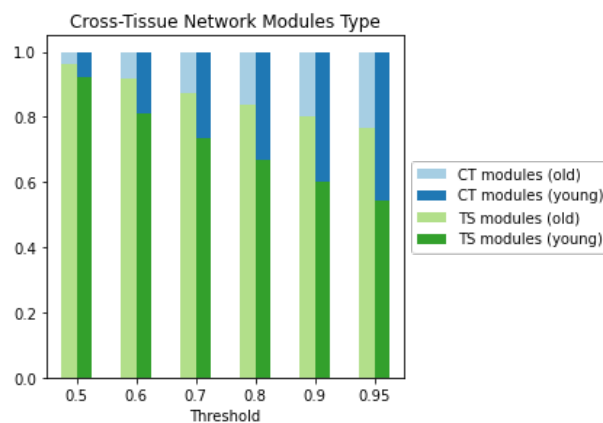
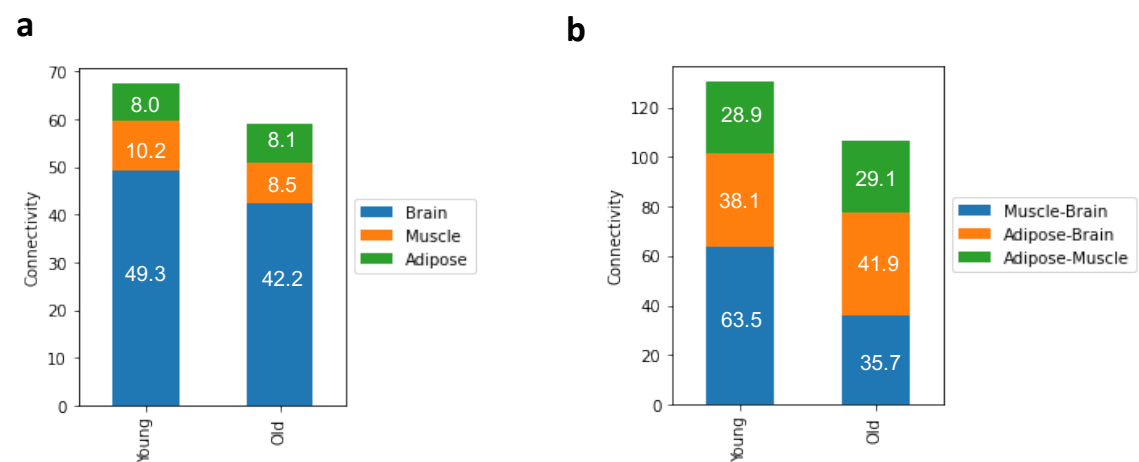


Figure S1 shows the comparison between the modules' composition between old and young proportions of cross tissue (CT) and tissue specific (TS) modules across thresholds (0.5-0.95). X-axis is the threshold level used to define module type and the y-axis represents the percentage of modules type (CT/TS) across the thresholds. Dark blue/ green represent CT/TS modules in the young cohort, respectively; light blue/ green, represent CT/ TS modules in the old cohort, respectively. It can be seen that the young cohort includes higher proportions of CT modules than the old across the tested thresholds.

Figure S2: Connectivity comparison between young and old subjects.

Global gene connectivity (sum of adjacency values) in modules identified in different age groups by tissue in. (a) Sum of gene-to-gene connectivity (sum of adjacency values) for Tissue specific (TS) modules comparing young and old cohorts. (b) Sum of gene-to-gene connectivity for cross-tissue (CT)

modules comparing the young and old cohorts, divided by tissue pair. It can be seen that the global inter-tissue and intra-tissue connectivity is higher in the young cohort.



We note that Figure S2a and S2b present the old versus young comparison of the total aggregated connectivity of genes for the CT and TS modules. This aggregative connectivity averages the gain and loss connectivity across modules for each age group. As some modules in the young network gain connectivity and some loss, we conducted a further module-specific evaluation while comparing the young modules mapped to the old.

Figure S3: MDC distribution of all modules in the young network.

Error! Reference source not found. shows the MDC of all modules in the young network (see Table S4: Modular Differential Connectivity (MDC) of 90 young modules and their enrichment). Gain of Connectivity (GOC) modules with $MDC > 1$ and Loss of Connectivity (LOC) modules with $MDC < 1$. Statistically significant is indicated by asterisk ($p \leq 0.05$).

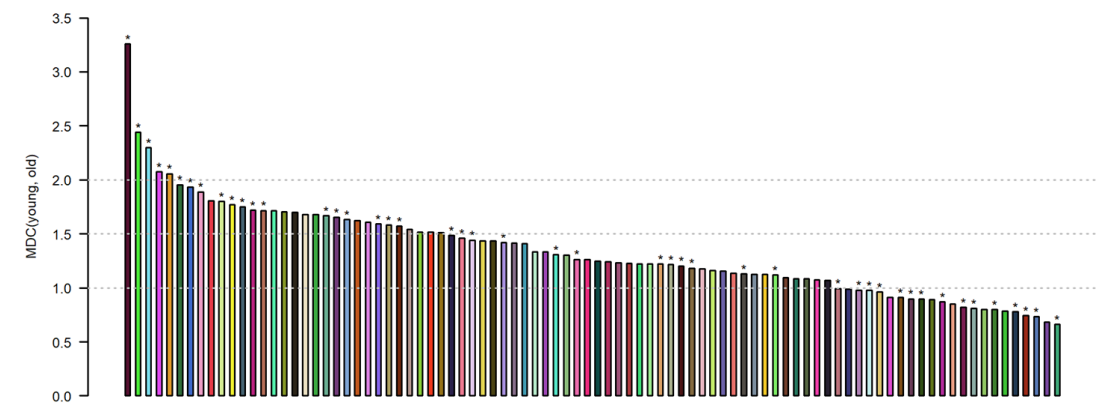


Figure S4: Clustered heatmap of modules 1, 66, 13 and 47 gene expression features transformed to pathway scores using ssGSEA and PCA method.

A hierarchical clustering heatmap of the top 50 pathways to identify clusters of pathways that could discriminate between the two age classes, using a different pathway scores method based on kernel principal component analysis (kPCA). For this the kernel PCA with a radial basis function (RBF) kernel is used to model the distribution of data for the pathway. The first principal component (PC1) scores are calculated for each pathway matrix (genes in pathway) which enables to transform the gene expression data to pathway scores. Two distinct pathway clusters were observed for each age group (green color represents the young cohort while red represents the old cohort).

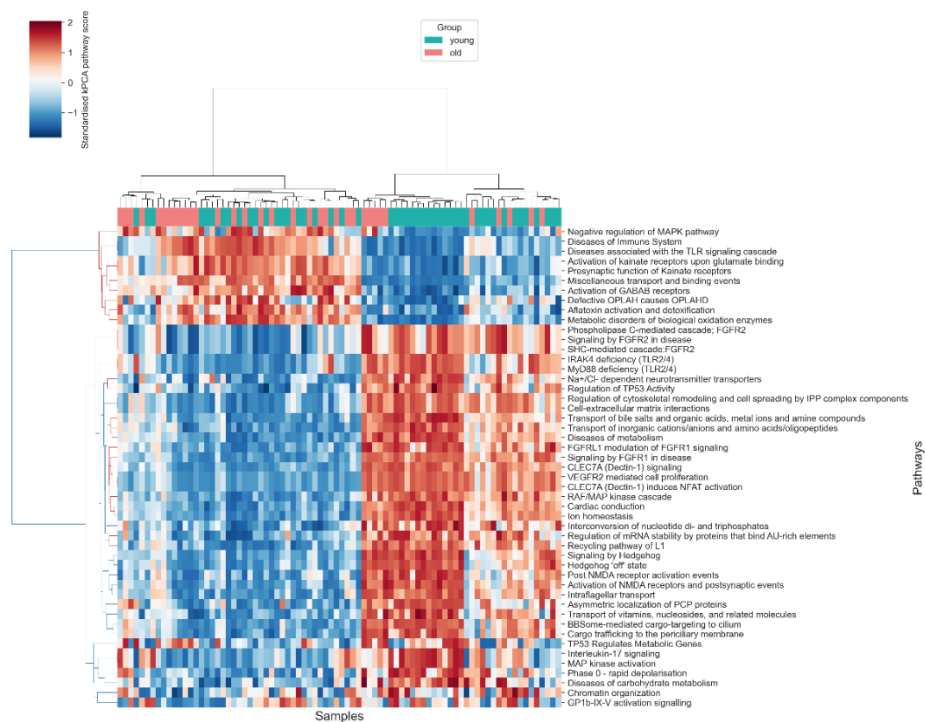


Figure S5: Correlation Coefficient of Predictors

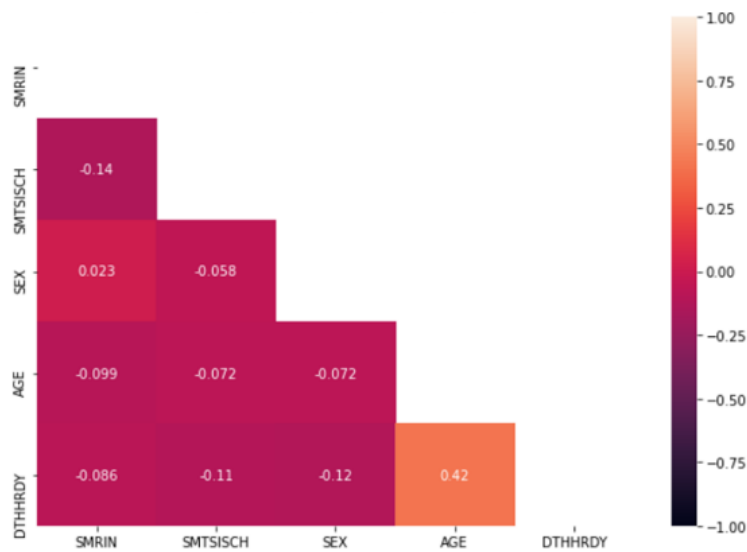


Figure S6: Optimization of scale-free properties of co-expression networks across tissues.

β -value calibration curves per tissue and between all tissue combinations, showing the TOM-adjusted scale-free network properties of tissues-specific and cross-tissue networks at different β -values.

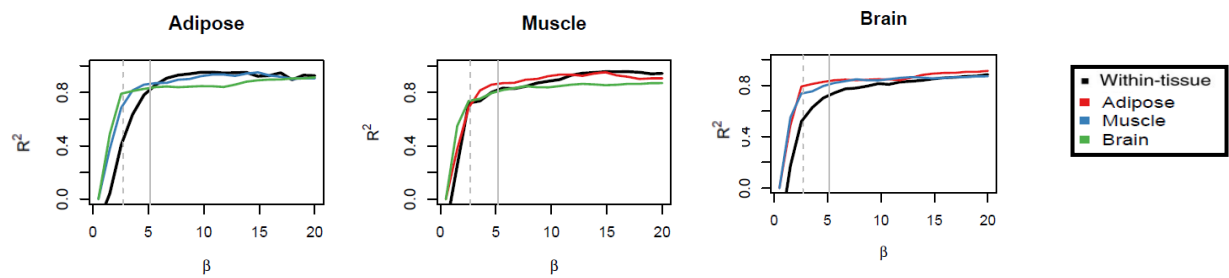


Figure S7: A comparison of the variance in gene expression between age groups in three tissues.

No significant differences in gene expression variance between the groups, suggesting that although gene-expression heterogeneity is an important factor, the differences in cross-tissue interactions patterns are not driven by intrinsic gene expression variability with age.

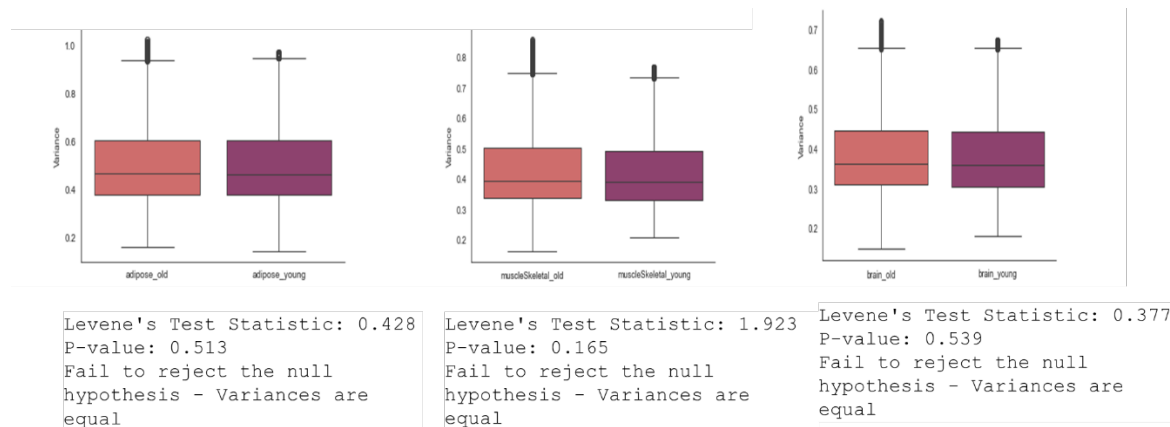


Figure S8: Examples of expression levels comparison of inter-tissue marker genes which expression values do not change significantly ($p\text{-value} < 0.05$) between the old and young cohorts.

(a) genes derived from adipose. (b) genes derived from brain. (c) genes derived from muscle skeletal.

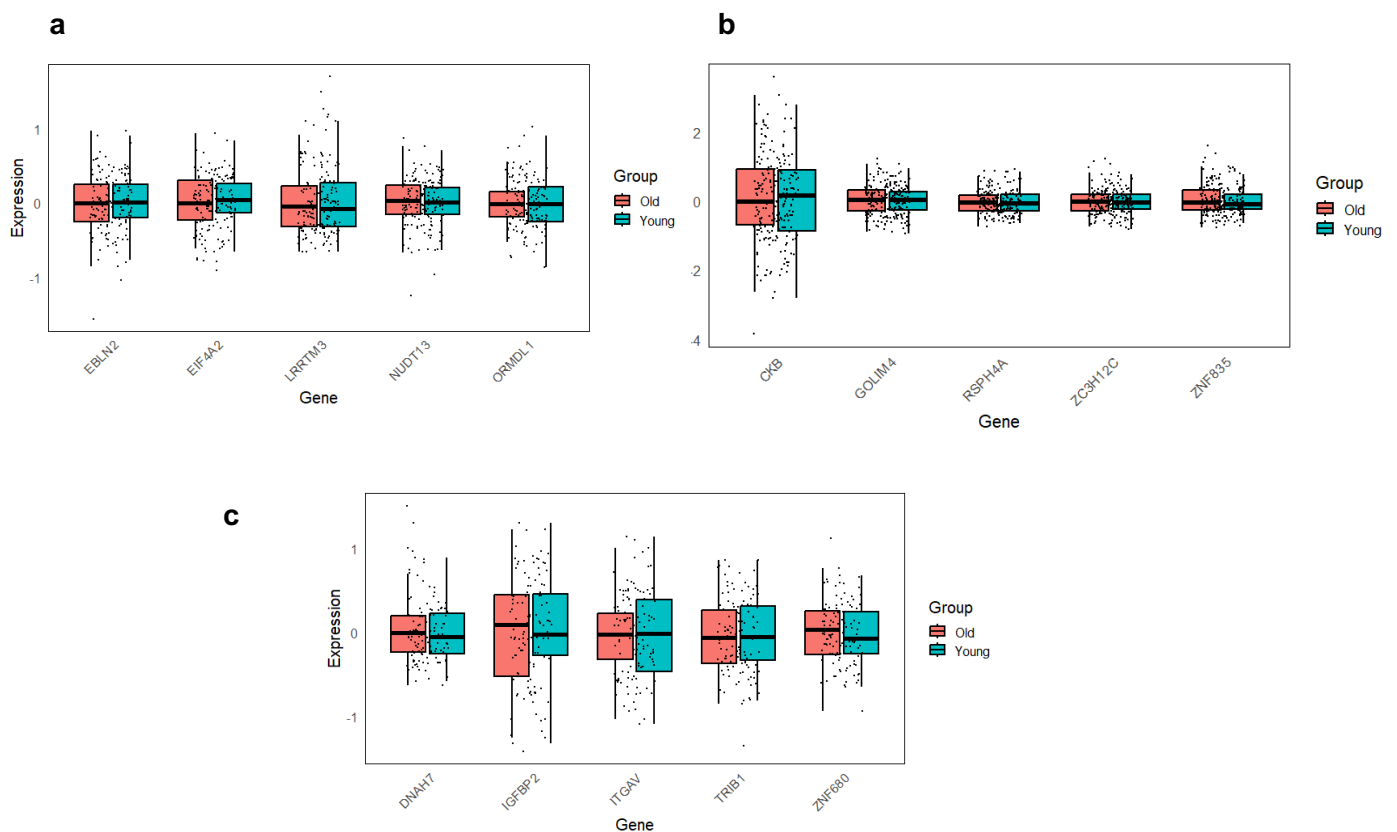


Figure S11. Connectivity inter-tissue network visualization of the top 10 genes and their immediate neighbors across three tissues.

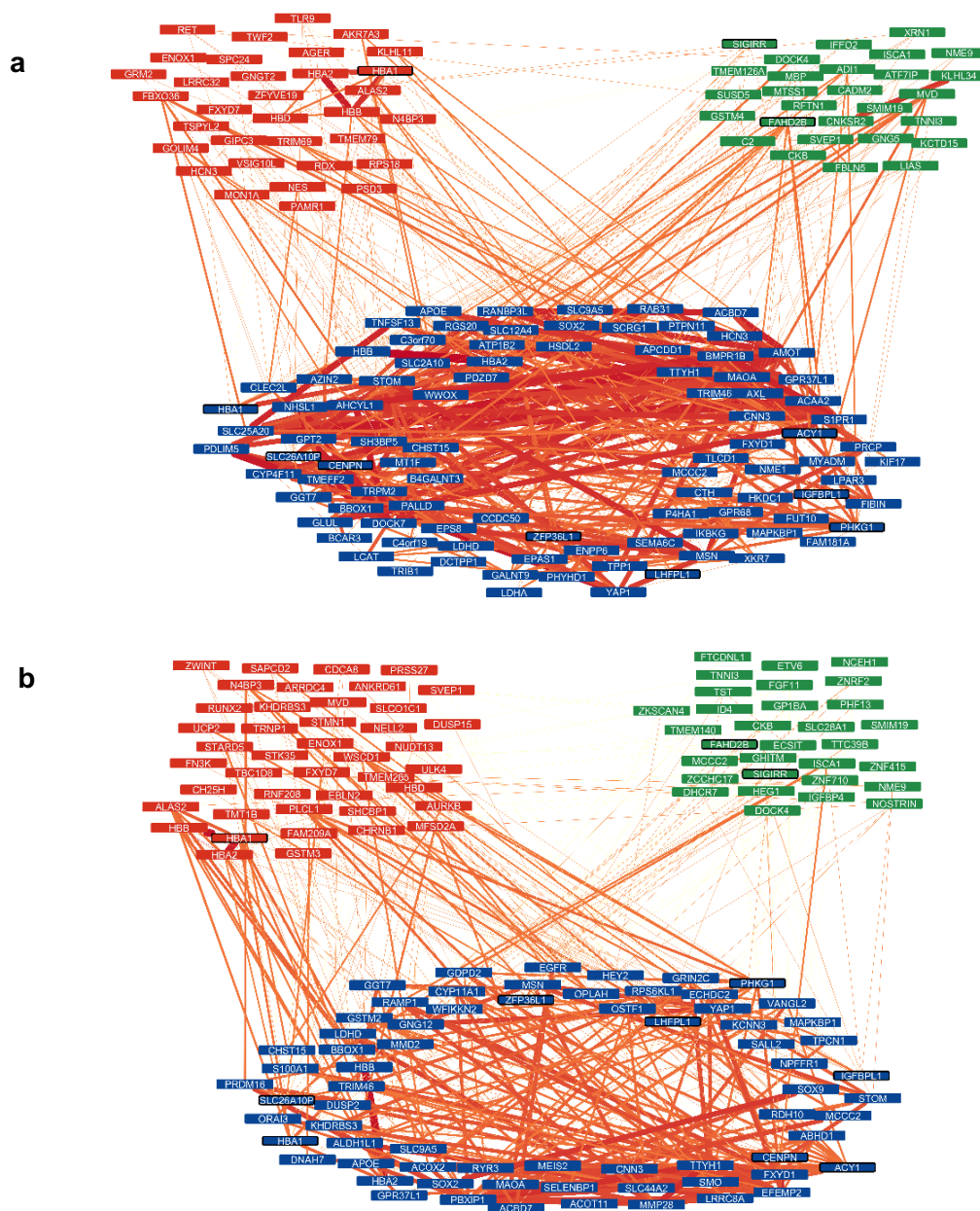
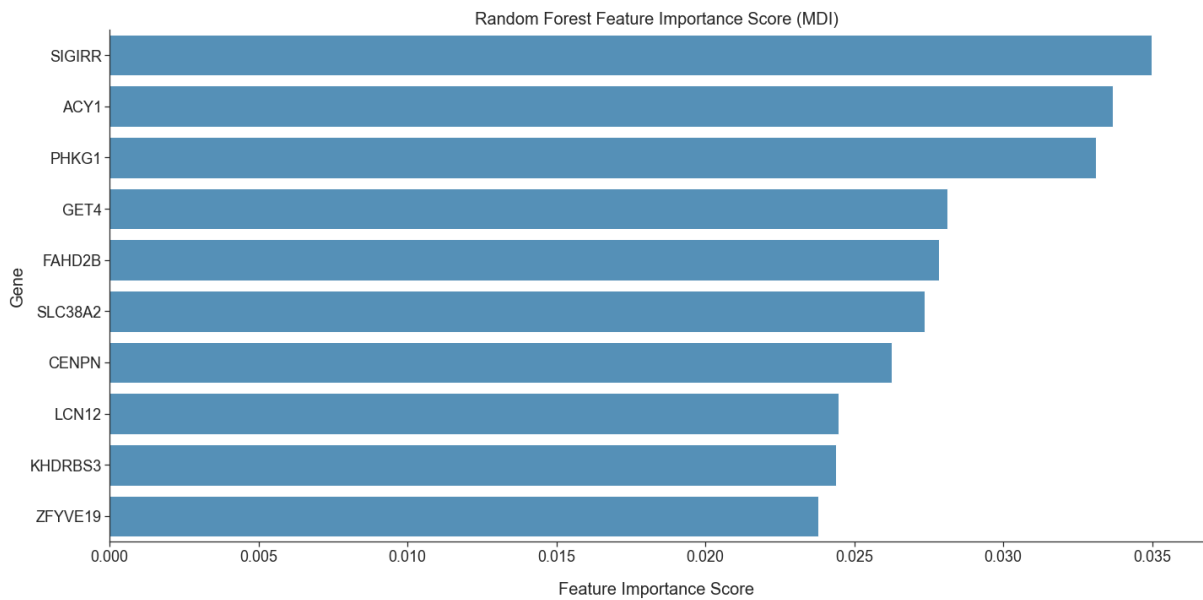


Figure S12. Batch effect correction impact on classification performance.

a. Identification of key inter-tissue aging genes using machine learning without batch correction

Performance of RF and XGB classifiers for predicting age using a feature space of inter-tissue marker genes and Random Forest feature importance scores of top 10 inter-tissue genes for predicting age.

Algorithm name	Accuracy (%)		Recall (%)		Precision (%)		F1 Score (%)		AUC (%)	
	All Features	Lasso	All Features	Lasso	All Features	Lasso	All Features	Lasso	All Features	Lasso
RF	65.9	75.7	87.7	91.9	65.9	74.1	75	81.6	65.7	82.6
XGB	56.2	63.6	70.9	75.1	61.3	67.7	65.4	70.7	51.9	72.2

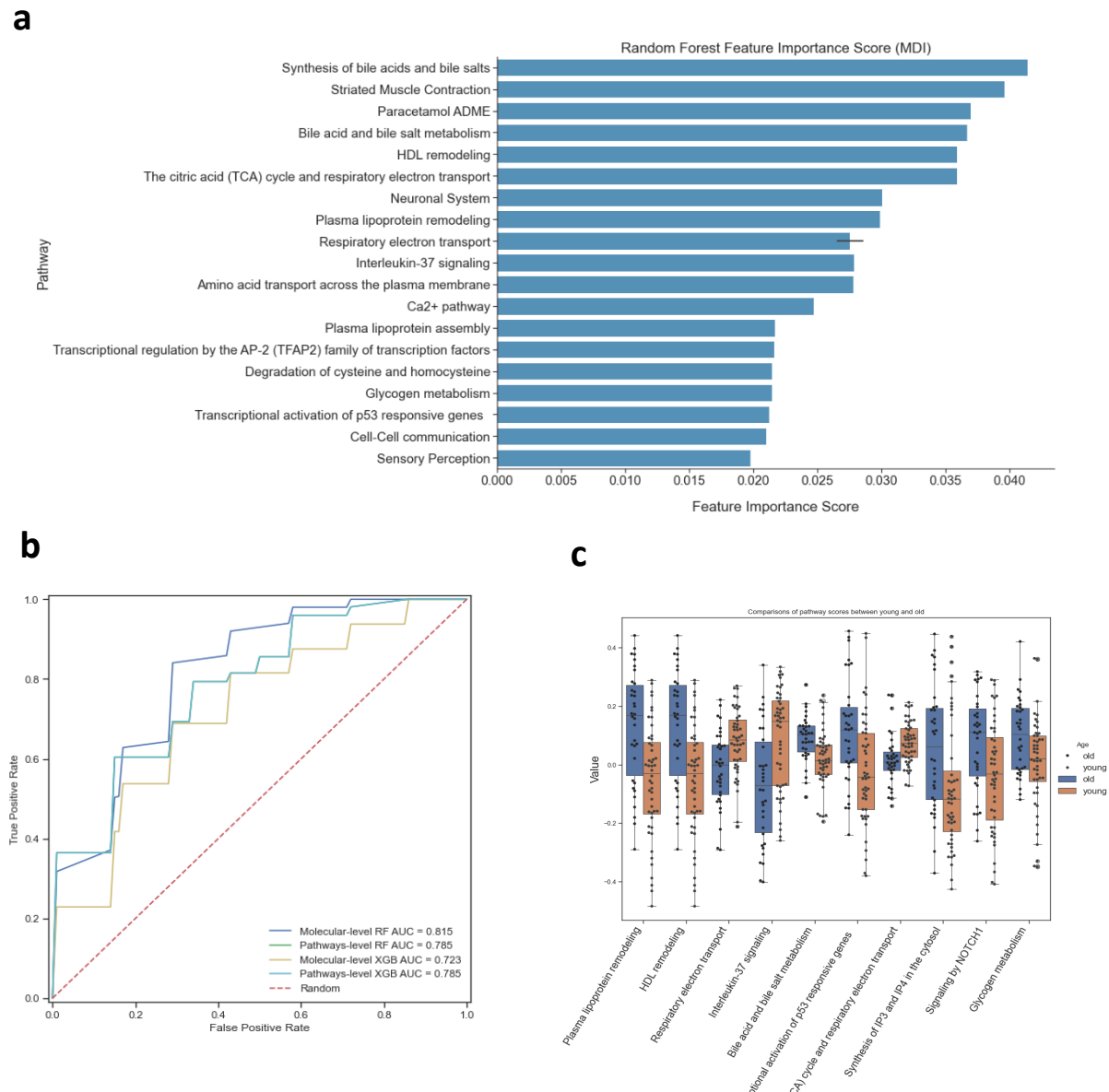


b. Identification of key inter-tissue aging pathways using single-sample enrichment analysis and machine learning without batch correction

Performance of RF and XGB classification models with cross-tissue pathway scores as features.

Algorithm name	Accuracy (%)	Recall (%)	Precision (%)	F1 Score (%)	AUC (%)
RF	75.54	83.3	76.8	79.8	81.5
XGB	73.3	83.3	75.4	78.4	78.5

Age classification using pathway scores without batch correction. (a) Comparison of top 10 differential pathway scores between age groups. (b) ROC curve for Random Forest (RF) and XGBoost (XGB) models for predicting age. 82 samples were used for the prediction of age using ssGSEA scores named pathway level (RF: green ; XGB: cyan) and gene expression levels, named molecular-level (RF: blue ; XGB: yellow) of 1003 genes extracted from significant GOC cross-tissue modules as features. Prediction accuracy was measured by the Area under the curve (AUC). (c) The relative importance of pathway-level features for the random forest classification model.



Supplementary TablesError! Reference source not found. & Error! Reference source not found. show the numbers of sample overlap between each pair of tissues for the old and young groups.

Table S1: Number of old samples (age ≥ 60) in GTEx

	Adipose- Subcutaneous	Muscle-skeletal	Brain-cortex
Adipose- subcutaneous	76	71	36
Muscle-skeletal		102	49
Brain-cortex			55

Table S2: Number of young samples (age < 60) in GTEx

	Adipose- Subcutaneous	Muscle-skeletal	Brain-cortex
Adipose- subcutaneous	96	85	53
Muscle-skeletal		124	64
Brain-cortex			71

Table S3: Old network modules details

Cluster ID	Cluster Size	Cluster Type	Cluster Tissues	Adipose	Brain	Muscle	Dominant Tissue
1	306	CT	Adipose,Brain,Muscle	140	100	66	Adipose
2	290	CT	Adipose,Brain,Muscle	95	139	56	Brain
3	199	CT	Adipose,Brain,Muscle	49	91	59	Brain
4	193	TS	Adipose,Brain,Muscle	190	2	1	Adipose
5	187	CT	Adipose,Brain,Muscle	7	175	5	Brain
6	184	TS	Adipose,Brain,Muscle	5	178	1	Brain
7	179	CT	Adipose,Brain,Muscle	38	138	3	Brain
8	171	TS	Adipose,Brain,Muscle	4	165	2	Brain
9	163	CT	Adipose,Brain,Muscle	47	41	75	Muscle
10	144	CT	Adipose,Brain,Muscle	29	86	29	Brain
11	141	TS	Adipose	141	0	0	Adipose
12	140	TS	Muscle	0	0	140	Muscle
13	132	CT	Adipose,Brain,Muscle	26	71	35	Brain

14	128	TS	Brain,Muscle	0	2	126	Muscle
15	127	TS	Adipose	127	0	0	Adipose
16	123	CT	Brain,Muscle	0	8	115	Muscle
17	123	TS	Adipose,Brain,Muscle	1	119	3	Brain
18	122	TS	Adipose,Brain,Muscle	3	118	1	Brain
19	119	CT	Adipose,Brain,Muscle	26	33	60	Muscle
20	118	CT	Adipose,Brain,Muscle	2	103	13	Brain
21	116	TS	Adipose,Brain	1	115	0	Brain
22	114	TS	Adipose,Brain	113	1	0	Adipose
23	111	TS	Adipose,Brain	3	108	0	Brain
24	109	TS	Muscle	0	0	109	Muscle
25	105	CT	Adipose,Brain,Muscle	59	14	32	Adipose
26	103	CT	Adipose,Brain	94	9	0	Adipose
27	103	CT	Adipose,Brain,Muscle	66	29	8	Adipose
28	101	TS	Brain	0	101	0	Brain
29	99	CT	Adipose,Brain,Muscle	16	61	22	Brain
30	98	TS	Adipose	98	0	0	Adipose
31	98	TS	Adipose,Brain,Muscle	2	93	3	Brain
32	96	TS	Adipose	96	0	0	Adipose
33	94	TS	Muscle	0	0	94	Muscle
34	92	TS	Muscle	0	0	92	Muscle
35	92	TS	Adipose	92	0	0	Adipose
36	91	TS	Adipose	91	0	0	Adipose
37	89	TS	Adipose,Brain	85	4	0	Adipose
38	86	TS	Brain	0	86	0	Brain
39	85	TS	Muscle	0	0	85	Muscle
40	85	TS	Muscle	0	0	85	Muscle
41	84	TS	Brain	0	84	0	Brain
42	82	TS	Adipose	82	0	0	Adipose
43	80	TS	Brain,Muscle	0	1	79	Muscle
44	77	CT	Adipose,Brain,Muscle	5	22	50	Muscle
45	77	TS	Brain	0	77	0	Brain
46	76	TS	Muscle	0	0	76	Muscle
47	75	TS	Adipose,Brain	72	3	0	Adipose
48	75	CT	Adipose,Brain,Muscle	3	69	3	Brain

49	74	TS	Brain	0	74	0	Brain
50	70	TS	Brain	0	70	0	Brain
51	69	TS	Muscle	0	0	69	Muscle
52	68	TS	Brain,Muscle	0	1	67	Muscle
53	67	CT	Adipose,Brain,Muscle	8	38	21	Brain
54	66	TS	Adipose	66	0	0	Adipose
55	65	TS	Brain	0	65	0	Brain
56	64	TS	Adipose	64	0	0	Adipose
57	63	TS	Muscle	0	0	63	Muscle
58	63	TS	Brain	0	63	0	Brain
59	58	TS	Brain	0	58	0	Brain
60	57	TS	Muscle	0	0	57	Muscle
61	54	TS	Muscle	0	0	54	Muscle
62	54	TS	Adipose	54	0	0	Adipose
63	53	TS	Adipose	53	0	0	Adipose
64	53	TS	Muscle	0	0	53	Muscle
65	51	TS	Muscle	0	0	51	Muscle
66	49	CT	Adipose,Muscle	38	0	11	Adipose
67	48	TS	Adipose	48	0	0	Adipose
68	46	TS	Muscle	0	0	46	Muscle
69	46	TS	Muscle	0	0	46	Muscle
70	46	TS	Brain	0	46	0	Brain
71	45	TS	Muscle	0	0	45	Muscle
72	44	TS	Muscle	0	0	44	Muscle
73	44	TS	Brain	0	44	0	Brain
74	43	TS	Muscle	0	0	43	Muscle
75	43	TS	Muscle	0	0	43	Muscle
76	43	TS	Muscle	0	0	43	Muscle
77	43	TS	Muscle	0	0	43	Muscle
78	43	CT	Adipose,Brain	18	25	0	Brain
79	42	TS	Muscle	0	0	42	Muscle
80	40	TS	Adipose	40	0	0	Adipose
81	40	TS	Brain	0	40	0	Brain
82	39	TS	Muscle	0	0	39	Muscle
83	39	CT	Adipose,Brain	34	5	0	Adipose

84	39	TS	Adipose	39	0	0	Adipose
85	39	TS	Brain,Muscle	0	1	38	Muscle
86	39	TS	Brain	0	39	0	Brain
87	39	TS	Brain	0	39	0	Brain
88	38	TS	Adipose	38	0	0	Adipose
89	38	TS	Brain	0	38	0	Brain
90	38	CT	Adipose,Brain,Muscle	6	24	8	Brain
91	37	TS	Adipose	37	0	0	Adipose
92	37	TS	Brain	0	37	0	Brain
93	36	TS	Brain	0	36	0	Brain
94	34	TS	Adipose	34	0	0	Adipose
95	34	TS	Adipose	34	0	0	Adipose
96	33	TS	Adipose	33	0	0	Adipose
97	33	TS	Brain	0	33	0	Brain
98	33	TS	Adipose	33	0	0	Adipose
99	33	TS	Brain,Muscle	0	32	1	Brain
100	32	TS	Muscle	0	0	32	Muscle
101	32	CT	Adipose,Brain,Muscle	1	28	3	Brain
102	32	TS	Brain	0	32	0	Brain
103	31	TS	Adipose	31	0	0	Adipose
104	31	CT	Adipose,Muscle	24	0	7	Adipose
105	31	TS	Adipose	31	0	0	Adipose
106	31	CT	Adipose,Muscle	27	0	4	Adipose
107	31	CT	Adipose,Muscle	22	0	9	Adipose
108	31	TS	Brain	0	31	0	Brain
109	30	TS	Muscle	0	0	30	Muscle
110	30	TS	Muscle	0	0	30	Muscle
111	30	TS	Muscle	0	0	30	Muscle

Table S3: Young network modules details

Cluster ID	Cluster Size	Cluster Type	Cluster Tissues	Adipose	Brain	Muscle	Dominant Tissue
1	679	CT	Adipose,Brain,Muscle	116	456	107	Brain
2	299	TS	Brain	0	299	0	Brain

3	243	CT	Adipose,Brain,Muscle	145	18	80	Adipose
4	238	CT	Adipose,Brain,Muscle	36	173	29	Brain
5	235	TS	Adipose,Muscle	2	0	233	Muscle
6	225	CT	Adipose,Brain,Muscle	90	42	93	Muscle
7	210	CT	Adipose,Brain,Muscle	114	28	68	Adipose
8	205	TS	Brain	0	205	0	Brain
9	204	CT	Adipose,Muscle	87	0	117	Muscle
10	204	CT	Adipose,Brain,Muscle	11	192	1	Brain
11	202	TS	Muscle	0	0	202	Muscle
12	199	TS	Adipose	199	0	0	Adipose
13	187	CT	Adipose,Brain,Muscle	51	74	62	Brain
14	184	TS	Brain	0	184	0	Brain
15	184	CT	Adipose,Muscle	98	0	86	Adipose
16	179	CT	Adipose,Brain,Muscle	81	28	70	Adipose
17	172	TS	Brain	0	172	0	Brain
18	167	TS	Adipose,Brain,Muscle	160	2	5	Adipose
19	164	TS	Muscle	0	0	164	Muscle
20	162	CT	Adipose,Brain	74	88	0	Brain
21	149	CT	Adipose,Brain,Muscle	64	20	65	Muscle
22	146	CT	Adipose,Brain,Muscle	86	4	56	Adipose
23	134	CT	Adipose,Brain,Muscle	29	81	24	Brain
24	133	TS	Adipose,Muscle	1	0	132	Muscle
25	123	TS	Adipose,Muscle	4	0	119	Muscle
26	122	TS	Muscle	0	0	122	Muscle
27	120	TS	Adipose	120	0	0	Adipose
28	119	TS	Adipose	119	0	0	Adipose
29	118	TS	Muscle	0	0	118	Muscle
30	116	CT	Adipose,Brain,Muscle	40	22	54	Muscle
31	114	CT	Adipose,Muscle	33	0	81	Muscle
32	114	TS	Brain	0	114	0	Brain
33	110	CT	Adipose,Brain,Muscle	7	102	1	Brain
34	106	TS	Brain	0	106	0	Brain
35	105	CT	Adipose,Brain,Muscle	12	5	88	Muscle
36	103	CT	Adipose,Brain,Muscle	53	7	43	Adipose
37	101	TS	Adipose,Brain	3	98	0	Brain

38	98	CT	Adipose,Brain,Muscle	17	79	2	Brain
39	95	TS	Muscle	0	0	95	Muscle
40	93	CT	Adipose,Brain,Muscle	50	6	37	Adipose
41	93	TS	Adipose,Muscle	2	0	91	Muscle
42	93	TS	Brain	0	93	0	Brain
43	92	CT	Adipose,Brain,Muscle	21	1	70	Muscle
44	91	CT	Adipose,Brain,Muscle	15	64	12	Brain
45	91	CT	Adipose,Brain,Muscle	34	22	35	Muscle
46	90	CT	Adipose,Brain,Muscle	20	5	65	Muscle
47	85	CT	Adipose,Brain,Muscle	76	4	5	Adipose
48	81	TS	Muscle	0	0	81	Muscle
49	81	TS	Brain	0	81	0	Brain
50	76	CT	Adipose,Brain,Muscle	40	3	33	Adipose
51	74	TS	Adipose	74	0	0	Adipose
52	74	CT	Adipose,Brain,Muscle	43	18	13	Adipose
53	67	TS	Adipose	67	0	0	Adipose
54	67	TS	Muscle	0	0	67	Muscle
55	67	TS	Brain	0	67	0	Brain
56	63	CT	Adipose,Brain,Muscle	5	2	56	Muscle
57	60	CT	Adipose,Brain,Muscle	54	4	2	Adipose
58	58	CT	Adipose,Brain,Muscle	35	7	16	Adipose
59	57	CT	Adipose,Muscle	20	0	37	Muscle
60	56	TS	Adipose,Brain,Muscle	1	54	1	Brain
61	56	TS	Adipose	56	0	0	Adipose
62	56	TS	Adipose	56	0	0	Adipose
63	55	TS	Muscle	0	0	55	Muscle
64	54	CT	Adipose,Brain,Muscle	1	49	4	Brain
65	53	CT	Adipose,Brain,Muscle	13	13	27	Muscle
66	52	CT	Adipose,Brain	48	4	0	Adipose
67	52	TS	Brain	0	52	0	Brain
68	51	TS	Brain	0	51	0	Brain
69	51	CT	Adipose,Brain,Muscle	36	4	11	Adipose
70	49	TS	Adipose,Brain	47	2	0	Adipose
71	48	CT	Adipose,Muscle	33	0	15	Adipose
72	47	CT	Adipose,Brain,Muscle	41	4	2	Adipose

73	46	TS	Adipose,Brain	45	1	0	Adipose
74	45	TS	Adipose	45	0	0	Adipose
75	45	TS	Adipose	45	0	0	Adipose
76	45	TS	Brain	0	45	0	Brain
77	42	CT	Adipose,Brain,Muscle	20	6	16	Adipose
78	42	TS	Brain	0	42	0	Brain
79	41	TS	Brain	0	41	0	Brain
80	40	TS	Brain	0	40	0	Brain
81	39	TS	Brain	0	39	0	Brain
82	37	TS	Brain	0	37	0	Brain
83	37	TS	Brain	0	37	0	Brain
84	36	TS	Brain	0	36	0	Brain
85	35	CT	Adipose,Brain	31	4	0	Adipose
86	35	TS	Muscle	0	0	35	Muscle
87	34	CT	Adipose,Brain,Muscle	23	2	9	Adipose
88	33	TS	Brain	0	33	0	Brain
89	30	TS	Adipose,Brain	1	29	0	Brain
90	30	TS	Muscle	0	0	30	Muscle

Table S4: Modular Differential Connectivity (MDC) of 90 young modules and their enrichment

Cluster ID	Cluster Size	Cluster Type	MDC	FDR	KEGG Description
1	679	CT	1.8	0	Glycine
2	299	TS	1.68	0	Cocaine addiction
3	243	CT	1.22	0.4	Glycine
4	238	CT	1.49	0	Aldosterone-regulated sodium reabsorption
5	235	TS	1.7	0	Central carbon metabolism in cancer
6	225	CT	1.2	0.54	Viral life cycle - HIV-1
7	210	CT	0.85	0	Sphingolipid signaling pathway
8	205	TS	1.25	0.42	Glutamatergic synapse
9	204	CT	1.13	0.72	Oxidative phosphorylation

10	204	CT	1.31	0.22	Coronavirus disease - COVID-19
11	202	TS	1.52	0.02	Diabetic cardiomyopathy
12	199	TS	1.09	0.9	Mineral absorption
13	187	CT	1.93	0	Fluid shear stress and atherosclerosis
14	184	TS	0.96	0	Lipid and atherosclerosis
15	184	CT	0.91	0	Malaria
16	179	CT	0.78	0	ECM-receptor interaction
17	172	TS	1.24	0.3	Ether lipid metabolism
18	167	TS	1.67	0	PPAR signaling pathway
19	164	TS	1.8	0	Pertussis
20	162	CT	1.57	0	Cellular senescence
21	149	CT	0.8	0	Steroid hormone biosynthesis
22	146	CT	1.46	0.02	Longevity regulating pathway
23	134	CT	1.18	0.54	Renin secretion
24	133	TS	1.43	0.08	Toxoplasmosis
25	123	TS	1.33	0.16	Complement and coagulation cascades
26	122	TS	1.7	0	Epithelial cell signaling in Helicobacter pylori infection
27	120	TS	1.12	0.72	Tuberculosis
28	119	TS	1.26	0.38	Carbon metabolism
29	118	TS	1.71	0	Mineral absorption
30	116	CT	0.8	0	Primary bile acid biosynthesis
31	114	CT	1.23	0.54	Leukocyte transendothelial migration
32	114	TS	1.68	0	Arrhythmogenic right ventricular cardiomyopathy
33	110	CT	1.16	0.62	Regulation of lipolysis in adipocytes
34	106	TS	1.77	0	Pertussis
35	105	CT	1.23	0.38	Hypertrophic cardiomyopathy
36	103	CT	0.87	0	Leishmaniasis
37	101	TS	1.51	0.04	Ribosome
38	98	CT	1.15	0.64	Neuroactive ligand-receptor interaction
39	95	TS	1.14	0.6	AMPK signaling pathway
40	93	CT	0.81	0	Apelin signaling pathway
41	93	TS	1.41	0.08	Human cytomegalovirus infection
42	93	TS	1.12	0.66	Glutamatergic synapse

43	92	CT	1.63	0	Ribosome
44	91	CT	1.59	0	Serotonergic synapse
45	91	CT	0.98	0.06	Ras signaling pathway
46	90	CT	1.13	0.66	Human cytomegalovirus infection
47	85	CT	2.44	0	African trypanosomiasis
48	81	TS	0.99	0.16	Protein digestion and absorption
49	81	TS	1.72	0	cAMP signaling pathway
50	76	CT	0.98	0.02	Chemical carcinogenesis - receptor activation
51	74	TS	1.58	0.02	Vascular smooth muscle contraction
52	74	CT	0.73	0	mTOR signaling pathway
53	67	TS	2.06	0	Cytokine-cytokine receptor interaction
54	67	TS	1.54	0.02	Choline metabolism in cancer
55	67	TS	1.09	0.78	Synaptic vesicle cycle
56	63	CT	1.42	0.06	HIF-1 signaling pathway
57	60	CT	1.22	0.48	Complement and coagulation cascades
58	58	CT	1.41	0.2	Gastric acid secretion
59	57	CT	1.31	0.2	Prolactin signaling pathway
60	56	TS	0.78	0	Protein digestion and absorption
61	56	TS	1.75	0.02	cGMP-PKG signaling pathway
62	56	TS	0.82	0.02	Mucin type O-glycan biosynthesis
63	55	TS	0.91	0.04	ECM-receptor interaction
64	54	CT	1.07	0.78	Staphylococcus aureus infection
65	53	CT	1.61	0.08	Fanconi anemia pathway
66	52	CT	2.3	0	Cell cycle
67	52	TS	2.08	0	Phosphatidylinositol signaling system
68	51	TS	0.9	0.08	ECM-receptor interaction
69	51	CT	1.09	0.62	Ras signaling pathway
70	49	TS	1.22	0.44	Glycerophospholipid metabolism
71	48	CT	1.26	0.44	Arginine and proline metabolism
72	47	CT	3.26	0	Dilated cardiomyopathy
73	46	TS	0.68	0	Cell adhesion molecules
74	45	TS	0.89	0.08	Lysosome
75	45	TS	0.9	0.08	T cell receptor signaling pathway
76	45	TS	1.95	0.04	Circadian entrainment

77	42	CT	0.74	0.02	Influenza A
78	42	TS	1.65	0.06	Circadian entrainment
79	41	TS	1.52	0.14	Longevity regulating pathway
80	40	TS	1.44	0.16	Biosynthesis of unsaturated fatty acids
81	39	TS	1.62	0.08	Folate biosynthesis
82	37	TS	1.07	0.54	Circadian entrainment
83	37	TS	1.34	0.38	Epithelial cell signaling in Helicobacter pylori infection
84	36	TS	1.43	0.2	Type II diabetes mellitus
85	35	CT	1.89	0	cGMP-PKG signaling pathway
86	35	TS	0.66	0	MAPK signaling pathway
87	34	CT	1.22	0.5	Cardiac muscle contraction
88	33	TS	1.72	0.04	Arginine and proline metabolism
89	30	TS	0.99	0.18	Apoptosis
90	30	TS	1.18	0.54	Vascular smooth muscle contraction

Table S5: Selected 1003 Genes with Significant Gain of Connectivity (GOC) in Young Group Compared to Old

Adipose- Subcutaneous
ZNF432, NOCT, ARID5B, MPZL2, ITPRIP, STOM, UGCG, IPMK, KLHL3, CSRN1, ARRDC4, PHLDA1, CNOT6L, CH25H, LRRC1, FEM1C, MYC, GJA1, BACH1, MAT2A, SEMA6B, ARL5B, NFIL3, NOS3, SOX17, CMIP, SYTL3, SPRY1, TMEM79, MPZL3, RUNX1, ADAMTS4, F11R, IL15, IL6, RNF138, SLC38A2, FANCA, SAPCD2, KIF18B, IQGAP3, APOBEC3B, AURKB, FAM111B, TYMS, RRM2, SHCBP1, CDK1, BUB1, PBK, TK1, UBE2C, KIFC1, UHRF1, LMNB1, RNF122, SWAP70, PIK3C2B, PRRG1, NECTIN2, ZFP36, ARMC7, CDKN1A, SRGN, HS3ST2, TNFRSF10B, SOCS2, PTBP3, SLC2A1, GADD45A, CHRN1, SP7, AKAP13, ZBTB21, PDGFD, NPAS2, METTL7B, MFSD2A, PTGDR, FN3K, STARD5, PLEKHA7, SVEP1, ALDH1A1, ZC3H12A, PYHIN1, ALAS2, FGF18, ZFYVE19, LRRC20, GOLIM4, UCP2, SPON1, TWF2, HBB, TLR9, HBD, RNF208, HBA1, POU5F1, RYR3, MAP3K5, SAXO2, HBA2, CYP4F12, WSCD1, HIC1, GRIA1, CDT1, IGSF10, DUSP15, VSIG10L, MAFF, TSPYL2, TRAIP, SPATA13, PLCXD3, NHLRC1, P2RY8, TMTC2, GPR4, YES1, CD248, NRROS, TNFRSF10D, MAPK15, RALGAPA2, PELI1, ERICH2, PAMR1, CDKN2A, ARHGAP18, N4BP3, SCCPDH, HCN3, FCN3, SLC01C1, LRRC32, GSTM3, SH3BP5, JUND, SDC4, SDC1, TMEM265, NEK7, PLK1, FAM124A, PTTG1, GNGT2, ENDOG, MVD, EBLN2, TRNP1, UPK3B, MELK, BGLAP, ARHGAP8, LY6G5B, GET4, RBM14, HGH1, RPS18, FXDY7, NEMP1, MRPL23, TMPRSS5, LEO1, U2AF1, PAQR6, SYCE2, USP24, AKR7A3, OMA1, MSX1, ICA1L, MON1A, GRM2, TP53INP1, ZNF483, RET, RAPSN, NUDT13, CENPV, CCDC17, MXD3, AKR7L, GP1BA, PGBD2, NELL2, LSMEM1, GIPC3, ATOH7, VWA1, KLHL11, COX14, RBM44, NR2F1,

P2RY14, ULK4, CHD7, PRSS27, CDK10, CFAP45, TRIM69, SESTD1, CCDC85C, TBC1D8, AGER, COX20, SREBF2, GJC2, LRRTM3, KCNRG, ZKSCAN8, STPG3, ENTPD4, HRH1, SP6, ZC3H6, NRN1L, PRG2, ANKRD61, BRWD3, EIF4A2, ZWINT, STMN1, CDC20, KIF20A, NEK11, DNAH1, PLCL1, ENOX1, LRRC39, FAM209A, CHST8, UNC5CL, RUNX2, SSUH2, STK35, STYXL1, ORMDL1, KLHDC7B, SESN2, CENPK, KHDRBS3, HJURP, PKMYT1, SPC24, CCNB2, BUB1B, CENPU, MKI67, CDCA5, CCNA2, NUF2, KIF2C, PIF1, CEP55, KIF11, KIF23, NUSAP1, ESPL1, TROAP, CDCA8, CCNB1, TOP2A, DLGAP5, KRTCAP3, ZNF132, MST1, NES, SYT11, TMCC2, KRT7, RDX, RHOF, RAP1GAP2, REM2, TSSK4, CDH24, SAMD1, CYP4V2, MYLK4, TCTE1, GNRH1, FAM13C, FBXO36, PSD3, NODAL, FANCI, CCT6B

Muscle- Skeletal

ETV6, LRRC32, ALDH1B1, RRAS2, MYLK3, MKRN1, MYO18B, BHMT2, DMGDH, MPHOSPH6, SLC47A1, NCEH1, FAHD2B, FAM50B, CYP39A1, MIGA2, CNKSR2, KCTD15, UBASH3B, ADAMTS1, TTC39B, MTERF3, ADAMTSL4, ZC3H12C, FBLN5, SMIM19, CCDC14, WDR73, PGBD5, OPLAH, RMI1, ZNRF2, NME9, ADI1, KCNQ5, KLHL34, RASA3, INSIG1, ZFTRAF1, ACTMAP, PARVB, TMEM120A, SIAH1, LAMA2, FBXL22, SLC9A8, MBP, STYX, UQCC6, FAM209B, ZGLP1, FTCDNL1, AP5Z1, KLC2, CCT6B, GNG5, SUSD5, SLC37A1, FAM177A1, TMEM140, PHF13, NODAL, AIFM1, CLDN12, FGF11, OMA1, LRRC52, NOSTRIN, ACSL6, TMEM65, GHITM, CKB, MVD, FOS, MTSS1, ZNF415, ZNF672, TMEM126A, ATF7IP, ZNF556, ID4, METAP1D, DHCR7, PC, GOLIM4, NR0B2, RSPH4A, ECSIT, SLC28A1, MPV17L, FCHO2, EOGT, KRTCAP2, SVEP1, WBP1L, C2, DISP1, TAF10, GSTM4, MAT2A, COMMD8, PLEKHA2, IFFO2, CRTAP, NDUFA3, HEG1, RCOR2, FBXO45, PTPRJ, FBXO10, CH25H, LAMC1, FBXL8, KRT7, ISCA1, TRIM45, RTN3, REEP2, SURF2, EXOC4, RFTN1, SLC27A1, DOCK4, PDCL3, ZNF710, OSGIN1, IGFBP4, PHIP, SLC6A6, MCCC2, CYB561D1, CALR, RTKN, RND3, CRYZ, PIK3R3, KLF12, PGF, DUSP1, RCL1, HYAL1, ZCCHC17, KCNJ2, MAD2L1BP, TIMM8A, ZNF835, ZNF780B, TST, ICE2, TNNT3, LIAS, CADM2, XRN1, QKI, ARHGEF37, SIGIRR, GP1BA, ZKSCAN4

Brain- Cortex

SLC36A1, RASSF8, SSPN, ITPR2, LRP1, ARHGEF6, SDC4, GDPD2, APOE, STK33, SLC44A2, ATP1B2, BBOX1, PALLD, CHAC1, CGNL1, SMO, MACF1, FGFR1, ATP13A4, MASP1, RHOF, AMOT, ARMC7, SOX9, SOX21, BBS2, SARDH, ATG101, AHNK, RREB1, NDP, EGLN3, SLC12A4, APPL2, HIGD1B, ITGAV, IDH1, HADHB, BCAR3, YAP1, TTPA, PRCP, SLC40A1, TUBB2B, IL33, TLR4, LRRC8A, MMD2, TNS3, EDNRB, THSD1, IGFBP1, SEMA7A, FGF2, BMP1B, CYP11A1, USP3, ETFA, FAM181A, RLBP1, GCSH, ACADS, PTGR2, STON2, PELI2, TMX1, GRTP1, ZIC5, TM6IM6, ASCL1, SLC01C1, FGD4, SERPINE2, SLC7A10, ITM2C, AGT, MEIS2, MRO, ADCK2, SLC41A1, WASF3, PPP1R3D, BCAN, VAV3, RIDA, RAMP1, IQCA1, SLC6A11, RHPN2, MCCC2, KHDRBS3, SH3BP5, POPDC3, NOTCH2, LDHA, IL6ST, NHSL1, ITGA7, NT5E, PNPLA8, MS1, SDS, PSAT1, OSTF1, CLDN10, DTNA, RAB33A, LRP4, SPX, RERG, SOX5, CABLES1, CRB1, GLUL, P4HA1, MAPKBP1, ACO1, HCN3, LACTB2, ZEB1, CCDC50, CABP1, LYPD5, PCNT, SLC2A6, PLPP7, TONSL, CCNF, TRIM46, SMIM12, PIP5KL1, MFSD3, CPLX1, RAC3, SNCG, PHOSPHO1, SH3BP5L, PLEKHD1, SLC25A22, CPNE7, PTPN11, PCGF5, SEMA6C, IGLON5, TRPM2, STAC2, WFIKK2, SLC22A6, SLC19A3, HBA2, HBA1, HBB, PASK, ACADM, KIF17, GPR68, SEC16B, TSHZ3, SLC35C1, TOX2, MINDY2, GGT7, RTBDN, SLC26A10P, HEY2, SLC9A5, ZFH2, MAP2K5, IMPA2, B4GALNT3, RHOF, ARRDC4, OVOL2, CNTFR, SKA2, CEND1, WLS, CTH, RAB29, CNN3, F3, PRDX6, DNAH7, NEK6, HSDL2, ALDH6A1, GPR75, OGFR1, GPAM, PPP1R3C, GNA13, MASTL, ADRA1A, RDH10, LRAT, ECHDC2, GJB6, FABP3, GPSM2, RWDD3, FKBP9, DOCK7, ANGPTL1, PARD3B, EPAS1, MYADML2, ATP6V0C, HYAL3, PDZD7, SLIT1, PALM3, KLHL17, FBLL1, TMEM198, ASB13, RAB40C, RPS6KL1, GALNT9, NOS1AP, ETRF1, CLEC2L, NME1, PLCXD2, ARHGDIG, TRNP1, XKR7, IGFBP2, OTX1, FHL2, PRKD3, SLC1A4, SDHD, SLC13A5, ROPN1L, PRDM16, SLC25A20, GRAMD1C, FKBP10, KCNJ10, TMEM94, FZD8, FIBIN, CCDC121, RMDN1, ACBD7, YES1, ORAI3, ARL4D, PHYHD1, IQCK, OPLAH, MSRB3, DPY19L3, GPC5, LHFPL1, HHIPL1, MOB2, IDH2, CHST15, SOX2, DHTKD1, NQO1, RNF182, FGD6, DCTPP1, MYADM, LRRC3B, PIPOX,

CDC42EP4, SNX18, ADI1, GOLIM4, DAG1, MCC, CHST11, MTM1, S1PR1, PAQR8, ADORA2B, EMX2, GPR37L1, P2RY1, ANTXR1, CCDC8, SDC2, NTSR2, ENHO, AHCYL1, ETFDH, ZNF622, LPAR3, GATM, TRIB1, STOX2, ZNF680, FUT10, EFEMP2, IL17D, SYNPO2, GNG12, STARD5, SUCLG2, ID4, SNTB1, CYP4F11, AQP4, BCL2, SLC25A33, LGI3, SLC25A18, PCP4, GSTM2, DIO2, DPF3, RGL3, ADGRG1, LGR4, C2orf72, MFAP3L, POU3F3, RYR3, MT1F, ASPH, SULT1C4, ELOVL2, ADH5, LCAT, PARVA, LEPROT, PLIN5, MMP28, IKBKG, FXYD1, RASSF5, SPON1, SALL3, CTSO, TRIL, LYN, ACY1, HOGA1, PLEKHO2, CD302, TMEM185B, PPP1R3G, POU2AF3, CADM1, SLC2A10, LRP10, WWOX, SLITRK2, ZFP36L1, DBX2, METTL7A, SEMA4B, SORCS2, LCN12, RBM43, POU3F2, MAML2, SLIT3, OAF, ZNF703, ZNRF3, RXRA, MAP3K5, TPCN1, EMID1, LAMB3, SLC30A10, AKR1C3, MYBPC1, MAOA, PTAR1, SLC38A3, NHS, WNT7B, NWD1, TMEM220, ATP13A5, PLCD1, TEAD1, C3orf70, PPARA, RAB31, TNNI3K, ACOX2, PITPNC1, IMPACT, MSI2, DDAH1, KCTD15, C16orf89, MERTK, ADGRA3, PLOD2, C4orf19, GJA1, SPARCL1, GABRA2, EPS8, NPAS3, SLC7A11, FREM2, PLCB3, PAMR1, HSD17B12, NADK2, TNIK, FAM167A, PDLIM3, TNFSF13, ZNF385A, ACOX1, GRIN2C, S100A1, TLCD1, EFCAB14, ALDH4A1, CACHD1, AHCYL2, ABHD3, DUSP2, GAREM2, CPT2, CD109, HKDC1, TSPAN7, WIF1, CFAP70, ACSS1, APCDD1, NPFFR1, FAM107A, ADD3, HTR7, CYP4V2, DDIT4L, SCD5, ALDH1L1, IGSF11, LRIG1, IL17RD, FAM171B, TMEFF2, SFXN5, ABHD1, CAMKMT, EPHX1, KCNN3, TP53BP2, SELENBP1, RXRG, ALDH9A1, SLC44A3, SYPL2, AZIN2, CENPV, FGF11, MYO10, FEM1C, GLUD1, RGR, SLC39A12, NACC2, STOM, NTRK2, AK3, PMP2, ADHFE1, RGS20, ERLIN2, CHST7, MSN, TMEM47, EGFR, GNA12, SLC2A12, SLC18B1, PRSS35, PSD2, SLC25A48, LIX1, ASRGL1, EIF4EBP2, VANG1, ADGRV1, RHOBTB3, ENPP6, PHKG1, ALDH7A1, BAALC, ABCA1, SLC16A9, HEPACAM, STOX1, NDRG2, SALL2, ARHGAP42, HTRA1, GPT2, RANBP3L, TPP1, SCRG1, POC1A, GABRG1, PDLIM5, INHBB, RFTN2, CAPN2, SLC15A2, DDR2, SDC3, AKR7A3, RAVR2, AK4, PLPP3, ACOT11, BDH2, INTU, ETNPPL, CENPN, RIMKLB, A2ML1, GABRB1, SCARA3, LRP5, PLIN4, TTYH1, AXL, PBXIP1, TBC1D16, ACSF2, ANKDD1A, PEX11A, ACAA2, LDHD

Table S6: 124 endocrine inter-tissue marker genes [Koplev. et. al., 2022] that overlap with our inter-tissue genes derived from the CT modules.

Gene Name
PRG2
LAMA2
ADAMTS1
SPON1
SLIT3
DAG1
INHBB
SPARCL1
THSD1
SPX
IL6ST
SDC4
IGFBP2
EGFL6
BMP1

CAMP
LCN2
HILPDA
GDF15
SLAMF1
C7
EPOR
GFOD1
CFHR1
RELN
TGFB3
NENF
LOX
CXCL8
GLT1D1
HBEGF
COL5A2
APOM
COL18A1
IGFBP7
BMP4
PPBP
ACE
C15orf61
IGIP
CXCL16
SVEP1
CRTAP
C2
FGF7
IGLON5
COL8A2
MFAP4
ADAMTS15
SLIT2
IL1RL1
CXCL1
FMOD
STC2
AGRN
CDNF
CES4A
PTEN
FNDC5

ADM
S100A13
PRELP
LAMB2
WNT10B
CCL3
CCL4
SVBP
GHR
ANTXR2
IL15RA
LAMA4
ADCYAP1
DNASE1
LBP
CD63
IGSF1
MMP19
LPL
EDIL3
GALNT1
TGFB1
FCGR3A
CDCP1
CXCL3
NLRP3
IL10
CHI3L1
IL16
ADAMTS16
IL1B
SPARC
LEPR
BMP5
CD164
SPP1
CXCL10
C1orf54
MIF
EGFLAM
LIFR
ADAMTS4
IL6
SRGN

HSPG2
VEGFA
CCDC126
QSOX2
PRDX4
FCGBP
LILRA2
CD163
EMILIN2
RNASE1
F13A1
DPT
RNASE6
IL18
C3
SERPINA1
QSOX1
QPCT
CRHBP
BCHE
ISG15