

Supplementary Materials:

Not secure | ctdbase.org/detail.go?type=relationship&geneAcc=51421&diseaseAcc=MESH%3AD065626&view=reference

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Comparative Toxicogenomics Database

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AMOTL2 ↔ Non-alcoholic Fatty Liver Disease

This gene-disease association may be inferred in part via [curated interactions](#) between [AMOTL2](#) and any chemicals listed below, and a curated association between those chemicals and [Non-alcoholic Fatty Liver Disease](#).

Filter by Association type: ALL Filter

1-24 of 24 results.

	Reference	Association
1	✓ Das KP, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. Toxicology. 2017 Mar 1;378:37-52.	Inferred via 1 chemical: pinixinic acid
2	✓ Duval C, et al. Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL/6J Diet-Induced Obesity Mouse Model. Environ Health Perspect. 2017 Mar;125(3):428-436.	Inferred via 1 chemical: Tetrachlorodibenzodioxin
3	✓ Fader KA, et al. Convergence of hepcidin deficiency, systemic iron overloading, heme accumulation, and REV-ERBa/β activation in aryl hydrocarbon receptor-elicited hepatotoxicity. Toxicol Appl Pharmacol. 2017 Apr 15;321:1-17.	Inferred via 1 chemical: Tetrachlorodibenzodioxin
4	✓ Lin Y, et al. Downregulation of miR-192 causes hepatic steatosis and lipid accumulation by inducing SREBF1: Novel mechanism for bisphenol A-triggered non-alcoholic fatty liver disease. Biochim Biophys Acta. 2017 Sep;1862(9):869-882.	Inferred via 1 chemical: bisphenol A
5	✓ Ditzel EJ, et al. Altered Hepatic Transport by Fetal Arsenite Exposure in Diet-Induced Fatty Liver Disease. J Biochem Mol Toxicol. 2016 Feb 18.	Inferred via 1 chemical: sodium arsenite
6	✓ Michaut A, et al. A cellular model to study drug-induced liver injury in nonalcoholic fatty liver disease: Application to acetaminophen. Toxicol Appl Pharmacol. 2016 Feb 1;292:40-55.	Inferred via 1 chemical: Acetaminophen
7	✓ Nault R, et al. From the Cover: Coagulation-Driven Hepatic Fibrosis Requires Protease Activated Receptor-1 (PAR-1) in a Mouse Model of TCDD-	Inferred via 1 chemical: Tetrachlorodibenzodioxin

Figure S1A: Print screen shows correlation between AMOTL2 and NAFLD/NASH using Comparative Toxicogenomics Database, <http://ctdbase.org/detail.go?type=relationship&geneAcc=51421&diseaseAcc=MESH%3AD065626&view=reference>

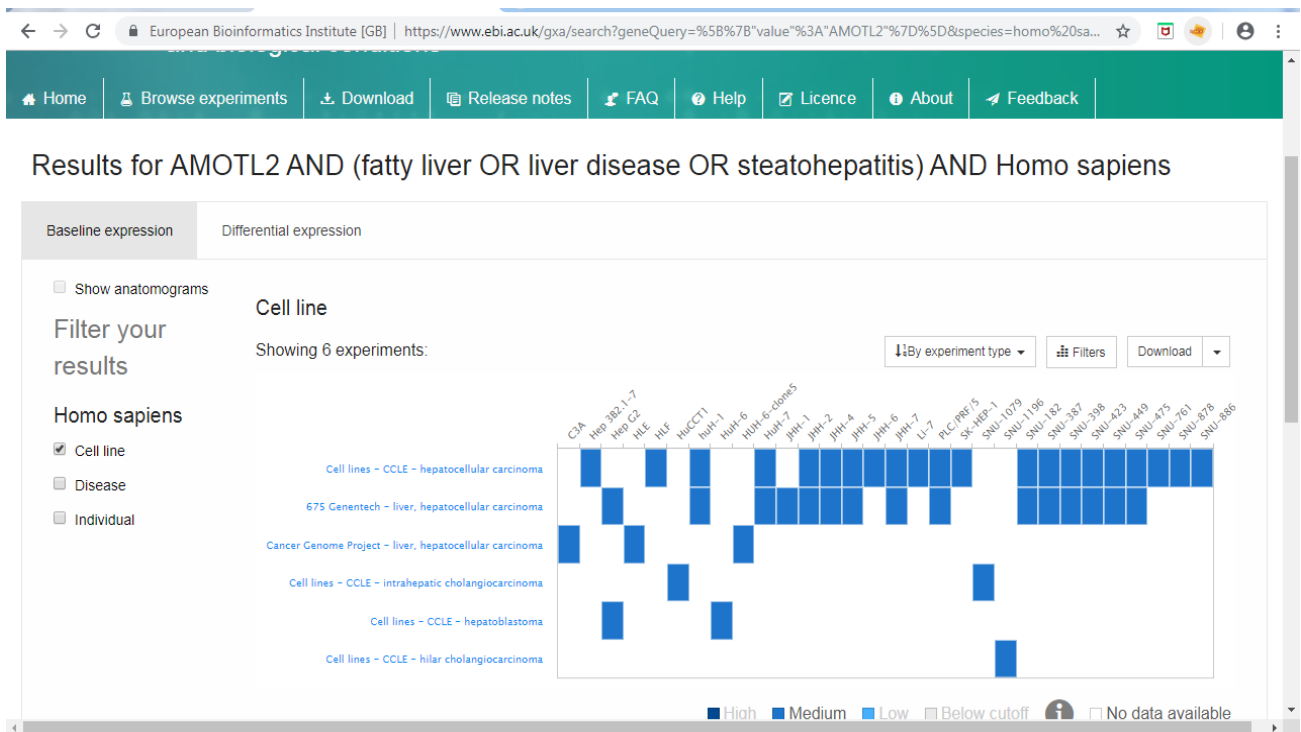


Figure S1B: Print screen shows correlation between AMOTL2 and NAFLD/NASH using Gene atlas database, https://www.ebi.ac.uk/gxa/search?geneQuery=%5B%7B%22value%22%3A%22AMOTL2%22%7D%5D&species=homo%20sapiens&conditionQuery=%5B%7B%22value%22%3A%22fatty%20liver%22%7D%2C%7B%22value%22%3A%22li%20ver%20disease%22%7D%2C%7B%22value%22%3A%22steatohepatitis%22%7D%5D&bs=%7B%22homo%20sapiens%22%3A%5B%22CELL_LINE%22%5D%7D&ds=%7B%22kingdom%22%3A%5B%22animals%22%5D%7D#baseline

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SOX11 ↔ Non-alcoholic Fatty Liver Disease

This gene-disease association may be inferred in part via [curated interactions](#) between [SOX11](#) and any chemicals listed below, and a curated association between those chemicals and [Non-alcoholic Fatty Liver Disease](#).

Filter by Association type: ALL Filter

1-50 of 63 results.

Reference	Association
1. ✓ Jung TW, et al. Maresin 1 attenuates NAFLD by suppression of endoplasmic reticulum stress via AMPK-SERCA2b pathway. J Biol Chem. 2018 Mar 16;293(11):3981-3988.	Inferred via 1 chemical: Dietary Fats
2. ✓ Kim KY, et al. Deoxydopodophyllotoxin in Anthriscus sylvestris alleviates fat accumulation in the liver via AMP-activated protein kinase, impeding SREBP-1c signal. Chem Biol Interact. 2018 Oct 1;294:151-157.	Inferred via 1 chemical: Dietary Fats
3. ✓ Li X, et al. Modulation of xenobiotic nuclear receptors in high-fat diet induced non-alcoholic fatty liver disease. Toxicology. 2018 Dec 1;410:199-213.	Inferred via 1 chemical: Dietary Fats
4. ✓ Nakamura M, et al. Differential impacts of mineralocorticoid receptor antagonist potassium canrenoate on liver and renal changes in high fat diet-mediated early hepatocarcinogenesis model rats. J Toxicol Sci. 2018;43(10):611-621.	Inferred via 1 chemical: Dietary Fats
5. ✓ Wu C, et al. Alisol A 24-acetate ameliorates nonalcoholic steatohepatitis by inhibiting oxidative stress and stimulating autophagy through the AMPK/mTOR pathway. Chem Biol Interact. 2018 Aug 1;291:111-119.	Inferred via 2 chemicals: Choline Methionine
6. ✓ Das KP, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. Toxicology. 2017 Mar 1;378:27-53.	Inferred via 1 chemical: pinixic acid

Figure S1C: Print screen shows correlation between SOX11 and NAFLD/NASH using Comparative Toxicogenomics Database, <http://ctdbase.org/detail.go?type=relationship&geneAcc=6664&diseaseAcc=MESH%3AD065626&view=reference>

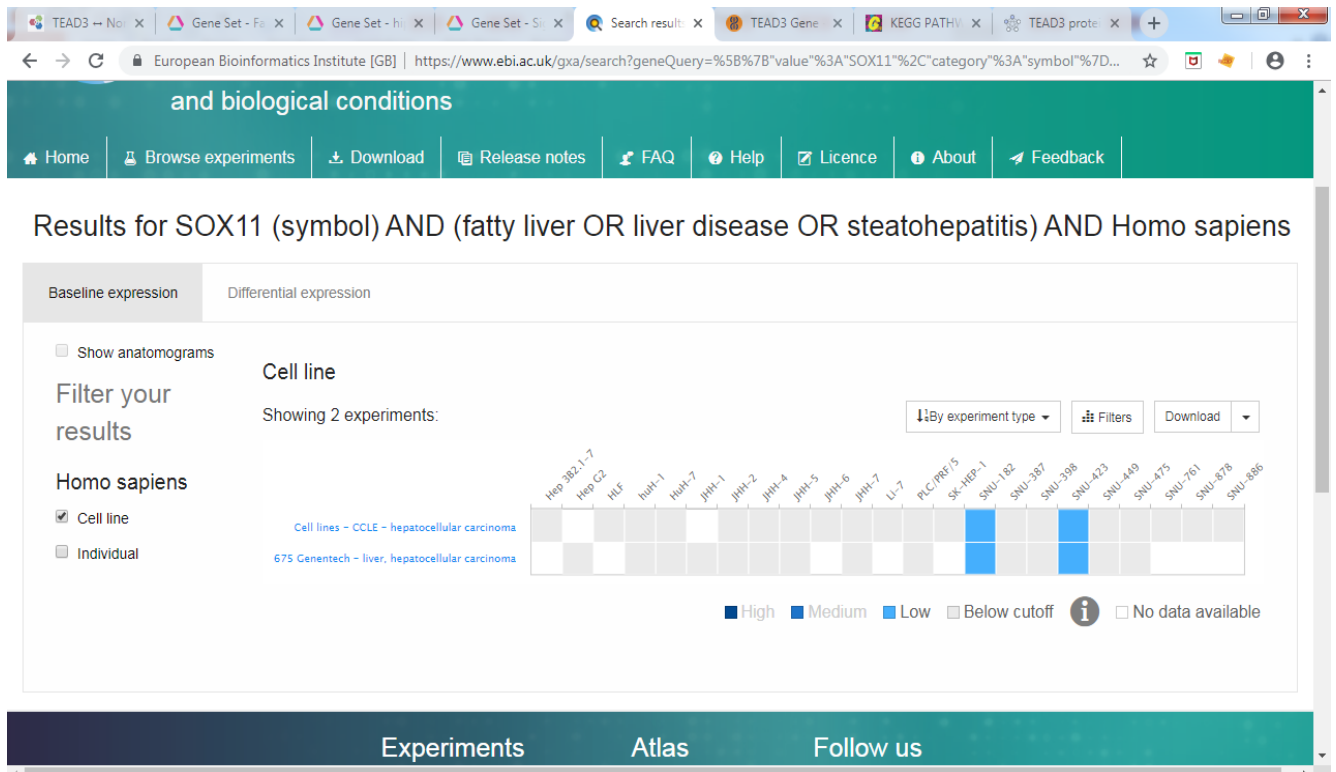


Figure S1D: Print screen shows correlation between SOX11 and NAFLD/NASH using Gene atlas database, <https://www.ebi.ac.uk/gxa/search?geneQuery=%5B%7B%22value%22%3A%22SOX11%22%2C%22category%22%3A%22symbol%22%7D%5D&species=homo%20sapiens&conditio>
[Query=%5B%7B%22value%22%3A%22fatty%20liver%22%7D%2C%7B%22value%22%3A%22liver%20disease%22%7D%2C%7B%22value%22%3A%22steatohepatitis%22%7D%5D&species=homo%20sapiens%22%3A%5B%22CELL%22%7D%5D%7D#baseline](https://www.ebi.ac.uk/gxa/search?geneQuery=%5B%7B%22value%22%3A%22fatty%20liver%22%7D%2C%7B%22value%22%3A%22liver%20disease%22%7D%2C%7B%22value%22%3A%22steatohepatitis%22%7D%5D&species=homo%20sapiens%22%3A%5B%22CELL%22%7D%5D%7D#baseline)

UniProtKB:P97471	Smad4	involved_in	GO:0009653 (P)	ECO:0000318	PMID:21873635	FB:FBgn0011648 more...	10090 Mus musculus	GO_Central
UniProtKB:P97471	Smad4	involved_in	GO:0030154 (P)	ECO:0000318	PMID:21873635	FB:FBgn0011648 more...	10090 Mus musculus	GO_Central

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SMAD4 ↔ **Non-alcoholic Fatty Liver Disease**

This gene-disease association may be inferred in part via [curated interactions](#) between *SMAD4* and any chemicals listed below, and a curated association between those chemicals and *Non-alcoholic Fatty Liver Disease*.

Filter by Association type: Filter

1-50 of 81 results.

First Previous 1 2 Next Last

Reference	Association
1. Kim JW, et al. Cigarette smoking differentially regulates inflammatory responses in a mouse model of nonalcoholic steatohepatitis depending on exposure time point. <i>Food Chem Toxicol.</i> 2020 Jan;135:110930.	Inferred via 1 chemical: Dietary Fats
2. Thongnak L, et al. Effects of dapagliflozin and statins attenuate renal injury and liver steatosis in high-fat/high-fructose diet-induced insulin resistant rats. <i>Toxicol Appl Pharmacol.</i> 2020 Jun 1;396:114997.	Inferred via 1 chemical: Dietary Fats
3. Han HY, et al. Preventive Effect of Citrus aurantium Peel Extract on High-Fat Diet-Induced Non-alcoholic Fatty Liver in Mice. <i>Biol Pharm Bull.</i> 2019;42(2):255-260.	Inferred via 1 chemical: Dietary Fats
4. Han X, et al. Acanthoic acid modulates lipogenesis in nonalcoholic fatty liver disease via FXR/LXR α -dependent manner. <i>Chem Biol Interact.</i> 2019 Sep 25;311:108794.	Inferred via 1 chemical: Dietary Fats
5. Kus E, et al. LSEC Fenestrae Are Preserved Despite Pro-inflammatory Phenotype of Liver Sinusoidal Endothelial Cells in Mice on High Fat Diet.	Inferred via 1 chemical: Dietary Fats

Jump to section: [Aliases](#) [Paralogs](#) [Disorders](#) [Pathways](#) [Domains](#) [Products](#) [Drugs](#) [Proteins](#) [Expression](#) [Publications](#) [Function](#) [Sources](#) [Genomics](#) [Summaries](#) [Localization](#) [Transcripts](#) [Orthologs](#) [Variants](#)

[Pathways & Interactions for SMAD4 Gene](#)

PathCards [SuperPathways for SMAD4 Gene](#)

GeneAnalytics Identify cells, diseases, pathways, functions & compounds, relevant to your genes of interest. [SIGN UP FREE >](#)

Filter: (1 result)

SuperPathway	Contained pathways
1 Hippo signaling pathway	Hippo signaling pathway

GenesLikeMe Genes that share pathways with SMAD4: [view](#)

Figure S1E: Print screen shows correlation between SMAD4 and NAFLD/NASH using Comparative Toxicogenomics Database,

← → ↻ Not secure | amp.pharm.mssm.edu/Harmonizome/gene_set/Fatty+Liver/CTD+Gene-Disease+Associations

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Fatty Liver Gene Set

Dataset [CTD Gene-Disease Associations](#)



Category Disease or phenotype associations

Type Disease

Description The presence of steatosis in the liver. ([Human Phenotype Ontology, HP_0001397](#))

External Link <http://ctdbase.org/detail.go?type=disease&acc=MESH:D005234>


Similar Terms

Downloads & Tools  

Genes

11463 genes/proteins associated with the disease **Fatty Liver** from the curated CTD Gene-Disease Associations dataset.

Show entries Filter

Symbol	Name	Standardized Value 
AMOTL2	angiotensin like 2	1.63384

Showing 1 to 1 of 1 entries (filtered from 11,463 total entries) Previous 1 Next

Figure S2A; Print screen shows correlation between AMOTL2 and Fatty liver using Harmonizome database: http://amp.pharm.mssm.edu/Harmonizome/gene_set/Fatty+Liver/CTD+Gene-Disease+Associations

Harmonizome All Q SEARCH DOWNLOAD VISUALIZE PREDICT API MOBILE ABOUT

Hippo Signaling Gene Set

Dataset [GO Biological Process Annotations](#)



Category Structural or functional annotations

Type Biological process

Description The series of molecular signals mediated by the serine/threonine kinase Hippo or one of its orthologs. In *Drosophila*, Hippo in complex with the scaffold protein Salvador (Sav), phosphorylates and activates Warts (Wts), which in turn phosphorylates and inactivates the Yorkie (Yki) transcriptional activator. The core fly components hippo, sav, wts and mats are conserved in mammals as STK4/3 (MST1/2), SAV1/WW45, LATS1/2 and MOB1. ([Gene Ontology, GO_0035329](#))

External Link <http://amigo.geneontology.org/amigo/term/GO:0035329>

Similar Terms

Downloads & Tools  

Genes

26 genes participating in the **hippo signaling** biological process from the curated GO Biological Process Annotations dataset.

Show entries Filter

Symbol	Name
AMOTL2	angiotensin like 2

Figure S2B; Print screen shows correlation between AMOTL2 and Hippo signaling using Harmonizome

Fatty Liver *Gene Set*

Dataset: CTD Gene-Disease Associations

Category: Disease or phenotype associations

Type: Disease

Description: The presence of steatosis in the liver. (Human Phenotype Ontology, HP_0001397)

External Link: <http://ctdbase.org/detail.go?type=disease&acc=MESH:D005234>

Similar Terms:

Downloads & Tools:

Genes

11463 genes/proteins associated with the disease **Fatty Liver** from the curated CTD Gene-Disease Associations dataset.

Show entries Filter:

Symbol	Name	Standardized Value
SOX11	SRY (sex determining region Y)-box 11	1.7716



Showing 1 to 1 of 1 entries (filtered from 11,463 total entries) Previous 1 Next

Figure S2C; Print screen shows correlation between SOX11 and Fatty liver using Harmonizome, http://amp.pharm.mssm.edu/Harmonizome/gene_set/Fatty+Liver/CTD+Gene-Disease+Associations

Process	Evidence Code	Pubs
cardiac ventricle formation	ISS	
cell differentiation	IBA	PubMed
closure of optic fissure	ISS	
cornea development in camera-type eye	ISS	
embryonic digestive tract morphogenesis	ISS	
embryonic skeletal system morphogenesis	ISS	

Figure S2D: Print screen shows correlation between SOX11 and Hippo signaling using ncbi Gene, <https://www.ncbi.nlm.nih.gov/gene/6664>

Positive Regulation Of Hippo Signaling Gene Set

Dataset	GO Biological Process Annotations
Category	Structural or functional annotations
Type	Biological process
Description	Any process that activates or increases the frequency, rate or extent of hippo signaling. (Gene Ontology, GO_0035332)
External Link	http://amigo.geneontology.org/amigo/term/GO:0035332
Similar Terms	<input type="text"/>
Downloads & Tools	 

Genes

1 genes participating in the **positive regulation of hippo signaling** biological process from the curated GO Biological Process Annotations dataset.

Show entries Filter

Symbol	Name
SOX11	SRY (sex determining region Y)-box 11

Figure S2E: Print screen shows correlation between SOX11 and Hippo signaling using Harmonizome, http://amp.pharm.mssm.edu/Harmonizome/gene_set/positive+regulation+of+hippo+signaling/GO+Biological+Process+Annotations

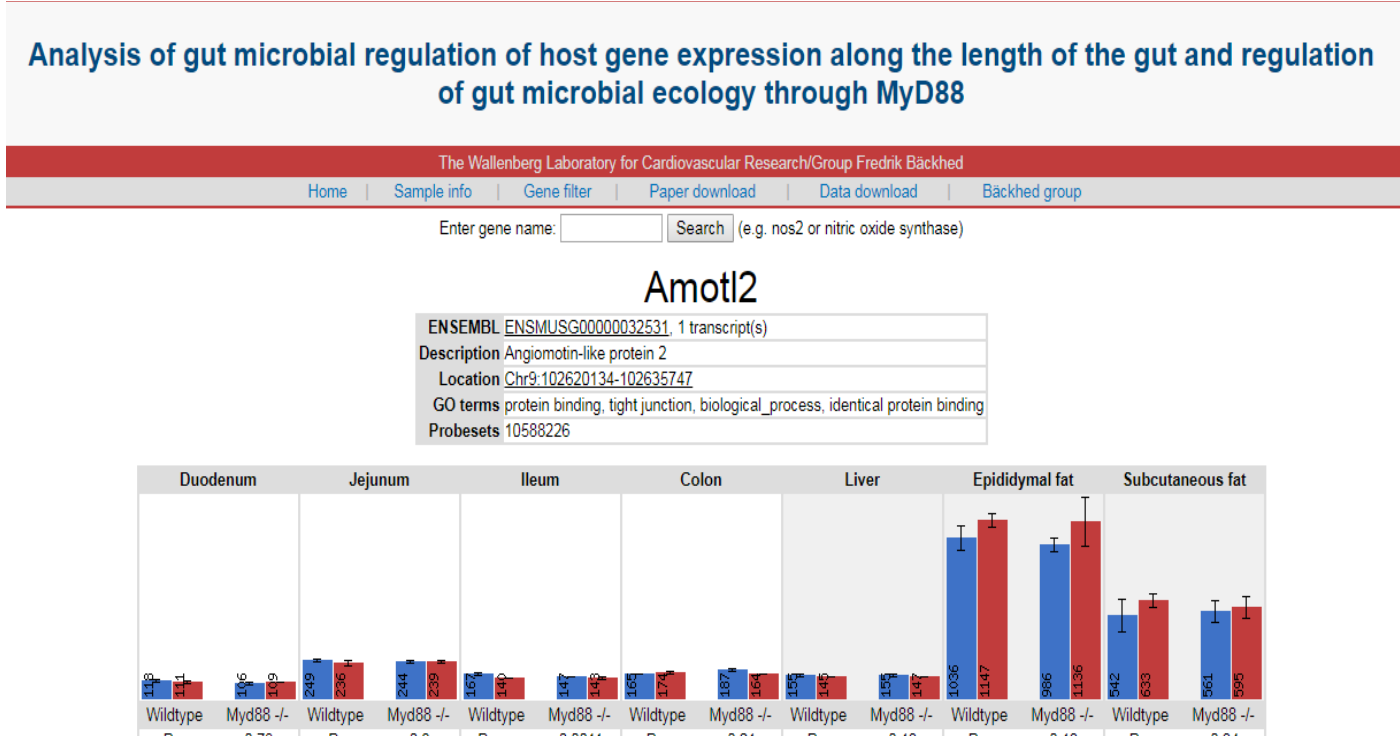


Figure S3A: Print screen shows Gut microbiota/ AMOTL2 crosstalk using Encyclopedia of gut microbiota regulated genes, http://microbiota.wall.gu.se/larsson/view_gene.php?gene=8913.

Analysis of gut microbial regulation of host gene expression along the length of the gut and regulation of gut microbial ecology through MyD88

The Wallenberg Laboratory for Cardiovascular Research/Group Fredrik Bäckhed

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Enter gene name: Search (e.g. nos2 or nitric oxide synthase)

Sox11

ENSEMBL [ENSMUSG00000063632](#), 1 transcript(s)

Description Transcription factor SOX-11

Location [Chr12:28019129-28027439](#)

GO terms DNA binding, RNA polymerase II transcription factor activity, enhancer binding, nucleus, transcription, regulation of transcription, DNA-dependent, multicellular organismal development, nervous system development, transcription activator activity...

Probesets 10399725

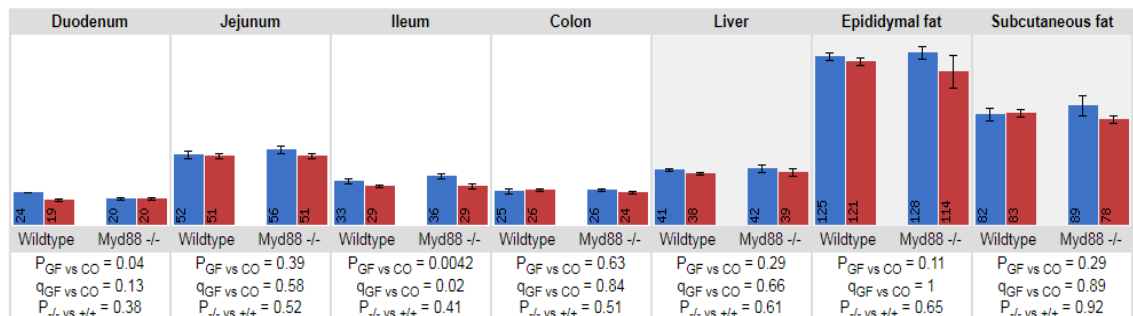


Figure S3B: Print screen shows Gut microbiota/ SOX11 crosstalk using Encyclopedia of gut microbiota regulated genes, http://microbiota.wall.gu.se/larsson/view_gene.php?gene=17626

Analysis of gut microbial regulation of host gene expression along the length of the gut and regulation of gut microbial ecology through MyD88

The Wallenberg Laboratory for Cardiovascular Research/Group Fredrik Bäckhed

Home | Sample info | Gene filter | Paper download | Data download | Backhed group

Enter gene name: Search (e.g. nos2 or nitric oxide synthase)

Smad4

ENSEMBL [ENSMUSG00000024515](#), 2 transcript(s)

Description Mothers against decapentaplegic homolog 4 (Mothers against DPP homolog 4)(SMAD 4)(Smad4)(Deletion target in pancreatic carcinoma 4 homolog)

Location [Chr18:73798670-73863395](#)

GO terms branching involved in ureteric bud morphogenesis, gastrulation with mouth forming second, kidney development, DNA binding, transcription factor activity, protein binding, collagen binding, intracellular...

Probesets 10459705

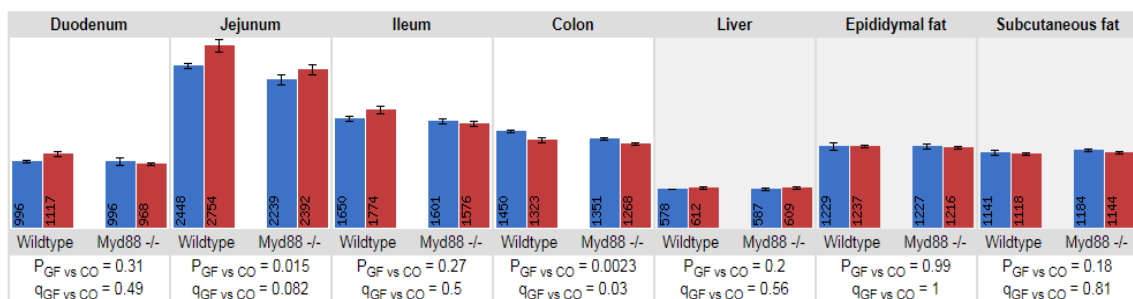


Figure S3C: Print screen shows Gut microbiota/ SMAD4 crosstalk using Encyclopedia of gut microbiota regulated genes, http://microbiota.wall.gu.se/larsson/view_gene.php?gene=4475

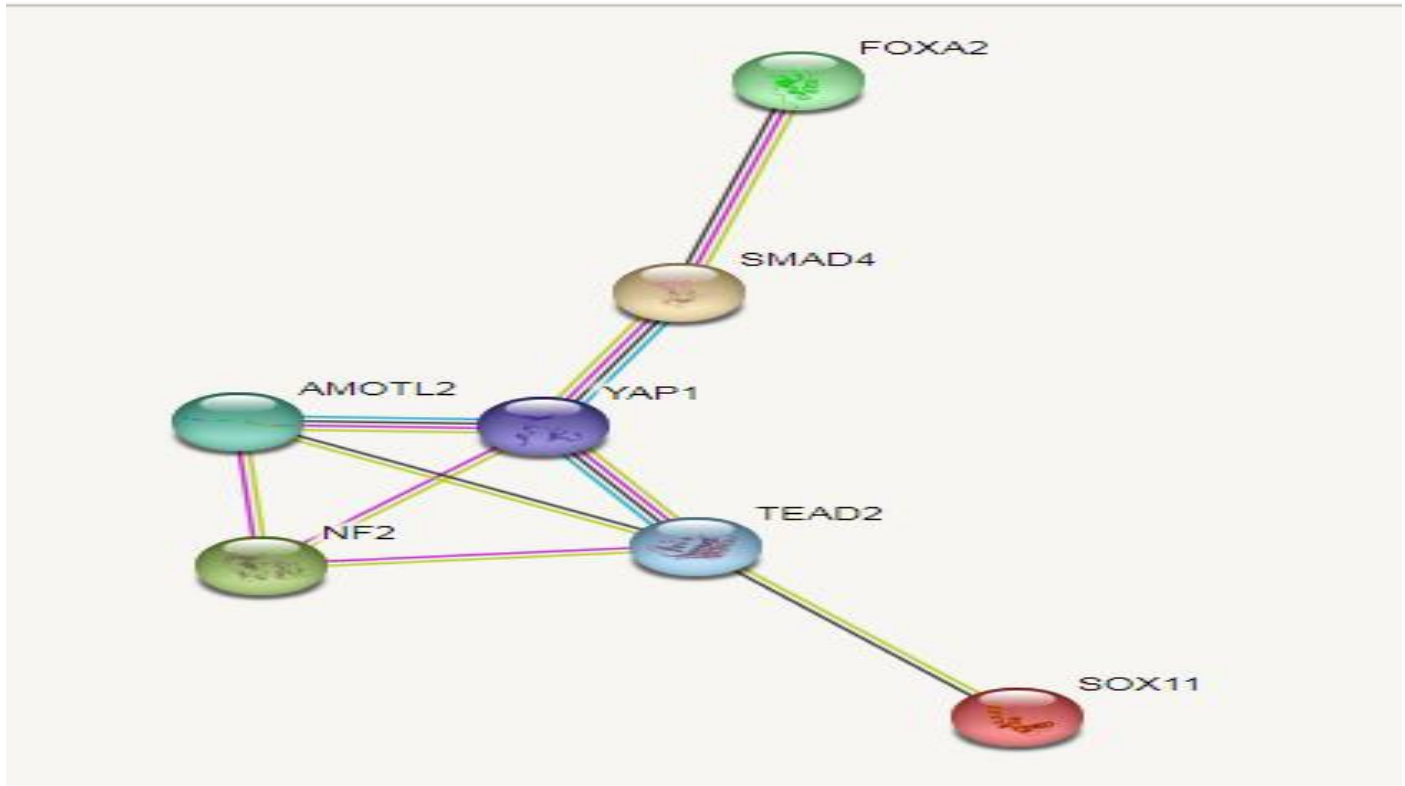
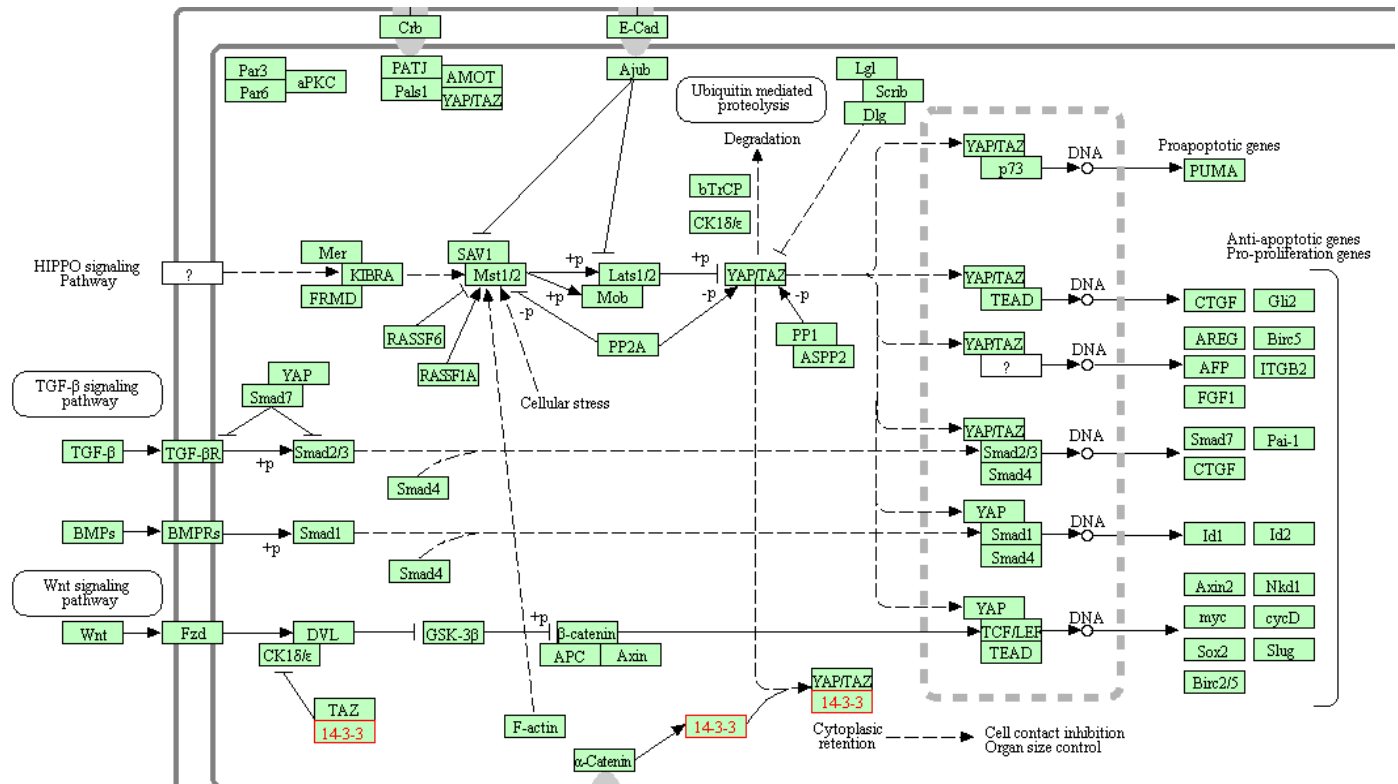


Figure S4A: print screen shows protein-protein interaction between the selected mRNAs and HIPPO target effectors by STRING database. <https://string-db.org/cgi/network.pl?taskId=w75m42gDhIj1>



SMAD4

Entrezid 4089

Genesymbol SMAD4

Alias DPC4;JIP;MADH4;MYHRS

Description Homo sapiens SMAD family member 4 (SMAD4), mRNA.

Chromosome 18

Ensemblid ENSG00000141646

Transcripts:

Refseq [△]	Ensemblid [△]	Length [△]	Startcds [△]	Endcds [△]
NM_005359	ENST00000342988	8789	539	2197

Interactions:

Mirna [△]	Refseqid [△]	Genesymbol [△]	Score [△]	Position [△]	Binding Site [△]	Au [△]	Me [△]	N Pairings [△]
hsa-miR-6806-5p	NM_005359	SMAD4	1.00	3UTR	4361,4394	0.38	-8.828	19
hsa-miR-6806-5p	NM_005359	SMAD4	0.85	3UTR	7430,7454	0.62	-11.09	19
hsa-miR-6806-3p	NM_005359	SMAD4	0.92	3UTR	2389,2415	0.6	-5.837	20
hsa-miR-6806-3p	NM_005359	SMAD4	0.85	3UTR	4316,4333	0.43	-12.371	15
hsa-miR-6806-3p	NM_005359	SMAD4	1.00	3UTR	8134,8156	0.59	-9.286	15
hsa-miR-6807-5p	NM_005359	SMAD4	0.92	5UTR	133,158	0.23	-10.876	17
hsa-miR-6807-3p	NM_005359	SMAD4	0.96	3UTR	4305,4330	0.46	-3.938	21

Figure S5C: SMAD4 mRNA is a direct target of miRNA-6807-5p that was retrieved from miRwalk database. It shows direct interaction between miRNA-6807-5p and SMAD4 Mrna.

<http://mirwalk.umm.uni-heidelberg.de/human/gene/16399/?page=277>

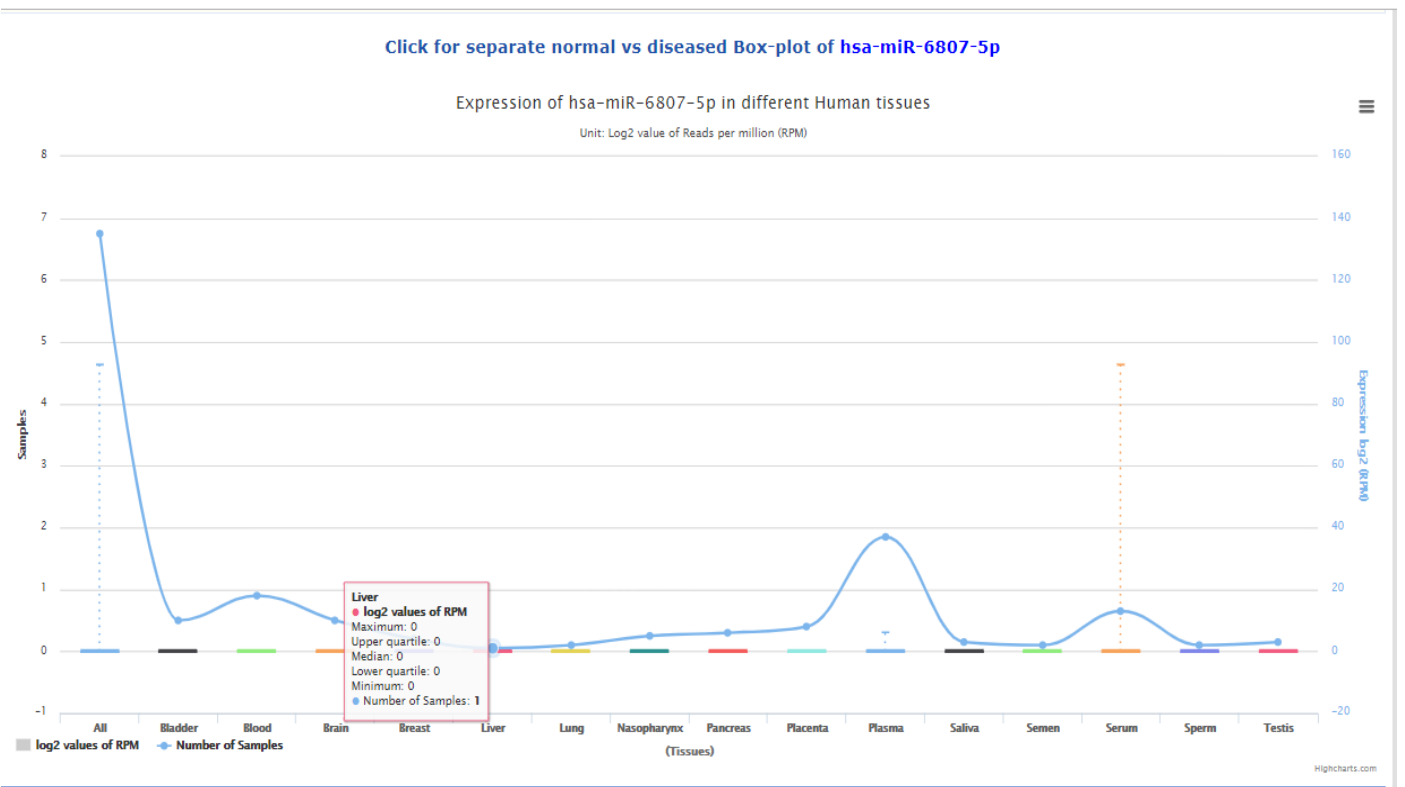


Figure S6A: Gene expression of has-miR-6807-5p in liver that was retrieved from miRmine database

<http://guanlab.cmb.med.umich.edu/mirmine/single.php?mirna=hsa-miR-6807-5p&tissue=liver&cline=>

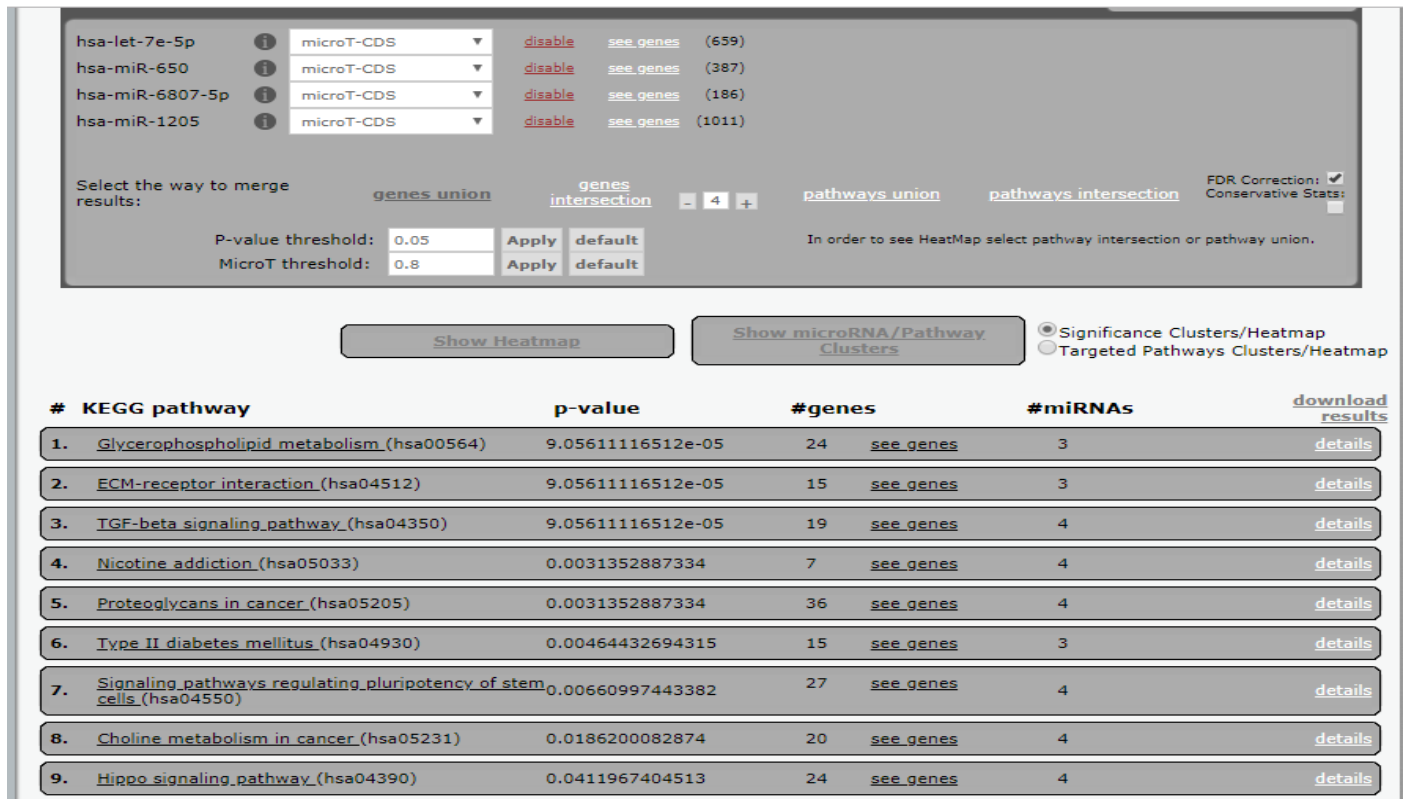


Figure S6B: Print screen shows pathway enrichment analysis of has-miR-6807-5p that was done by DIANA database tools: miRpath, <http://snf-515788.vm.okeanos.grnet.gr/>. It highlights the role of this miRNA in Hippo signaling.