

**"Fluid Flow Shear Stress and Tissue Remodeling – an Orthodontic Perspective:
Evidence Synthesis and Differential Gene Expression Network analysis"**

**Results from the gene list analysis
Over-representation analysis (ORA)**

Contents

7 Introduction.....	2
7.1 General information	2
7.2 References	2
7.3 STRING network from the <i>Homo sapiens</i> (<i>H. s.</i>) gene list	3
7.3.1 Complete network.....	3
7.3.1.1 Characteristics of the complete network	3
7.3.1.2 Gene list enrichment analysis.....	4
7.3.1.3 Hub genes by cytoHubba.....	6
7.3.2 GLayer community detection.....	8
7.3.2.1 GLayer cluster #1 – Gene list enrichment	8
7.3.2.2 GLayer cluster #2 – Gene list enrichment	9
7.3.2.3 GLayer cluster #3 – Gene list enrichment	10
7.3.2.4 GLayer cluster #4 – Gene list enrichment	10
7.4 STRING network from the <i>Mus musculus</i> (<i>M.m.</i>) gene list	11
7.4.1 Complete network.....	11
7.4.1.1 Characteristics of the complete network	11
7.4.1.2 Gene list enrichment	12
7.4.1.3 Hub genes by cytoHubba.....	14
7.4.2 GLayer community clustering	16
7.4.2.1 GLayer cluster #1 – Gene list enrichment	16
7.4.2.2 GLayer cluster #2 – Gene list enrichment	17
7.4.2.3 GLayer cluster #3 – Gene list enrichment	18
7.4.2.4 GLayer cluster #4 – Gene list enrichment	18

7 Introduction

7.1 General information

For this systematic review, a previously published workflow (Sun et al. 2021) was adopted and applied as follows. Gene lists were generated from the extracted data ([Supplement 3](#)) and consisted of unambiguously identified genetic loci with reported gene expression after fluid flow application (differential expressed genes, DEGs). The gene lists were prepared for human and mouse cell types separately. Therefore, the human gene list consisted of DEGs identified in human primary periodontal ligament cells (hPDLs), human primary osteoblasts (hOBs), and human mesenchymal stem cells (hMSCs). The mouse gene list consisted of DEGs identified in mouse primary osteoblasts (mOBs) and the mouse immortalized osteocyte cell line MLO-Y4.

The following workflow was applied to each gene list:

- STRING search within *Cytoscape* version 3.9.1 (Shannon et al. 2003) using *stringApp* version 2.0.1 (Doncheva et al. 2019) with the following settings: species specified as either "*Homo sapiens*" or "*Mus musculus*", confidence cutoff set to 0.7; no further restrictions were applied
- The *stringApp* was used for STRING enrichment of the complete network and the identified clusters using GeneOntology/Biological Process (Thomas 2017), KEGG Pathways (Du et al. 2014), and WikiPathways (Martens et al. 2021; Pico et al. 2008). To increase specificity in the pathways and ontology terms a cut-off of > 0.05 (i.e., 5 %) was applied meaning that at least 5% of the genes from the gene list must be covered by the individual term (Sun et al. 2021) with a minimum of 4 genes from the specific gene list. General pathways related to cancer and/or infectious diseases like "Chagas disease" (hsa05142) or "Pertussis" (hsa05133) were removed, and their accession numbers were reported. From each database, the top 15 according to false discovery rate (FDR) value were reported if available.
- Clustering was applied with the GLay community detection algorithm (Su et al. 2010) as implemented in *clusterMaker2* version 2.3.4 (Morris et al. 2011) using default values. Each cluster was extracted as a separate network and individually analyzed with STRING enrichment.
- Hub genes were identified with *cytoHubba* (version 0.1) (Chin et al. 2014) as described (Sun et al. 2021): the total score cut-off was set to $\geq 2 \times$ mean SUMtotal score.

7.2 References

- Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY (2014). *cytoHubba*: identifying hub objects and sub-networks from complex interactome. BMC Syst Biol; 8(Suppl 4):S11.
- Doncheva NT, Morris JH, Gorodkin J, Jensen LJ (2019). Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data. Journal of Proteome Research; 18(2):623-632.
- Du J, Yuan Z, Ma Z, Song J, Xie X, Chen Y (2014). KEGG-PATH: Kyoto encyclopedia of genes and genomes-based pathway analysis using a path analysis model. Mol Biosyst; 10(9):2441-7.
- Martens M, Ammar A, Riutta A, Waagmeester A, Slenter DN, Hanspers K, R AM, Digles D, Lopes EN, Ehrhart F, Dupuis LJ, Winckers LA, Coort SL, Willighagen EL, Evelo CT, Pico AR, Kutmon M (2021). WikiPathways: connecting communities. Nucleic Acids Res; 49(D1):D613-D621.
- Morris JH, Apeltsin L, Newman AM, Baumbach J, Wittkop T, Su G, Bader GD, Ferrin TE (2011). *clusterMaker*: a multi-algorithm clustering plugin for Cytoscape. BMC Bioinformatics; 12:436.
- Pico AR, Kelder T, van Iersel MP, Hanspers K, Conklin BR, Evelo C (2008). WikiPathways: pathway editing for the people. PLoS Biol; 6(7):e184.
- Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res; 13(11):2498-504.
- Su G, Kuchinsky A, Morris JH, States DJ, Meng F (2010). GLay: community structure analysis of biological networks. Bioinformatics; 26(24):3135-7.
- Sun C, Janjic Rankovic M, Folwaczny M, Otto S, Wichelhaus A, Baumert U (2021). Effect of Tension on Human Periodontal Ligament Cells: Systematic Review and Network Analysis. Front Bioeng Biotechnol; 9:695053.
- Thomas PD (2017). The Gene Ontology and the Meaning of Biological Function. Methods Mol Biol; 1446:15-24.

7.3 STRING network from the *Homo sapiens* (*H. s.*) gene list

7.3.1 Complete network

7.3.1.1 Characteristics of the complete network

- Gene list consisted of 80 genetic loci.
- Contains data from the hMSC, hPDLF and hOBs data extraction tables
- Network characteristics of the undirected STRING network:

Parameter	Complete network	Connected network only
Number of nodes	80	73
Number of edges	308	308
Average number of neighbors	8.438	8.438
Network diameter	8	6
Network radius	6	4
Characteristic path length	2.613	2.613
Clustering coefficient	0.536	0.536
Network density	0.117	0.117
Network heterogeneity	0.758	0.753
Network centralization	0.265	0.265
Connected components	8	1

- STRING enrichment with all 80 nodes and for each of the clusters was done. The cut-off of 5% and a minimum content of 4 entries from the gene list were applied. The results were sorted according to the false discovery rate (FDR) value and the top 15 enrichment terms from each database were assembled into the tables. Some general terms, mostly dealing with cancer or specific infectious diseases, were removed. The database entries ("Term name") were reported.
- Hub genes were identified by application of a cut-off, that was defined as $\geq 2 \times \text{mean}(\text{SUMtotal})$.
- Clustering analysis applied with GLay community detection algorithm with default values detected 4 clusters with a minimum of 5 members with an average cluster size of 7.273 and an average modularity of 0.685.

Summary for the complete STRING network and the 4 clusters.

Gene list	Genes (n) in STRING network	Cluster number	Number of genes (n) and genes in cluster	Cluster score
H.s.	Genes in the H.s. PPI network (73): ADIPOQ, ALPL, BAX, BCL2, BGLAP, BMP2, BMP7, CCL3, CCL5, CD44, COL1A1, CXCL8, CYP24A1, CYP27B1, EGR1, ENG, FGF2, FOS, FOSB, FOSL1, FOSL2, GLI1, HIF1A, HMOX1, IBSP, IGF1, IGFBP1, IL1B, IL1RN, IL6, ITGB1, JUN, KDR, MAP3K8, MMP1, MMP2, MRTFA, MYH11, MYH2, NANOG, NFKB1, NOS1, NOS2, NOS3, PDGFA, PDGFRA, PDGFRB, PECAM1, POU5F1, PPARA, PTCH1, PTGES, PTGS1, PTGS2, RHOA, RUNX2, S100A4, S100A7, S100A8, SOX2, SP7, SPP1, TAGLN, TGFB1, THY1, TIMP1, TIMP2, TNFAIP6, TNFRSF11B, TNFSF11, VDR, VEGFA, VWF Genes outside the H.s. PPI network (7): DUSP6, GADD45B, IER3, PON1, TRPV1, TRPV4, WIF1 Hub genes (cut-off: SUMscore ≥ 4596.61 ; n=11): VEGFA, IL6, FGF2, IL1B, MMP2, TGFB1, MMP1, IGF1, TIMP1, RUNX2, JUN	1	(20) ALPL, BAX, BCL2, BGLAP, BMP2, BMP7, COL1A1, CYP24A1, CYP27B1, GLI1, IBSP, <u>IGF1</u> , IGFBP1, PTCH1, <u>RUNX2</u> , SP7, SPP1, TNFRSF11B, TNFSF11, VDR	0.191
		2	(26) ADIPOQ, CCL3, CCL5, CXCL8, HMOX1, <u>IL1B</u> , IL1RN, <u>IL6</u> , <u>JUN</u> , MAP3K8, <u>MMP1</u> , <u>MMP2</u> , NFKB1, NOS1, NOS2, NOS3, PPARA, PTGES, PTGS1, PTGS2, S100A7, <u>TGFB1</u> , <u>TIMP1</u> , TIMP2, TNFAIP6, <u>VEGFA</u>	0.239
		3	(22) CD44, ENG, <u>FGF2</u> , HIF1A, ITGB1, KDR, MRTFA, MYH11, MYH2, NANOG, PDGFA, PDGFRA, PDGFRB, PECAM1, POU5F1, RHOA, S100A4, S100A8, SOX2, TAGLN, THY1, VWF	0.211
		4	(5) EGR1, FOS, FOSB, FOSL1, FOSL2	0.044

7.3.1.2 Gene list enrichment analysis

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
522	30	0.057	Positive regulation of cell migration	4.54E-23	HMOX1, TGFB1, COL1A1, GLI1, TNFAIP6, PDGFRA, PDGFRB, IL1B, KDR, FGF2, THY1, NOS3, IGF1, CXCL8, PDGFA, PTGS2, S100A7, JUN, BMP2, BMP7, ITGB1, BCL2, IL6, RHOA, TRPV4, HIF1A, PECAM1, CCL5, CCL3, VEGFA	3.18E-26	GO:0030335
265	21	0.079	Ossification	1.47E-18	CYP24A1, MMP2, TGFB1, COL1A1, IBSP, CYP27B1, GLI1, IGF1, SOX2, PTGS2, BGLAP, RUNX2, ALPL, BMP2, SPP1, BMP7, BCL2, TNFSF11, RHOA, SP7, CCL3	5.95E-21	GO:0001503
313	19	0.061	Response to lipopolysaccharide	8.22E-15	TGFB1, NFKB1, CYP27B1, IL1B, NOS3, FOS, CXCL8, NOS2, PTGES, PTGS2, S100A7, S100A8, JUN, ALPL, IL6, RHOA, CCL5, CCL3, NOS1	5.82E-17	GO:0032496
338	19	0.056	Extracellular matrix organization	2.92E-14	TIMP1, MMP2, TGFB1, COL1A1, IBSP, PDGFRA, VWF, TIMP2, KDR, FGF2, TNFRSF11B, MMP1, PDGFA, ENG, SPP1, ITGB1, MYH11, CD44, PECAM1	2.23E-16	GO:0030198
292	18	0.062	Regulation of erk1 and erk2 cascade	4.16E-14	TGFB1, PDGFRA, PDGFRB, IL1B, KDR, FGF2, DUSP6, PDGFA, S100A7, JUN, BMP2, TNFSF11, ADIPOQ, CD44, TRPV4, CCL5, CCL3, VEGFA	3.30E-16	GO:0070372
315	18	0.057	Angiogenesis	1.36E-13	HMOX1, MMP2, PDGFRA, PDGFRB, KDR, FGF2, THY1, NOS3, CXCL8, PDGFA, PTGS2, S100A7, JUN, ENG, ITGB1, HIF1A, PECAM1, VEGFA	1.16E-15	GO:0001525
328	18	0.055	Response to steroid hormone	2.52E-13	TGFB1, COL1A1, FOSB, IL1RN, FOS, FOSL1, PTGS2, BGLAP, ENG, ALPL, SPP1, BMP7, BCL2, PPARA, IL6, ADIPOQ, RHOA, VDR	2.26E-15	GO:0048545
209	15	0.072	Positive regulation of erk1 and erk2 cascade	1.58E-12	TGFB1, PDGFRA, PDGFRB, KDR, FGF2, PDGFA, S100A7, JUN, BMP2, TNFSF11, CD44, TRPV4, CCL5, CCL3, VEGFA	1.54E-14	GO:0070374
52	10	0.192	Regulation of pri-mirna transcription by rna polymerase ii	6.13E-12	TGFB1, EGR1, POU5F1, FGF2, FOS, FOSL1, JUN, BMP2, PPARA, HIF1A	6.35E-14	GO:1902893
164	13	0.079	Response to corticosteroid	2.67E-11	COL1A1, FOSB, IL1RN, FOS, FOSL1, PTGS2, BGLAP, ENG, ALPL, BCL2, IL6, ADIPOQ, RHOA	3.08E-13	GO:0031960
127	12	0.094	Osteoblast differentiation	3.32E-11	CYP24A1, COL1A1, IBSP, GLI1, SOX2, BGLAP, RUNX2, ALPL, BMP2, SPP1, SP7, CCL3	3.88E-13	GO:0001649
29	8	0.276	Response to vitamin d	1.48E-10	CYP24A1, CYP27B1, PTGS2, BGLAP, ALPL, SPP1, BMP7, VDR	1.85E-12	GO:0033280
197	13	0.066	Regulation of ossification	2.12E-10	TGFB1, CYP27B1, GLI1, IGF1, PTCH1, BGLAP, RUNX2, BMP2, BMP7, BCL2, IL6, HIF1A, CCL3	2.75E-12	GO:0030278
160	12	0.075	Response to nutrient	3.70E-10	HMOX1, CYP24A1, COL1A1, CYP27B1, TNFRSF11B, PTGS2, BGLAP, ALPL, SPP1, BMP7, ADIPOQ, VDR	4.95E-12	GO:0007584
120	11	0.092	Odontogenesis	3.96E-10	COL1A1, PDGFRA, BAX, BGLAP, RUNX2, ALPL, BMP2, BMP7, TNFSF11, PPARA, RHOA	5.37E-12	GO:0042476
KEGG Pathways							
(Excluded: hsa05142, hsa05133, hsa04932, hsa05140, hsa05152, hsa05130, hsa05167)							
98	13	0.133	AGE-RAGE signaling pathway in diabetic complications	1.12E-13	MMP2, TGFB1, COL1A1, NFKB1, EGR1, IL1B, BAX, NOS3, CXCL8, JUN, BCL2, IL6, VEGFA	6.67E-16	hsa04933
130	14	0.108	Fluid shear stress and atherosclerosis	1.12E-13	HMOX1, MMP2, NFKB1, IL1B, KDR, NOS3, FOS, PDGFA, JUN, BCL2, RHOA, TRPV4, PECAM1, VEGFA	6.77E-16	hsa05418
92	12	0.130	IL-17 signaling pathway	9.47E-13	NFKB1, FOSB, IL1B, FOS, CXCL8, FOSL1, MMP1, PTGS2, S100A7, S100A8, JUN, IL6	1.13E-14	hsa04657
198	14	0.071	Focal adhesion	1.02E-11	COL1A1, IBSP, PDGFRA, VWF, PDGFRB, KDR, IGF1, PDGFA, JUN, SPP1, ITGB1, BCL2, RHOA, VEGFA	1.52E-13	hsa04510
85	11	0.129	Rheumatoid arthritis	1.02E-11	TGFB1, IL1B, FOS, CXCL8, MMP1, JUN, TNFSF11, IL6, CCL5, CCL3, VEGFA	1.67E-12	hsa05323
288	15	0.052	MAPK signaling pathway	6.08E-11	GADD45B, TGFB1, NFKB1, PDGFRA, PDGFRB, MAP3K8, IL1B, KDR, FGF2, DUSP6, IGF1, FOS, PDGFA, JUN, VEGFA	1.27E-12	hsa04010
78	10	0.128	EGFR tyrosine kinase inhibitor resistance	9.14E-11	PDGFRA, PDGFRB, KDR, FGF2, BAX, IGF1, PDGFA, BCL2, IL6, VEGFA	2.45E-12	hsa01521
196	13	0.066	Proteoglycans in cancer	9.14E-11	MMP2, TGFB1, COL1A1, NANOG, KDR, FGF2, IGF1, PTCH1, ITGB1, CD44, RHOA, HIF1A, VEGFA	2.59E-12	hsa05205
128	11	0.086	Relaxin signaling pathway	3.14E-10	MMP2, TGFB1, COL1A1, NFKB1, NOS3, FOS, MMP1, NOS2, JUN, NOS1, VEGFA	1.03E-11	hsa04926
101	10	0.099	Toll-like receptor signaling pathway	6.71E-10	NFKB1, MAP3K8, IL1B, FOS, CXCL8, JUN, SPP1, IL6, CCL5, CCL3	2.60E-11	hsa04620
103	10	0.097	Parathyroid hormone synthesis, secretion and action	7.46E-10	CYP24A1, CYP27B1, EGR1, FOS, BGLAP, RUNX2, BCL2, TNFSF11, RHOA, VDR	3.11E-11	hsa04928
106	10	0.094	HIF-1 signaling pathway	9.05E-10	HMOX1, TIMP1, NFKB1, NOS3, IGF1, NOS2, BCL2, IL6, HIF1A, VEGFA	4.04E-11	hsa04066
160	11	0.069	MicroRNAs in cancer	1.94E-09	HMOX1, CYP24A1, NFKB1, PDGFRA, PDGFRB, PDGFA, PTGS2, BCL2, CD44, RHOA, VEGFA	9.80E-11	hsa05206
122	10	0.082	Osteoclast differentiation	2.74E-09	TGFB1, NFKB1, FOSB, IL1B, FOSL2, TNFRSF11B, FOS, FOSL1, JUN, TNFSF11	1.47E-10	hsa04380
112	8	0.071	TNF signaling pathway	3.83E-07	NFKB1, MAP3K8, IL1B, FOS, PTGS2, JUN, IL6, CCL5	3.07E-08	hsa04668
WikiPathways							
(Excluded: WP3646, WP706, WP615, WP4707)							
270	25	0.093	IL-18 signaling pathway	1.09E-23	HMOX1, TIMP1, MMP2, COL1A1, NFKB1, IER3, IL1B, BAX, TNFRSF11B, FOS, CXCL8, MMP1, NOS2, PTGS2, JUN, RUNX2, BMP2, SPP1, BCL2, TNFSF11, IL6, ADIPOQ, CCL5, CCL3, VEGFA	1.61E-26	WP4754
63	14	0.222	Lung fibrosis	2.42E-17	HMOX1, TIMP1, MMP2, TGFB1, IL1B, FGF2, IGF1, CXCL8, PDGFA, SPP1, BMP7, IL6, CCL5, CCL3	7.13E-20	WP3624

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
196	14	0.071	Focal adhesion	2.26E-11	COL1A1, IBSP, PDGFRA, VWF, PDGFRB, KDR, IGF1, PDGFA, JUN, SPP1, ITGB1, BCL2, RHOA, VEGFA	1.33E-13	WP306
302	16	0.053	Focal adhesion: PI3K-Akt-mTOR-signaling pathway	2.26E-11	COL1A1, IBSP, PDGFRA, VWF, PDGFRB, KDR, FGF2, NOS3, IGF1, NOS2, PDGFA, SPP1, ITGB1, HIF1A, NOS1, VEGFA	1.61E-13	WP3932
182	13	0.071	Vitamin D receptor pathway	1.04E-10	CYP24A1, TGFB1, CYP27B1, TIMP2, IGFBP1, TNFRSF11B, BGLAP, S100A4, S100A8, SPP1, TNFSF11, HIF1A, VDR	1.07E-12	WP2877
14	7	0.500	Osteoblast signaling	1.19E-10	COL1A1, IBSP, PDGFRA, PDGFRB, TNFRSF11B, BGLAP, TNFSF11	1.58E-12	WP322
53	9	0.170	Cardiac progenitor differentiation	2.17E-10	TGFB1, NANOG, PDGFRA, POU5F1, KDR, FGF2, THY1, IGF1, SOX2	3.30E-12	WP2406
114	11	0.096	Gastrin signaling pathway	2.17E-10	NFKB1, EGR1, FOS, CXCL8, PTGS2, JUN, BMP2, ITGB1, CD44, RHOA, VEGFA	3.20E-12	WP4659
83	10	0.120	EGFR tyrosine kinase inhibitor resistance	2.25E-10	PDGFRA, PDGFRB, KDR, FGF2, BAX, IGF1, PDGFA, BCL2, IL6, VEGFA	4.31E-12	WP4806
35	8	0.229	Photodynamic therapy-induced NF-kB survival signaling	3.30E-10	MMP2, NFKB1, IL1B, CXCL8, MMP1, PTGS2, IL6, VEGFA	6.82E-12	WP3617
19	7	0.368	Overview of nanoparticle effects	3.97E-10	HMOX1, BAX, CXCL8, PTGS1, PTGS2, BCL2, IL6	8.77E-12	WP3287
91	10	0.110	Corticotropin-releasing hormone signaling pathway	4.24E-10	TGFB1, NFKB1, FOSB, FOSL2, NOS3, FOS, CXCL8, FOSL1, BCL2, RHOA	9.99E-12	WP2355
62	9	0.145	Endochondral ossification	4.69E-10	TGFB1, FGF2, IGF1, PTCH1, RUNX2, ALPL, SPP1, BMP7, VEGFA	1.18E-11	WP474
62	9	0.145	Endochondral ossification with skeletal dysplasias	4.69E-10	TGFB1, FGF2, IGF1, PTCH1, RUNX2, ALPL, SPP1, BMP7, VEGFA	1.18E-11	WP4808
103	10	0.097	Toll-like receptor signaling pathway	1.05E-09	NFKB1, MAP3K8, IL1B, FOS, CXCL8, JUN, SPP1, IL6, CCL5, CCL3	3.11E-11	WP75

7.3.1.3 Hub genes by cytoHubba

Top hub genes identified in the human STRING network derived from the human (n = 80) DEG list. Different score measures were calculated by cytoHubba (Chin et al. 2014). The cut-off was calculated (total score ≥ 4596.6) for this network (Sun et al. 2021). In this table, the genes were ordered in descending order according to the total score (above the dashed line). These hub genes were colored red in **Figure 5**.

Gene symbol	Local-based methods				Global-based methods							Total score (SUMscore)
	MCC	DMNC	MNC	Degree	EPC	BottleNeck	EcCentricity	Closeness	Radiality	Betweenness	Stress	
VEGFA	13848	0.43507	27	27	25.267	7	0.22813	47.75	4.84132	606.77843	3298	17892.30
IL6	13384	0.38528	26	26	24.612	16	0.22813	46.41667	4.7526	529.21808	3438	17495.61
FGF2	13014	0.41184	25	25	24.269	8	0.22813	45.5	4.72726	414.27583	2194	15755.41
IL1B	12324	0.44216	20	20	22.915	1	0.22813	43.41667	4.67656	265.59285	2026	14728.27
MMP2	11570	0.52927	14	14	21.578	2	0.22813	38.75	4.47378	123.37719	842	12630.94
TGFB1	11070	0.52077	15	15	21.686	5	0.22813	40.91667	4.62587	187.55267	1260	12620.53
MMP1	11042	0.64479	11	11	19.381	2	0.22813	38.08333	4.49913	76.44875	454	11659.29
IGF1	6021	0.42605	18	19	22.65	3	0.22813	42.16667	4.62587	366.18963	2086	8583.23
TIMP1	6552	0.64479	11	11	19.579	1	0.22813	37.58333	4.47378	39.22588	408	7084.73
RUNX2	2214	0.38589	16	18	19.324	7	0.22813	42.25	4.65122	926.30616	3724	6972.15
JUN	939	0.36854	19	20	21.127	6	0.22813	43.66667	4.71458	774.21035	2978	4806.32
SPP1	2258	0.44871	16	16	20.191	12	0.22813	40.58333	4.58785	238.62252	1276	3882.66
ITGB1	425	0.38056	15	16	19.675	3	0.22813	39.33333	4.47378	478.34297	2604	3605.43
CD44	1444	0.41146	20	20	22.896	2	0.22813	42.25	4.60052	229.02873	1320	3105.41
BGLAP	2186	0.55995	11	11	16.026	4	0.22813	35.41667	4.28368	105.72414	664	3038.24
BMP2	1501	0.4726	13	14	18.239	2	0.22813	38.58333	4.47378	200.99715	1012	2804.99
CXCL8	1233	0.4726	13	14	19.065	2	0.22813	39.41667	4.52448	212.09527	1222	2759.80
COL1A1	1514	0.44706	13	13	19.344	2	0.22813	37.83333	4.43576	119.10746	684	2407.40
SP7	2160	0.69213	9	9	14.849	1	0.22813	33.25	4.16962	4.26216	44	2280.45
HIF1A	888	0.43064	15	15	21.237	4	0.22813	41	4.63854	168.50333	1024	2182.04
IBSP	1452	0.57279	9	9	16.012	1	0.22813	34.75	4.29635	50.66444	330	1907.52
PTGS2	386	0.64146	8	10	15.327	3	0.22813	36.25	4.38507	288.83725	1038	1790.67
RHOA	76	0.4082	8	8	14.465	4	0.22813	35.33333	4.3724	267.23542	1344	1762.04
FOS	154	0.30655	13	13	16.652	3	0.22813	39.33333	4.5625	255.5747	1182	1681.66
VDR	4	0.30779	2	4	5.811	3	0.1825	27.93333	3.81476	280	1252	1583.05
TNFSF11	738	0.45891	10	10	17.545	1	0.22813	37.5	4.49913	76.73088	684	1579.96
NFKB1	25	0.56839	4	5	10.041	2	0.1825	30	3.94149	142	1034	1256.73
KDR	606	0.49759	12	12	18.515	1	0.22813	37.66667	4.44844	64.69924	442	1199.06
NOS3	222	0.44117	11	11	16.31	2	0.22813	37.25	4.43576	130.88846	758	1193.55
TNFRSF11B	723	0.5854	7	8	14.494	1	0.22813	35.5	4.39774	40.14662	318	1152.35
MYH2	5	0.30898	3	4	5.233	2	0.1825	26.8	3.65	147.03333	876	1073.21
CCL5	272	0.47733	9	9	15.588	2	0.22813	36.25	4.41042	86.88346	586	1021.84
PECAM1	648	0.57691	11	11	18.171	1	0.22813	36.5	4.38507	27.13656	192	950.00
ENG	606	0.54298	11	11	17.569	1	0.22813	36.66667	4.39774	30.01735	196	914.42
ALPL	720	0.71324	6	6	11.571	1	0.1825	30.7	4.03021	0	0	780.20
MRTFA	2	0	1	2	3.492	2	0.1825	25.63333	3.61198	88.29837	530	658.22
HMOX1	252	0.52483	8	8	14.249	2	0.1825	33.98333	4.22031	40.73981	284	647.90
BAX	2	0	1	2	3.769	2	0.1825	26.76667	3.77674	142	442	625.49
NOS2	248	0.49567	8	8	12.709	2	0.1825	33.65	4.19497	40.06345	264	621.30
PDGFRB	218	0.45891	10	10	18.032	3	0.22813	36.58333	4.41042	30.33452	258	589.05
VWF	265	0.62199	7	8	15.494	1	0.22813	35.16667	4.35972	23.00077	140	499.87
MYH11	3	0.30779	2	3	3.591	1	0.1825	24.96667	3.53594	51.70163	326	419.29
THY1	216	0.52506	9	9	15.914	1	0.22813	33.91667	4.22031	19.10858	84	392.91
SOX2	150	0.54881	7	7	13.805	1	0.22813	33.5	4.23299	12.55508	76	305.87
NANOG	150	0.54881	7	7	13.682	1	0.22813	33.5	4.23299	12.55508	76	305.75
PDGFRA	144	0.61814	6	6	13.283	1	0.22813	33.91667	4.30903	4.74409	68	282.10
POU5F1	168	0.5854	7	7	12.483	1	0.22813	32.5	4.15694	2.29372	16	251.25
ADIPOQ	25	0.56839	4	5	11.69	1	0.1825	32.73333	4.20764	27.11053	98	209.49
CCL3	120	0.64826	5	5	11.671	1	0.1825	31.68333	4.11892	0	0	179.30
FOSL2	120	0.64826	5	5	8.302	1	0.1825	29.23333	3.91615	0	0	173.28
FOSL1	120	0.64826	5	5	7.74	1	0.1825	29.23333	3.91615	0	0	172.72
EGR1	120	0.64826	5	5	7.652	1	0.1825	29.23333	3.91615	0	0	172.63
FOSB	120	0.64826	5	5	7.545	1	0.1825	29.23333	3.91615	0	0	172.53
PDGFA	32	0.42794	6	6	12.693	1	0.22813	32.25	4.1316	3.35105	22	120.08
S100A8	3	0.30779	2	3	8.626	1	0.1825	30.01667	4.03021	6.96859	56	115.13
GLI1	2	0	1	2	3.617	1	0.1825	26.76667	3.77674	11.13053	46	97.47
PPARA	3	0.30779	2	3	6.985	1	0.1825	28.56667	3.92882	4.33333	16	69.30
BMP7	6	0.46346	3	3	7.933	1	0.1825	29.81667	4.01753	0	0	55.41
IL1RN	6	0.46346	3	3	8.655	1	0.1825	28.83333	3.90347	0	0	55.04
NOS1	6	0.46346	3	3	6.327	1	0.1825	25.66667	3.59931	0	0	49.24
PTCH1	2	0	1	2	3.676	1	0.1825	25.26667	3.59931	2.00362	8	48.73
TIMP2	2	0.30779	2	2	6.04	1	0.1825	26.08333	3.70069	0	0	43.31
TNFAIP6	2	0.30779	2	2	5.472	1	0.1825	25.66667	3.65	0	0	42.28
PTGS1	2	0.30779	2	2	3.57	1	0.1825	24.25	3.49792	0	0	38.81
PTGES	2	0.30779	2	2	3.458	1	0.1825	24.25	3.49792	0	0	38.70
S100A7	1	0	1	1	3.815	1	0.1825	26.65	3.81476	0	0	38.46
IGFBP1	1	0	1	1	3.748	1	0.1825	25.98333	3.72604	0	0	37.64

Gene symbol	Local-based methods				Global-based methods							Total score (SUMscore)
	MCC	DMNC	MNC	Degree	EPC	BottleNeck	EcCentricity	Closeness	Radiality	Betweenness	Stress	
TAGLN	2	0	1	2	1.855	1	0.15208	19.98333	2.77552	2	2	34.77
CYP27B1	2	0.30779	2	2	2.187	1	0.15208	20.48333	2.9276	0	0	33.06
CYP24A1	2	0.30779	2	2	2.076	1	0.15208	20.48333	2.9276	0	0	32.95
MAP3K8	1	0	1	1	2.519	1	0.15208	20.93333	3.04167	0	0	30.65
BCL2	1	0	1	1	1.533	1	0.15208	19.56667	2.87691	0	0	28.13
S100A4	1	0	1	1	1.636	1	0.15208	19.31667	2.75017	0	0	27.85
DUSP6	0	0	0	0	1	0	0	0	0	0	0	1.00
IER3	0	0	0	0	1	0	0	0	0	0	0	1.00
TRPV1	0	0	0	0	1	0	0	0	0	0	0	1.00
PON1	0	0	0	0	1	0	0	0	0	0	0	1.00
TRPV4	0	0	0	0	1	0	0	0	0	0	0	1.00
WIF1	0	0	0	0	1	0	0	0	0	0	0	1.00
GADD45B	0	0	0	0	1	0	0	0	0	0	0	1.00

7.3.2 GLayer community detection

7.3.2.1 GLayer cluster #1 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
265	15	0.057	Ossification	2.73E-20	CYP24A1, COL1A1, IBSP, CYP27B1, GLI1, IGF1, BGLAP, RUNX2, ALPL, BMP2, SPP1, BMP7, BCL2, TNFSF11, SP7	2.13E-24	GO:0001503
127	10	0.079	Osteoblast differentiation	2.25E-13	CYP24A1, COL1A1, IBSP, GLI1, BGLAP, RUNX2, ALPL, BMP2, SPP1, SP7	3.50E-17	GO:0001649
29	7	0.241	Response to vitamin d	1.24E-11	CYP24A1, CYP27B1, BGLAP, ALPL, SPP1, BMP7, VDR	2.90E-15	GO:0033280
84	8	0.095	Response to vitamin	6.71E-11	CYP24A1, COL1A1, CYP27B1, BGLAP, ALPL, SPP1, BMP7, VDR	2.09E-14	GO:0033273
160	9	0.056	Response to nutrient	8.51E-11	CYP24A1, COL1A1, CYP27B1, TNFRSF11B, BGLAP, ALPL, SPP1, BMP7, VDR	3.31E-14	GO:0007584
92	8	0.087	Biomineral tissue development	8.90E-11	COL1A1, IBSP, CYP27B1, IGF1, BGLAP, ALPL, BMP2, SPP1	4.16E-14	GO:0031214
120	8	0.067	Odontogenesis	3.67E-10	COL1A1, BAX, BGLAP, RUNX2, ALPL, BMP2, BMP7, TNFSF11	3.14E-13	GO:0042476
77	6	0.078	Regulation of tissue remodeling	8.80E-08	BAX, TNFRSF11B, BGLAP, SPP1, TNFSF11, VDR	1.78E-10	GO:0034103
117	6	0.051	Regulation of osteoblast differentiation	6.98E-07	GLI1, IGF1, PTCH1, RUNX2, BMP2, BMP7	1.96E-09	GO:0045667
50	5	0.100	Bone mineralization	7.56E-07	IBSP, CYP27B1, IGF1, BGLAP, BMP2	2.18E-09	GO:0030282
24	4	0.167	Cellular response to vitamin	4.55E-06	CYP24A1, COL1A1, BGLAP, VDR	1.59E-08	GO:0071295
33	4	0.121	Positive regulation of tissue remodeling	1.30E-05	BAX, SPP1, TNFSF11, VDR	5.11E-08	GO:0034105
43	4	0.093	Regulation of bone resorption	3.20E-05	TNFRSF11B, BGLAP, SPP1, TNFSF11	1.37E-07	GO:0045124
60	4	0.067	Positive regulation of osteoblast differentiation	9.26E-05	IGF1, RUNX2, BMP2, BMP7	4.83E-07	GO:0045669
75	4	0.053	Regulation of bone mineralization	1.70E-04	CYP27B1, BGLAP, BMP2, BMP7	1.13E-06	GO:0030500
KEGG Pathways							
103	7	0.068	Parathyroid hormone synthesis, secretion and action	3.56E-09	CYP24A1, CYP27B1, BGLAP, RUNX2, BCL2, TNFSF11, VDR	1.06E-11	hsa04928
62	4	0.065	Basal cell carcinoma	9.19E-05	GLI1, BAX, PTCH1, BMP2	5.47E-07	hsa05217
WikiPathways							
14	5	0.357	Osteoblast signaling	5.05E-09	COL1A1, IBSP, TNFRSF11B, BGLAP, TNFSF11	7.44E-12	WP322
62	6	0.097	Endochondral ossification	1.18E-08	IGF1, PTCH1, RUNX2, ALPL, SPP1, BMP7	5.21E-11	WP474
62	6	0.097	Endochondral ossification with skeletal dysplasias	1.18E-08	IGF1, PTCH1, RUNX2, ALPL, SPP1, BMP7	5.21E-11	WP4808
15	4	0.267	OSX and miRNAs in tooth development	3.43E-07	RUNX2, ALPL, BMP7, SP7	3.03E-09	WP3971
22	4	0.182	FGF23 signaling in hypophosphatemic rickets and related disorders	1.13E-06	CYP24A1, CYP27B1, ALPL, SPP1	1.16E-08	WP4790
33	4	0.121	Type I collagen synthesis in the context of osteogenesis imperfecta	4.33E-06	COL1A1, TNFRSF11B, TNFSF11, SP7	5.11E-08	WP4786
44	4	0.091	Interleukin-11 signaling pathway	1.13E-05	IBSP, BGLAP, RUNX2, BCL2	1.49E-07	WP2332
55	4	0.073	Overlap between signal transduction pathways contributing to LMNA laminopathies	2.14E-05	TNFRSF11B, RUNX2, BMP2, SPP1	3.47E-07	WP4879

7.3.2.2 GLayer cluster #2 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
136	8	0.059	Regulation of smooth muscle cell proliferation	3.40E-09	HMOX1, MMP2, NOS3, PTGS2, JUN, IL6, ADIPOQ, CCL5	9.78E-12	GO:0048660
144	8	0.056	Positive regulation of small molecule metabolic process	4.86E-09	NFKB1, IL1B, NOS3, NOS2, PTGS2, PPARA, ADIPOQ, NOS1	1.51E-11	GO:0062013
34	5	0.147	Lipopolysaccharide-mediated signaling pathway	2.42E-07	TGFB1, IL1B, NOS3, CCL5, CCL3	1.53E-09	GO:0031663
88	6	0.068	Positive regulation of smooth muscle cell proliferation	3.36E-07	HMOX1, MMP2, PTGS2, JUN, IL6, CCL5	2.21E-09	GO:0048661
98	6	0.061	Positive regulation of leukocyte chemotaxis	5.64E-07	CXCL8, S100A7, IL6, CCL5, CCL3, VEGFA	4.08E-09	GO:0002690
49	5	0.102	Negative regulation of blood pressure	1.03E-06	NOS3, NOS2, PPARA, ADIPOQ, NOS1	8.28E-09	GO:0045776
56	5	0.089	Positive regulation of blood vessel endothelial cell migration	1.70E-06	HMOX1, TGFB1, NOS3, PTGS2, VEGFA	1.55E-08	GO:0043536
23	4	0.174	Positive regulation of cyclase activity	4.23E-06	TIMP2, NOS3, NOS2, NOS1	4.19E-08	GO:0031281
24	4	0.167	Positive regulation of lyase activity	4.79E-06	TIMP2, NOS3, NOS2, NOS1	4.88E-08	GO:0051349
28	4	0.143	Positive regulation of vascular endothelial growth factor production	7.90E-06	TGFB1, IL1B, PTGS2, IL6	8.54E-08	GO:0010575
81	5	0.062	Granulocyte chemotaxis	8.13E-06	IL1B, CXCL8, CCL5, CCL3, VEGFA	8.86E-08	GO:0071621
36	4	0.111	Positive regulation of fatty acid metabolic process	1.68E-05	IL1B, PTGS2, PPARA, ADIPOQ	2.16E-07	GO:0045923
38	4	0.105	Protein kinase b signaling	1.99E-05	TGFB1, IL1B, CCL5, CCL3	2.63E-07	GO:0043491
52	4	0.077	Regulation of vascular associated smooth muscle cell proliferation	5.57E-05	HMOX1, MMP2, JUN, ADIPOQ	8.54E-07	GO:1904705
KEGG Pathways (Excluded: hsa05142, hsa05140, hsa05133, hsa05146, hsa05321, hsa05144, hsa05134, hsa04932)							
85	9	0.106	Rheumatoid arthritis	8.93E-13	TGFB1, IL1B, CXCL8, MMP1, JUN, IL6, CCL5, CCL3, VEGFA	2.66E-15	hsa05323
98	9	0.092	AGE-RAGE signaling pathway in diabetic complications	1.49E-12	MMP2, TGFB1, NFKB1, IL1B, NOS3, CXCL8, JUN, IL6, VEGFA	8.87E-15	hsa04933
128	9	0.070	Relaxin signaling pathway	7.27E-12	MMP2, TGFB1, NFKB1, NOS3, MMP1, NOS2, JUN, NOS1, VEGFA	8.65E-14	hsa04926
92	8	0.087	IL-17 signaling pathway	3.37E-11	NFKB1, IL1B, CXCL8, MMP1, PTGS2, S100A7, JUN, IL6	5.02E-13	hsa04657
101	8	0.079	Toll-like receptor signaling pathway	5.69E-11	NFKB1, MAP3K8, IL1B, CXCL8, JUN, IL6, CCL5, CCL3	1.02E-12	hsa04620
106	7	0.066	HIF-1 signaling pathway	3.95E-09	HMOX1, TIMP1, NFKB1, NOS3, NOS2, IL6, VEGFA	1.06E-10	hsa04066
112	7	0.063	TNF signaling pathway	5.13E-09	NFKB1, MAP3K8, IL1B, PTGS2, JUN, IL6, CCL5	1.53E-10	hsa04668
130	7	0.054	Fluid shear stress and atherosclerosis	1.15E-08	HMOX1, MMP2, NFKB1, IL1B, NOS3, JUN, VEGFA	4.12E-10	hsa05418
62	4	0.065	Cytosolic DNA-sensing pathway	2.15E-05	NFKB1, IL1B, IL6, CCL5	1.66E-06	hsa04623
67	4	0.060	Epithelial cell signaling in Helicobacter pylori infection	2.65E-05	NFKB1, CXCL8, JUN, CCL5	2.23E-06	hsa05120
WikiPathways (Excluded: WP3646, WP5113, WP2431, WP5039, WP4891)							
270	15	0.056	IL-18 signaling pathway	8.67E-19	HMOX1, TIMP1, MMP2, NFKB1, IL1B, CXCL8, MMP1, NOS2, PTGS2, JUN, IL6, ADIPOQ, CCL5, CCL3, VEGFA	1.28E-21	WP4754
63	9	0.143	Lung fibrosis	4.89E-14	HMOX1, TIMP1, MMP2, TGFB1, IL1B, CXCL8, IL6, CCL5, CCL3	2.16E-16	WP3624
35	8	0.229	Photodynamic therapy-induced NF-kB survival signaling	6.94E-14	MMP2, NFKB1, IL1B, CXCL8, MMP1, PTGS2, IL6, VEGFA	4.09E-16	WP3617
10	6	0.600	Aspirin and miRNAs	3.16E-12	NFKB1, NOS3, PTGS1, PTGS2, PPARA, VEGFA	2.33E-14	WP4707
103	8	0.078	Toll-like receptor signaling pathway	1.33E-10	NFKB1, MAP3K8, IL1B, CXCL8, JUN, IL6, CCL5, CCL3	1.18E-12	WP75
32	6	0.188	Signal transduction through IL1R	6.67E-10	TGFB1, NFKB1, IL1RN, IL1B, JUN, IL6	7.87E-12	WP4496
139	8	0.058	Regulation of toll-like receptor signaling pathway	8.70E-10	NFKB1, MAP3K8, IL1B, CXCL8, JUN, IL6, CCL5, CCL3	1.16E-11	WP1449
155	8	0.052	Nonalcoholic fatty liver disease	1.80E-09	TGFB1, NFKB1, IL1B, CXCL8, JUN, PPARA, IL6, ADIPOQ	2.66E-11	WP4396
19	5	0.263	Overview of nanoparticle effects	7.05E-09	HMOX1, CXCL8, PTGS1, PTGS2, IL6	1.14E-10	WP3287
89	6	0.067	T-cell receptor (TCR) signaling pathway	1.07E-07	TGFB1, NFKB1, MAP3K8, IL1B, JUN, IL6	2.36E-09	WP69
46	5	0.109	NO/cGMP/PKG mediated neuroprotection	2.57E-07	NFKB1, IL1B, NOS3, NOS2, NOS1	6.17E-09	WP4008
105	6	0.057	Senescence and autophagy in cancer	2.57E-07	TGFB1, IL1B, CXCL8, JUN, IL6, CCL3	6.06E-09	WP615
19	4	0.211	LTF danger signal response pathway	7.57E-07	NFKB1, IL1B, CXCL8, IL6	2.12E-08	WP4478
66	5	0.076	AGE/RAGE pathway	1.14E-06	MMP2, NFKB1, NOS3, NOS2, JUN	3.36E-08	WP2324
24	4	0.167	IL1 and megakaryocytes in obesity	1.58E-06	TIMP1, NFKB1, TIMP2, IL1B	4.88E-08	WP2865

7.3.2.3 GLayer cluster #3 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
67	5	0.075	Endothelial cell migration	3.83E-06	KDR, FGF2, ITGB1, RHOA, PECAM1	1.46E-08	GO:0043542
56	4	0.071	Leukocyte cell-cell adhesion	7.71E-05	S100A8, ITGB1, CD44, PECAM1	5.58E-07	GO:0007159
62	4	0.065	Myofibril assembly	1.00E-04	PDGFRA, PDGFRB, ITGB1, MYH11	8.21E-07	GO:0030239
65	4	0.062	Somatic stem cell population maintenance	1.20E-04	NANOG, POU5F1, FGF2, SOX2	9.83E-07	GO:0035019
75	4	0.053	Positive regulation of lipase activity	1.80E-04	PDGFRA, PDGFRB, FGF2, RHOA	1.70E-06	GO:0060193
KEGG Pathways (Excluded: hsa05218)							
78	5	0.064	EGFR tyrosine kinase inhibitor resistance	2.02E-06	PDGFRA, PDGFRB, KDR, FGF2, PDGFA	3.01E-08	hsa01521
WikiPathways							
53	7	0.132	Cardiac progenitor differentiation	1.97E-10	NANOG, PDGFRA, POU5F1, KDR, FGF2, THY1, SOX2	2.90E-13	WP2406
24	4	0.167	Angiogenesis	4.07E-06	PDGFRA, KDR, FGF2, HIF1A	2.40E-08	WP1539
83	5	0.060	EGFR tyrosine kinase inhibitor resistance	5.48E-06	PDGFRA, PDGFRB, KDR, FGF2, PDGFA	4.04E-08	WP4806

7.3.2.4 GLayer cluster #4 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Category	Description	FDR value	Genes	p-value	Term name
33	5	0.152	STRING Clusters	Mixed, incl. bzip maf transcription factor, and bhlh transcription factor binding	9.54E-11	EGR1, FOSB, FOSL2, FOS, FOSL1	2.10E-14	CL:6308
8	4	0.500	STRING Clusters	Mixed, incl. ap-1 transcription factor, and arc, c-lobe	6.13E-10	EGR1, FOSB, FOSL2, FOS	4.05E-13	CL:6326
9	4	0.444	InterPro Domains	AP-1 transcription factor	3.96E-09	FOSB, FOSL2, FOS, FOSL1	5.85E-13	IPR000837
36	4	0.111	Pfam	bZIP transcription factor	1.86E-07	FOSB, FOSL2, FOS, FOSL1	7.47E-11	PF00170
33	4	0.121	Pfam	bZIP Maf transcription factor	1.86E-07	FOSB, FOSL2, FOS, FOSL1	5.40E-11	PF03131
44	4	0.091	Pfam	Basic region leucine zipper	1.86E-07	FOSB, FOSL2, FOS, FOSL1	1.59E-10	PF07716
39	4	0.103	Reactome Pathways	NGF-stimulated transcription	2.19E-07	EGR1, FOSB, FOS, FOSL1	1.01E-10	HSA-9031628
54	4	0.074	InterPro Domains	Basic-leucine zipper domain	1.17E-06	FOSB, FOSL2, FOS, FOSL1	3.46E-10	IPR004827
38	3	0.079	SMART Domains	Basic region leucine zipper	6.18E-05	FOSL2, FOS, FOSL1	8.51E-08	SM00338
20	3	0.150	GO Biological Process	Response to corticosterone	1.80E-04	FOSB, FOS, FOSL1	1.42E-08	GO:0051412
40	3	0.075	GO Biological Process	Positive regulation of pri-mirna transcription by rna polymerase ii	4.20E-04	EGR1, FOS, FOSL1	9.85E-08	GO:1902895
45	3	0.067	GO Biological Process	Response to progesterone	4.40E-04	FOSB, FOS, FOSL1	1.38E-07	GO:0032570
11	2	0.182	GO Biological Process	Response to gravity	0.0057	FOS, FOSL1	4.07E-06	GO:0009629

7.4 STRING network from the *Mus musculus* (M.m.) gene list

7.4.1 Complete network

7.4.1.1 Characteristics of the complete network

- Gene list of 76 genetic loci
- Contains data from the osteoblast and osteocyte data extraction tables
- Network characteristics of the undirected STRING network:

Parameter	Complete network	Connected network only
Number of nodes	76	74
Number of edges	346	346
Average number of neighbors	9.351	9.351
Network diameter	5	5
Network radius	3	3
Characteristic path length	2.409	2.409
Clustering coefficient	0.584	0.584
Network density	0.128	0.128
Network heterogeneity	0.757	0.757
Network centralization	0.446	0.446
Connected components	3	1

- STRING enrichment with complete network
- Hub genes were identified by application of a cut-off, that was defined as $\geq 2 \times \text{mean}(\text{SUMtotal})$.
- Clustering analysis applied with GLayer with default values generated 4 clusters with an average size of 12.667. The modularity was 0.621 with clusters ranging from 1 (unclustered genes) to 33.
- For each cluster STRING enrichment was applied.

Gene list	Genes (n) in STRING network	Cluster number	Number of genes (n) and genes in cluster	Cluster score
<i>M.m.</i>	Genes in the <i>M.m.</i> PPI network (74): Actb, Alpl, Apc, Axin1, Bad, Bax, Bglap, Bmpr1a, Casp3, Ccl7, Ccna2, Ccnd1, Cd44, Ctnnb1, Cxcl1, Cxcl2, Dkk1, Dkk2, Dlx1, Dlx5, Dmp1, Esr1, Fabp4, Fos, Fzd6, Gja1, Gjc1, Hgf, Igf1, Igf1r, Il11, Il6, Itgav, Itgb3, Jun, Lef1, Lepr, Lif, Lpl, Lrp5, Mepe, Mki67, Mmp14, Ncoa1, Nos2, Npy, Pdpn, Phex, Piezo1, Pkd1, Pkd2, Pparg, Ptger2, Ptgs1, Ptgs2, Runx2, Sfrp1, Sfrp2, Sfrp4, Sost, Sp7, Spp1, Tgfb1, Tjp1, Tnf, Tnfrsf11b, Tnfsf11, Tuba1a, Vcl, Vegfa, Wnt1, Wnt3a, Wnt4, Wnt5a Genes outside the <i>M.m.</i> PPI network (2): Eral1, Piezo2 Hub genes (cut-off: SUMscore ≥ 12622.9; n=12): Ctnnb1, Wnt1, Wnt3a, Wnt5a, Dkk1, Wnt4, Lrp5, Sfrp1, Il6, Tnf, Actb, Jun	1	(21) Apc, Axin1, Bad, Bax, Casp3, Ccn1, Ccnd1, Dkk1, Dkk2, Esr1, Fzd6, Lef1, <u>Lrp5</u> , Mki67, <u>Sfrp1</u> , Sfrp2, Sfrp4, <u>Wnt1</u> , <u>Wnt3a</u> , Wnt4, <u>Wnt5a</u>	0.223
		2	(33) <u>Actb</u> , Ccl7, Cd44, Cxcl1, Cxcl2, Fabp4, Fos, Hgf, Igf1, Igf1r, Il11, <u>Il6</u> , Itgav, Itgb3, <u>Jun</u> , Lepr, Lif, Lpl, Mmp14, Ncoa1, Nos2, Npy, Pdpn, Pparg, Ptger2, Ptgs1, Ptgs2, Spp1, Tgfb1, <u>Tnf</u> , Tnfrsf11b, Tnfsf11, Vegfa	0.25
		3	(10) Bmpr1a, <u>Ctnnb1</u> , Gja1, Gjc1, Piezo1, Pkd1, Pkd2, Tjp1, Tuba1a, Vcl	0.06
		4	(10) Alpl, Bglap, Dlx1, Dlx5, Dmp1, Mepe, Phex, Runx2, Sost, Sp7	0.088

7.4.1.2 Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
493	27	0.055	Gland development	2.05E-22	Tgfb1, Cd44, Igf1r, Ctnnb1, Wnt3a, Tnfsf11, Wnt1, Tnf, Lrp5, Il6, Lef1, Hgf, Mki67, Sfrp1, Bmpr1a, Wnt4, Pkd1, Igf1, Gja1, Wnt5a, Esr1, Apc, Ncoa1, Pkd2, Ccnd1, Jun, Vegfa	5.26E-25	GO:0048732
210	20	0.095	Regulation of animal organ morphogenesis	1.84E-20	Tgfb1, Ctnnb1, Wnt3a, Fzd6, Tnf, Dkk1, Sfrp2, Hgf, Bax, Sfrp1, Bmpr1a, Wnt4, Wnt5a, Lif, Dmp1, Esr1, Apc, Tnfsf11b, Runx2, Vegfa	6.14E-23	GO:2000027
224	20	0.089	Regulation of ossification	5.46E-20	Sost, Tgfb1, Ctnnb1, Tnf, Dkk1, Lrp5, Il6, Sfrp2, Sfrp1, Bmpr1a, Wnt4, Dlx5, Igf1, Gja1, Wnt5a, Mepe, Bglap, Apc, Runx2, Vegfa	2.03E-22	GO:0030278
243	20	0.082	Wnt signaling pathway	2.09E-19	Sost, Sfrp4, Cd44, Ctnnb1, Wnt3a, Fzd6, Wnt1, Dkk1, Lrp5, Lef1, Sfrp2, Dkk2, Sfrp1, Wnt4, Pkd1, Wnt5a, Axin1, Apc, Pkd2, Ccnd1	9.23E-22	GO:0016055
240	19	0.079	Ossification	3.96E-18	Sost, Tgfb1, Wnt3a, Tnfsf11, Lrp5, Lef1, Alpl, Sfrp1, Ptg2, Dlx5, Igf1, Gja1, Dmp1, Bglap, Sp7, Phex, Mmp14, Spp1, Runx2	2.17E-20	GO:0001503
365	21	0.058	Regulation of epithelial cell proliferation	1.37E-17	Pparg, Tgfb1, Ctnnb1, Wnt3a, Itgb3, Tnf, Bad, Il6, Sfrp2, Bax, Sfrp1, Bmpr1a, Dlx5, Igf1, Gja1, Wnt5a, Esr1, Apc, Ccnd1, Jun, Vegfa	8.39E-20	GO:0050678
195	17	0.087	Morphogenesis of a branching epithelium	7.9E-17	Tgfb1, Cd44, Ctnnb1, Wnt1, Lrp5, Il6, Lef1, Sfrp2, Sfrp1, Wnt4, Pkd1, Igf1, Wnt5a, Esr1, Pkd2, Mmp14, Vegfa	5.88E-19	GO:0061138
367	20	0.054	Epithelial tube morphogenesis	2.32E-16	Tgfb1, Cd44, Ctnnb1, Wnt3a, Fzd6, Wnt1, Lrp5, Lef1, Sfrp2, Sfrp1, Wnt4, Pkd1, Igf1, Gja1, Wnt5a, Esr1, Pkd2, Mmp14, Casp3, Vegfa	1.97E-18	GO:0060562
79	13	0.165	Canonical wnt signaling pathway	6.05E-16	Sfrp4, Ctnnb1, Wnt3a, Fzd6, Wnt1, Lrp5, Lef1, Sfrp2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc	5.68E-18	GO:0060070
149	15	0.101	Regulation of peptidyl-serine phosphorylation	1.11E-15	Tgfb1, Cd44, Wnt3a, Tnf, Dkk1, Il6, Sfrp2, Hgf, Bax, Ptg2, Wnt5a, Lif, Axin1, Il11, Vegfa	1.12E-17	GO:0033135
163	15	0.092	Branching morphogenesis of an epithelial tube	3.54E-15	Tgfb1, Cd44, Ctnnb1, Wnt1, Lrp5, Lef1, Sfrp2, Wnt4, Pkd1, Igf1, Wnt5a, Esr1, Pkd2, Mmp14, Vegfa	3.90E-17	GO:0048754
207	16	0.077	Positive regulation of epithelial cell proliferation	3.78E-15	Tgfb1, Ctnnb1, Wnt3a, Itgb3, Tnf, Bad, Il6, Sfrp1, Bmpr1a, Dlx5, Igf1, Wnt5a, Esr1, Ccnd1, Jun, Vegfa	4.19E-17	GO:0050679
222	16	0.072	Response to mechanical stimulus	1.02E-14	Sost, Tgfb1, Ctnnb1, Fos, Tnf, Bad, Il6, Ptg2, Piezo2, Pkd1, Igf1, Gja1, Pkd2, Mmp14, Piezo1, Jun	1.18E-16	GO:0009612
142	14	0.099	Regulation of fat cell differentiation	1.65E-14	Pparg, Tgfb1, Wnt3a, Lpl, Wnt1, Tnf, Lrp5, Sfrp2, Sfrp1, Ptg2, Igf1, Wnt5a, Axin1, Vegfa	1.96E-16	GO:0045598
113	13	0.115	Regulation of morphogenesis of an epithelium	3.18E-14	Tgfb1, Ctnnb1, Fzd6, Tnf, Sfrp2, Hgf, Sfrp1, Wnt4, Gja1, Wnt5a, Lif, Esr1, Vegfa	3.97E-16	GO:1905330
KEGG Pathways (Excluded: mmu05200, mmu05224, mmu05225, mmu05165, mmu05010, mmu05226, mmu05210, mmu05217, mmu05167, mmu04934, mmu05213, mmu05146, mmu05161)							
157	18	0.115	Wnt signaling pathway	5.61E-20	Sost, Sfrp4, Ctnnb1, Wnt3a, Fzd6, Wnt1, Dkk1, Lrp5, Lef1, Sfrp2, Dkk2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1, Jun	5.07E-22	mmu04310
199	19	0.095	Proteoglycans in cancer	6.6E-20	Tgfb1, Cd44, Igf1r, Ctnnb1, Wnt3a, Itgb3, Fzd6, Wnt1, Tnf, Itgav, Hgf, Wnt4, Igf1, Wnt5a, Esr1, Casp3, Ccnd1, Actb, Vegfa	7.96E-22	mmu05205
137	13	0.095	Signaling pathways regulating pluripotency of stem cells	1.47E-13	Igf1r, Ctnnb1, Wnt3a, Fzd6, Wnt1, Bmpr1a, Wnt4, Dlx5, Igf1, Wnt5a, Lif, Axin1, Apc	3.99E-15	mmu04550
156	13	0.083	Hippo signaling pathway	6.32E-13	Tgfb1, Ctnnb1, Wnt3a, Fzd6, Wnt1, Lef1, Bmpr1a, Wnt4, Wnt5a, Axin1, Apc, Ccnd1, Actb	1.90E-14	mmu04390
196	13	0.066	Focal adhesion	7.58E-12	Igf1r, Ctnnb1, Itgb3, Vcl, Bad, Itgav, Hgf, Igf1, Ccnd1, Actb, Jun, Spp1, Vegfa	2.97E-13	mmu04510
86	10	0.116	Rheumatoid arthritis	2.62E-11	Tgfb1, Fos, Tnfsf11, Tnf, Il6, Cxcl1, Cxcl2, Il11, Jun, Vegfa	1.10E-12	mmu05323
112	10	0.089	TNF signaling pathway	2.78E-10	Fos, Tnf, Il6, Cxcl1, Ptg2, Lif, Cxcl2, Mmp14, Casp3, Jun	1.26E-11	mmu04668
90	9	0.100	IL-17 signaling pathway	1.08E-09	Ccl7, Fos, Tnf, Il6, Cxcl1, Ptg2, Cxcl2, Casp3, Jun	5.52E-11	mmu04657
119	9	0.076	Thyroid hormone signaling pathway	9.32E-09	Ctnnb1, Itgb3, Bad, Itgav, Wnt4, Esr1, Ncoa1, Ccnd1, Actb	5.62E-10	mmu04919
91	8	0.088	Endocrine resistance	2.67E-08	Igf1r, Fos, Bad, Bax, Igf1, Esr1, Ccnd1, Jun	1.77E-09	mmu01522
141	9	0.064	Fluid shear stress and atherosclerosis	3.32E-08	Ctnnb1, Itgb3, Fos, Tnf, Itgav, Bmpr1a, Actb, Jun, Vegfa	2.30E-09	mmu05418
101	8	0.079	AGE-RAGE signaling pathway in diabetic complications	5.07E-08	Tgfb1, Tnf, Il6, Bax, Casp3, Ccnd1, Jun, Vegfa	3.82E-09	mmu04933
156	9	0.058	mTOR signaling pathway	6.55E-08	Igf1r, Wnt3a, Fzd6, Wnt1, Tnf, Lrp5, Wnt4, Igf1, Wnt5a	5.33E-09	mmu04150
121	8	0.066	Osteoclast differentiation	1.66E-07	Pparg, Tgfb1, Itgb3, Fos, Tnfsf11, Tnf, Tnfsf11b, Jun	1.45E-08	mmu04380
78	7	0.090	EGFR tyrosine kinase inhibitor resistance	1.88E-07	Igf1r, Bad, Il6, Hgf, Bax, Igf1, Vegfa	1.70E-08	mmu01521
WikiPathways (Excluded: WP3857)							
106	16	0.151	Wnt signaling pathway (NetPath)	4.3E-19	Ctnnb1, Wnt3a, Fzd6, Wnt1, Dkk1, Lrp5, Lef1, Sfrp2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1, Jun, Runx2	2.17E-21	WP539
96	13	0.135	Wnt signaling pathway and pluripotency	5.63E-15	Cd44, Ctnnb1, Wnt3a, Fzd6, Wnt1, Lrp5, Lef1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1, Jun	5.69E-17	WP723
116	13	0.112	ESC pluripotency pathways	3.58E-14	Ctnnb1, Wnt3a, Fos, Fzd6, Wnt1, Lrp5, Bmpr1a, Wnt4, Wnt5a, Lif, Axin1, Apc, Jun	5.43E-16	WP339
59	11	0.186	Wnt signaling pathway	3.58E-14	Sfrp4, Ctnnb1, Wnt3a, Fzd6, Wnt1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1, Jun	6.80E-16	WP403
287	16	0.056	PluriNetWork: mechanisms associated with pluripotency	2.11E-13	Tgfb1, Cd44, Ctnnb1, Wnt3a, Fos, Dkk1, Lrp5, Lef1, Wnt5a, Lif, Axin1, Apc, Ncoa1, Casp3, Ccnd1, Spp1	5.33E-15	WP1763
50	10	0.200	TGF-beta signaling pathway	2.68E-13	Tgfb1, Ctnnb1, Fos, Wnt1, Tnf, Lef1, Lif, Jun, Spp1, Runx2	8.13E-15	WP113
132	12	0.091	Adipogenesis genes	2.23E-12	Pparg, Tgfb1, Sfrp4, Ctnnb1, Lpl, Wnt1, Tnf, Il6, Fabp4, Igf1, Lif, Ncoa1	7.88E-14	WP447
99	10	0.101	Spinal cord injury	8.85E-11	Tgfb1, Nos2, Fos, Tnf, Il6, Cxcl1, Gja1, Cxcl2, Casp3, Ccnd1	4.02E-12	WP2432

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
82	9	0.110	MicroRNAs in cardiomyocyte hypertrophy	5.06E-10	Tgfb1, Igf1r, Ctnnb1, Wnt3a, Tnf, Lrp5, Igf1, Wnt5a, Lif	2.55E-11	WP1560
183	11	0.060	Focal adhesion	1.11E-09	Itgb3, Vcl, Bad, Itgav, Hgf, Igf1, Ccnd1, Actb, Jun, Spp1, Vegfa	6.18E-11	WP85
62	8	0.129	Endochondral ossification	1.74E-09	Tgfb1, Igf1r, Alpl, Bmpr1a, Igf1, Spp1, Runx2, Vegfa	1.06E-10	WP1270
72	8	0.111	Primary focal segmental glomerulosclerosis (FSGS)	4.81E-09	Tgfb1, Ctnnb1, Itgb3, Vcl, Dkk1, Lrp5, Itgav, Mki67	3.16E-10	WP2573
61	7	0.115	Lung fibrosis	4.93E-08	Tgfb1, Tnf, Il6, Hgf, Igf1, Cxcl2, Spp1	3.49E-09	WP3632
80	7	0.088	Apoptosis	2.63E-07	Igf1r, Tnf, Bad, Bax, Igf1, Casp3, Jun	2.00E-08	WP1254
27	5	0.185	Cytokines and inflammatory response	9.70E-07	Tgfb1, Tnf, Il6, Cxcl1, Il11	7.84E-08	WP222
14	4	0.286	Osteoclast signaling	4.42E-06	Itgb3, Tnfsf11, Tnfrsf11b, Spp1	3.79E-07	WP454
51	5	0.098	Id signaling pathway	1.53E-05	Igf1r, Ctnnb1, Ccna2, Igf1, Vegfa	1.39E-06	WP512
98	6	0.061	IL-6 signaling pathway	1.63E-05	Fos, Bad, Il6, Ncoa1, Casp3, Jun	1.56E-06	WP387

7.4.1.3 Hub genes by cytoHubba

Top hub genes identified in the human STRING network derived from the mouse (n = 76) DEG list. Different score measures were calculated by cytoHubba (Chin et al. 2014). The cut-off was calculated (total score ≥ 12622.9) for this network (Sun et al. 2021). In this table the genes were ordered in descending order according to the total score (above the dashed line). These hub genes were colored red in **Figure 5**.

Gene symbol	Local-based methods				Global-based methods					Total score		
	MCC	DMNC	MNC	Degree	EPC	BottleNeck	EcCentricity	Closeness	Radiality	Betweenness	Stress	(SUMscore)
Ctnnb1	44794	0.359	41	41	31.360	32	0.325	56.833	4.508	1886.875	6374	53262.3
Wnt1	37562	0.619	16	16	24.323	2	0.243	40.417	3.855	72.993	522	38260.5
Wnt3a	37584	0.637	16	16	23.618	1	0.243	40.083	3.828	52.399	426	38163.8
Wnt5a	36000	0.728	13	13	21.773	1	0.243	37.917	3.735	15.650	212	36319.0
Dkk1	32088	0.619	16	16	24.371	1	0.243	40.417	3.855	65.943	530	32786.4
Wnt4	30960	0.746	12	12	20.297	1	0.243	37.417	3.721	12.894	184	31244.3
Lrp5	26904	0.641	15	15	24.022	1	0.243	39.917	3.841	52.169	476	27531.8
Sfrp1	26040	0.717	12	12	21.264	1	0.243	37.917	3.761	21.613	264	26414.5
Il6	15246	0.412	23	23	27.796	13	0.243	46.417	4.148	543.905	2292	18219.9
Tnf	15768	0.465	23	23	28.039	5	0.243	46.750	4.175	292.002	1602	17792.7
Actb	15372	0.509	21	21	26.991	2	0.243	45.583	4.135	277.308	1344	17114.8
Jun	12978	0.509	19	19	26.808	3	0.243	44.583	4.108	237.537	1350	14682.8
Axin1	10826	0.611	11	11	21.869	1	0.243	37.417	3.748	17.387	118	11048.3
Sfrp2	10080	0.787	8	8	16.885	1	0.243	35.417	3.668	8.102	148	10310.1
Dkk2	10080	0.787	8	8	17.588	1	0.195	29.950	3.094	0.250	2	10150.9
Vegfa	8712	0.550	17	17	26.329	1	0.243	42.917	4.028	101.264	696	9618.3
Tgfb1	8308	0.531	15	15	24.814	2	0.243	41.583	3.975	83.883	496	8991.0
Pparg	6832	0.429	17	17	26.004	2	0.243	43.417	4.068	317.338	1542	8801.5
Casp3	6752	0.600	13	15	23.689	3	0.243	41.750	3.988	322.006	1120	8295.3
Ptgs2	6128	0.585	12	14	22.847	3	0.243	41.083	3.961	339.244	1222	7787.0
Fos	5683	0.615	12	13	23.389	3	0.243	40.917	3.975	169.361	742	6691.5
Lef1	5934	0.536	13	13	23.074	1	0.243	39.917	3.895	45.092	314	6387.8
Fzd6	5040	0.768	7	7	16.720	1	0.243	34.750	3.641	0.000	0	5111.1
Igf1	3680	0.507	18	18	26.559	1	0.243	43.583	4.055	153.702	930	4875.6
Runx2	1287	0.411	20	21	27.084	3	0.243	44.750	4.068	414.938	1908	3730.5
Sost	1374	0.451	15	15	22.758	4	0.243	40.250	3.868	251.202	1096	2822.8
Ccnd1	1298	0.481	15	15	25.092	1	0.243	41.917	4.001	149.745	694	2244.5
Esr1	1242	0.549	13	13	23.034	1	0.243	40.750	3.961	55.897	372	1765.4
Spp1	612	0.491	15	15	24.884	2	0.243	41.583	3.975	143.773	904	1762.9
Cd44	320	0.539	10	12	21.015	4	0.243	39.750	3.908	305.362	1022	1738.8
Tnfrsf11	822	0.536	13	13	24.227	1	0.243	40.750	3.961	69.138	520	1507.9
Bglap	702	0.527	12	12	22.570	2	0.243	39.250	3.868	70.235	554	1418.7
Sp7	654	0.543	11	11	20.060	1	0.243	38.583	3.841	57.557	450	1247.8
Hgf	864	0.641	8	8	19.628	1	0.243	37.083	3.801	5.677	40	988.1
Apc	726	0.525	8	8	17.949	1	0.243	36.417	3.748	29.920	138	969.8
Sfrp4	840	0.695	7	7	16.569	1	0.243	35.417	3.695	2.011	16	929.6
Pkd1	3	0.308	2	3	6.276	3	0.325	33.333	3.641	284.000	504	842.9
Dmp1	156	0.379	10	10	17.588	1	0.195	34.867	3.521	96.914	484	814.5
Tjp1	56	0.408	8	8	14.837	2	0.243	36.917	3.788	119.308	530	779.5
Tnfrsf11b	288	0.525	9	9	19.284	1	0.195	37.283	3.775	28.860	262	658.9
Mki67	266	0.525	8	8	17.562	2	0.243	37.417	3.828	53.728	232	629.3
Itgav	210	0.479	10	10	20.186	1	0.243	36.333	3.681	36.518	224	552.4
Itgb3	210	0.479	10	10	19.616	1	0.243	36.333	3.681	36.518	224	551.9
Gja1	32	0.428	6	6	11.454	1	0.243	34.750	3.668	70.054	342	507.6
Pkd2	2	0.000	1	2	1.885	2	0.243	23.667	2.708	144.000	254	433.5
Cxcl1	264	0.622	7	7	16.563	1	0.195	33.533	3.508	5.463	42	380.9
Vcl	32	0.366	7	7	13.630	2	0.325	35.667	3.721	40.857	184	326.6
Igf1r	60	0.437	8	8	18.338	1	0.243	36.250	3.735	16.566	158	310.6
Cxcl2	144	0.618	6	6	15.224	1	0.195	32.533	3.455	3.446	24	236.5
Nos2	120	0.648	5	5	14.359	1	0.195	32.533	3.481	0.000	0	182.2
Alpl	120	0.648	5	5	13.440	1	0.195	30.950	3.335	0.000	0	179.6
Lif	6	0.284	4	4	8.373	1	0.195	30.950	3.375	8.750	54	120.9
Lepr	3	0.308	2	3	5.928	1	0.195	29.033	3.228	10.854	46	104.5
Ncoa1	18	0.454	5	5	12.255	1	0.195	30.867	3.335	3.541	18	97.6
Lpl	8	0.379	4	4	9.369	1	0.195	29.700	3.268	4.764	24	88.7
Ccl7	24	0.568	4	4	10.557	1	0.195	30.033	3.295	0.000	0	77.6
Bmpr1a	4	0.309	3	3	9.961	1	0.243	33.750	3.668	0.944	8	67.9
Npy	2	0.000	1	2	5.035	1	0.195	26.783	3.054	2.546	16	59.6
Dlx5	6	0.463	3	3	9.784	1	0.195	28.200	3.134	0.000	0	54.8
Tuba1a	6	0.463	3	3	7.557	1	0.195	28.783	3.214	0.000	0	53.2
Mepe	6	0.463	3	3	7.060	1	0.195	27.117	2.988	0.000	0	50.8
Phex	6	0.463	3	3	6.357	1	0.195	27.117	2.988	0.000	0	50.1
Il11	2	0.308	2	2	6.291	1	0.195	28.367	3.201	0.000	0	45.4
Ccn1	2	0.308	2	2	6.144	1	0.195	27.367	3.121	0.000	0	44.1
Fabp4	2	0.308	2	2	5.034	1	0.195	27.367	3.121	0.000	0	43.0
Bax	2	0.308	2	2	4.735	1	0.195	26.700	3.041	0.000	0	42.0
Bad	2	0.308	2	2	3.746	1	0.195	26.700	3.041	0.000	0	41.0
Gjc1	2	0.308	2	2	4.254	1	0.195	24.867	2.841	0.000	0	39.5
Dlx1	1	0.000	1	1	4.529	1	0.195	27.200	3.108	0.000	0	39.0
Ptgs1	1	0.000	1	1	4.145	1	0.195	25.950	3.001	0.000	0	37.3
Ptger2	1	0.000	1	1	4.089	1	0.195	25.950	3.001	0.000	0	37.2

Gene symbol	Local-based methods				Global-based methods							Total score (SUMscore)
	MCC	DMNC	MNC	Degree	EPC	BottleNeck	EcCentricity	Closeness	Radiality	Betweenness	Stress	
Mmp14	1	0.000	1	1	4.012	1	0.195	25.450	2.948	0.000	0	36.6
Pdpn	1	0.000	1	1	3.458	1	0.195	25.450	2.948	0.000	0	36.1
Piezo1	1	0.000	1	1	1.312	1	0.195	18.017	1.747	0.000	0	25.3
Piezo2	0	0.000	0	0	1.000	0	0.000	0.000	0.000	0.000	0	1.0
Eral1	0	0.000	0	0	1.000	0	0.000	0.000	0.000	0.000	0	1.0

7.4.2 GLay community clustering

7.4.2.1 GLay cluster #1 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
243	15	0.062	Wnt signaling pathway	4.54E-21	Sfrp4, Wnt3a, Fzd6, Wnt1, Dkk1, Lrp5, Lef1, Sfrp2, Dkk2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1	3.52E-25	GO:0016055
79	12	0.152	Canonical wnt signaling pathway	1.39E-20	Sfrp4, Wnt3a, Fzd6, Wnt1, Lrp5, Lef1, Sfrp2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc	3.24E-24	GO:0060070
126	9	0.071	Negative regulation of canonical wnt signaling pathway	3.26E-12	Sfrp4, Fzd6, Dkk1, Sfrp2, Dkk2, Sfrp1, Wnt5a, Axin1, Apc	2.53E-15	GO:0090090
133	7	0.053	Regulation of embryonic development	6.03E-09	Wnt3a, Wnt1, Dkk1, Sfrp2, Sfrp1, Wnt4, Wnt5a	3.84E-11	GO:0045995
4	4	1.000	Regulation of dermatome development	6.57E-09	Wnt3a, Wnt1, Sfrp2, Wnt4	4.23E-11	GO:0061183
71	6	0.085	Somitogenesis	1.03E-08	Wnt3a, Dkk1, Lef1, Sfrp2, Sfrp1, Wnt5a	7.70E-11	GO:0001756
31	5	0.161	Axis elongation	2.02E-08	Wnt3a, Sfrp2, Sfrp1, Wnt5a, Esr1	1.73E-10	GO:0003401
31	5	0.161	Non-canonical wnt signaling pathway	2.02E-08	Fzd6, Sfrp2, Sfrp1, Wnt4, Wnt5a	1.73E-10	GO:0035567
9	4	0.444	Regulation of dopaminergic neuron differentiation	4.34E-08	Wnt3a, Dkk1, Sfrp2, Sfrp1	4.31E-10	GO:1904338
98	6	0.061	Regulation of bmp signaling pathway	4.77E-08	Sfrp4, Wnt1, Dkk1, Sfrp2, Sfrp1, Wnt5a	4.85E-10	GO:0030510
99	6	0.061	Epithelial cell proliferation	5.02E-08	Bad, Bax, Mki67, Wnt5a, Esr1, Ccnd1	5.14E-10	GO:0050673
105	6	0.057	Regulation of fibroblast proliferation	6.59E-08	Wnt1, Ccna2, Bax, Sfrp1, Wnt5a, Esr1	7.21E-10	GO:0048145
113	6	0.053	Regulation of morphogenesis of an epithelium	9.84E-08	Fzd6, Sfrp2, Sfrp1, Wnt4, Wnt5a, Esr1	1.10E-09	GO:1905330
53	5	0.094	Negative regulation of bmp signaling pathway	1.71E-07	Wnt1, Dkk1, Sfrp2, Sfrp1, Wnt5a	2.07E-09	GO:0030514
62	5	0.081	Stem cell proliferation	3.29E-07	Wnt3a, Wnt1, Lef1, Sfrp2, Wnt5a	4.34E-09	GO:0072089
KEGG Pathways							
(Excluded: mmu05224, mmu05225, mmu05226, mmu05217, mmu04934, mmu05210, mmu05213)							
157	15	0.096	Wnt signaling pathway	2.21E-25	Sfrp4, Wnt3a, Fzd6, Wnt1, Dkk1, Lrp5, Lef1, Sfrp2, Dkk2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1	6.64E-28	mmu04310
156	9	0.058	Hippo signaling pathway	5.88E-13	Wnt3a, Fzd6, Wnt1, Lef1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1	1.59E-14	mmu04390
137	7	0.051	Signaling pathways regulating pluripotency of stem cells	1.11E-09	Wnt3a, Fzd6, Wnt1, Wnt4, Wnt5a, Axin1, Apc	4.68E-11	mmu04550
95	6	0.063	Melanogenesis	8.98E-09	Wnt3a, Fzd6, Wnt1, Lef1, Wnt4, Wnt5a	4.06E-10	mmu04916
WikiPathways							
106	13	0.123	Wnt signaling pathway (NetPath)	6.44E-23	Wnt3a, Fzd6, Wnt1, Dkk1, Lrp5, Lef1, Sfrp2, Sfrp1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1	3.25E-25	WP539
96	10	0.104	Wnt signaling pathway and pluripotency	1.41E-16	Wnt3a, Fzd6, Wnt1, Lrp5, Lef1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1	1.43E-18	WP723
59	9	0.153	Wnt signaling pathway	2.72E-16	Sfrp4, Wnt3a, Fzd6, Wnt1, Wnt4, Wnt5a, Axin1, Apc, Ccnd1	4.12E-18	WP403
41	8	0.195	Wnt signaling in kidney disease	3.19E-15	Wnt3a, Fzd6, Wnt1, Lrp5, Wnt4, Wnt5a, Axin1, Apc	6.44E-17	WP3857
116	8	0.069	ESC pluripotency pathways	5.99E-12	Wnt3a, Fzd6, Wnt1, Lrp5, Wnt4, Wnt5a, Axin1, Apc	1.51E-13	WP339

7.4.2.2 GLayer cluster #2 – Gene list enrichment

# Background genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
62	8	0.129	Regulation of bone remodeling	3.34E-11	Itgb3, Tnfsf11, Il6, Itgav, Lepr, Tnfrsf11b, Spp1, Vegfa	8.80E-14	GO:0046850
149	9	0.060	Regulation of peptidyl-serine phosphorylation	2.76E-10	Tgfb1, Cd44, Tnf, Il6, Hgf, Ptgs2, Lif, Il11, Vegfa	1.30E-12	GO:0033135
52	7	0.135	Regulation of bone resorption	5.09E-10	Itgb3, Tnfsf11, Il6, Itgav, Tnfrsf11b, Spp1, Vegfa	2.72E-12	GO:0045124
166	9	0.054	Regulation of smooth muscle cell proliferation	5.96E-10	Pparg, Igf1r, Itgb3, Tnf, Il6, Ptgs2, Igf1, Jun, Vegfa	3.28E-12	GO:0048660
175	9	0.051	Positive regulation of leukocyte differentiation	8.54E-10	Tgfb1, Itgb3, Fos, Tnfsf11, Tnf, Il6, Lif, Mmp14, Jun	5.17E-12	GO:1902107
109	8	0.073	Positive regulation of smooth muscle cell proliferation	9.76E-10	Igf1r, Itgb3, Tnf, Il6, Ptgs2, Igf1, Jun, Vegfa	6.06E-12	GO:0048661
115	8	0.070	Positive regulation of peptidyl-serine phosphorylation	1.38E-09	Tgfb1, Cd44, Tnf, Il6, Ptgs2, Lif, Il11, Vegfa	9.10E-12	GO:0033138
68	7	0.103	Positive regulation of myeloid leukocyte differentiation	2.21E-09	Tgfb1, Itgb3, Fos, Tnfsf11, Tnf, Lif, Jun	1.56E-11	GO:0002763
90	7	0.078	Negative regulation of cysteine-type endopeptidase activity involved in apoptotic process	1.04E-08	Cd44, Tnf, Il6, Hgf, Ptgs2, Igf1, Vegfa	9.86E-11	GO:0043154
115	7	0.061	Positive regulation of protein kinase b signaling	4.40E-08	Tgfb1, Igf1r, Tnfsf11, Tnf, Il6, Igf1, Vegfa	5.01E-10	GO:0051897
118	7	0.059	Tissue remodeling	5.11E-08	Tgfb1, Tnfsf11, Il6, Igf1, Lif, Mmp14, Vegfa	5.94E-10	GO:0048771
86	6	0.070	Positive regulation of gliogenesis	3.03E-07	Pparg, Tgfb1, Tnf, Il6, Igf1, Lif	4.49E-09	GO:0014015
95	6	0.063	Regulation of blood vessel endothelial cell migration	5.09E-07	Pparg, Tgfb1, Tnf, Ptgs2, Igf1, Vegfa	7.90E-09	GO:0043535
47	5	0.106	Regulation of acute inflammatory response	8.24E-07	Pparg, Tnfsf11, Tnf, Il6, Ptgs2	1.34E-08	GO:0002673
113	6	0.053	Myeloid leukocyte migration	1.23E-06	Ccl7, Tnfsf11, Cxcl1, Cxcl2, Spp1, Vegfa	2.12E-08	GO:0097529
KEGG Pathways (Excluded: mmu05140, mmu05414, mmu05142, mmu05146, mmu05133)							
86	10	0.116	Rheumatoid arthritis	4.22E-14	Tgfb1, Fos, Tnfsf11, Tnf, Il6, Cxcl1, Cxcl2, Il11, Jun, Vegfa	1.27E-16	mmu05323
112	9	0.080	TNF signaling pathway	1.26E-11	Fos, Tnf, Il6, Cxcl1, Ptgs2, Lif, Cxcl2, Mmp14, Jun	1.14E-13	mmu04668
199	10	0.050	Proteoglycans in cancer	2.36E-11	Tgfb1, Cd44, Igf1r, Itgb3, Tnf, Itgav, Hgf, Igf1, Actb, Vegfa	3.56E-13	mmu05205
90	8	0.089	IL-17 signaling pathway	7.89E-11	Ccl7, Fos, Tnf, Il6, Cxcl1, Ptgs2, Cxcl2, Jun	1.43E-12	mmu04657
121	8	0.066	Osteoclast differentiation	6.35E-10	Pparg, Tgfb1, Itgb3, Fos, Tnfsf11, Tnf, Tnfrsf11b, Jun	1.34E-11	mmu04380
88	7	0.080	Hypertrophic cardiomyopathy	3.13E-09	Tgfb1, Itgb3, Tnf, Il6, Itgav, Igf1, Actb	8.50E-11	mmu05410
78	5	0.064	EGFR tyrosine kinase inhibitor resistance	2.19E-06	Igf1r, Il6, Hgf, Igf1, Vegfa	1.45E-07	mmu01521
87	5	0.057	Viral protein interaction with cytokine and cytokine receptor	3.51E-06	Ccl7, Tnf, Il6, Cxcl1, Cxcl2	2.43E-07	mmu04061
91	5	0.055	Hematopoietic cell lineage	4.17E-06	Cd44, Itgb3, Tnf, Il6, Il11	3.01E-07	mmu04640
98	5	0.051	Toll-like receptor signaling pathway	5.69E-06	Fos, Tnf, Il6, Jun, Spp1	4.28E-07	mmu04620
99	5	0.051	NF-kappa B signaling pathway	5.74E-06	Tnfsf11, Tnf, Cxcl1, Ptgs2, Cxcl2	4.50E-07	mmu04064
WikiPathways (Excluded: WP2432)							
132	9	0.068	Adipogenesis genes	9.14E-11	Pparg, Tgfb1, Lpl, Tnf, Il6, Fabp4, Igf1, Lif, Ncoa1	4.62E-13	WP447
61	7	0.115	Lung fibrosis	7.59E-10	Tgfb1, Tnf, Il6, Hgf, Igf1, Cxcl2, Spp1	7.67E-12	WP3632
50	6	0.120	TGF-beta signaling pathway	1.22E-08	Tgfb1, Fos, Tnf, Lif, Jun, Spp1	2.12E-10	WP113
27	5	0.185	Cytokines and inflammatory response	3.51E-08	Tgfb1, Tnf, Il6, Cxcl1, Il11	1.06E-09	WP222
14	4	0.286	Osteoclast signaling	3.52E-07	Itgb3, Tnfsf11, Tnfrsf11b, Spp1	1.25E-08	WP454
62	5	0.081	Endochondral ossification	1.08E-06	Tgfb1, Igf1r, Igf1, Spp1, Vegfa	4.91E-08	WP1270
82	5	0.061	MicroRNAs in cardiomyocyte hypertrophy	3.64E-06	Tgfb1, Igf1r, Tnf, Igf1, Lif	1.84E-07	WP1560

7.4.2.3 GLayer cluster #3 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
			None satisfying applied criteria.				
KEGG Pathways							
			None satisfying applied criteria.				
WikiPathways							
			None satisfying applied criteria.				

7.4.2.4 GLayer cluster #4 – Gene list enrichment

# Back-ground genes	# Genes	Fraction	Description	FDR value	Genes	p-value	Term name
GO Biological Process							
92	5	0.054	Biomineral tissue development	2.37E-06	Alpl, Mepe, Dmp1, Bglap, Phex	3.67E-10	GO:0031214
KEGG Pathways							
			None satisfying applied criteria.				
WikiPathways							
			None satisfying applied criteria.				