Marker genes for obesity and NASH progression

Kiel clinical expression study

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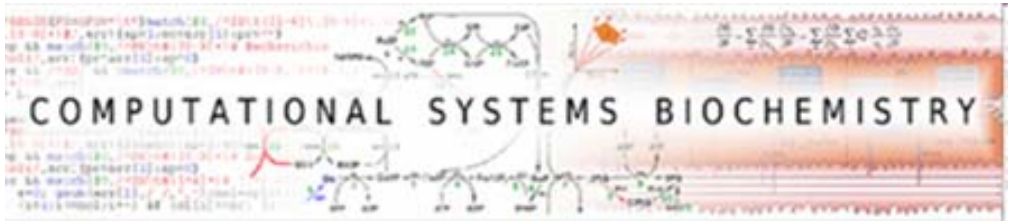

Outline

- Introduction
- Obesity markers
- Steatosis markers
- Inflammation markers
- Fibrosis markers
- General disease markers

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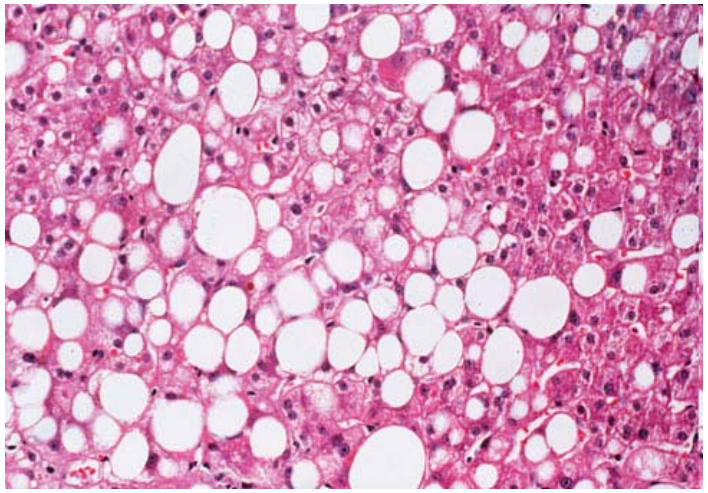
Kiel study

- Hospital liver biopsies
  - liver disease patients
  - bariatric surgery candidates
- Full-genome gene expression
- Detailed patient information
  - BMI (quant.)
  - liver fat % measure (quant.)
  - Ballooning cells (qual.)
  - Inflammation (qual.)
  - Fibrosis (qual.)
  - age, diabetes, gallstone, weight, height, bariatric surgery

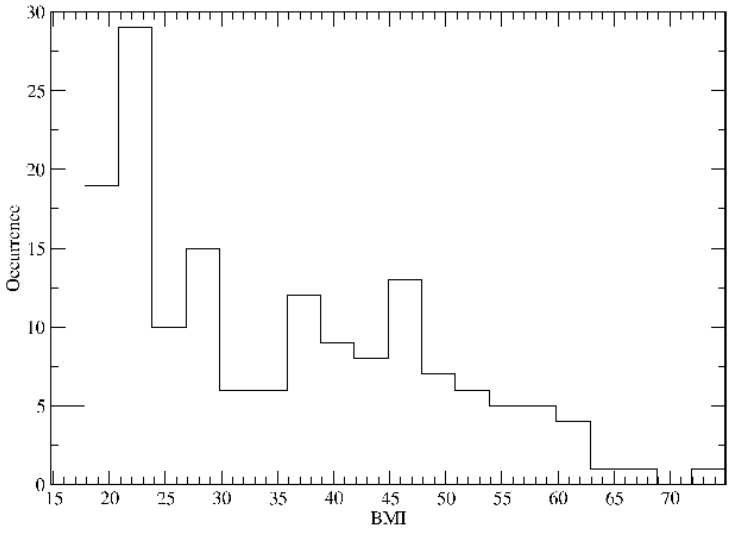


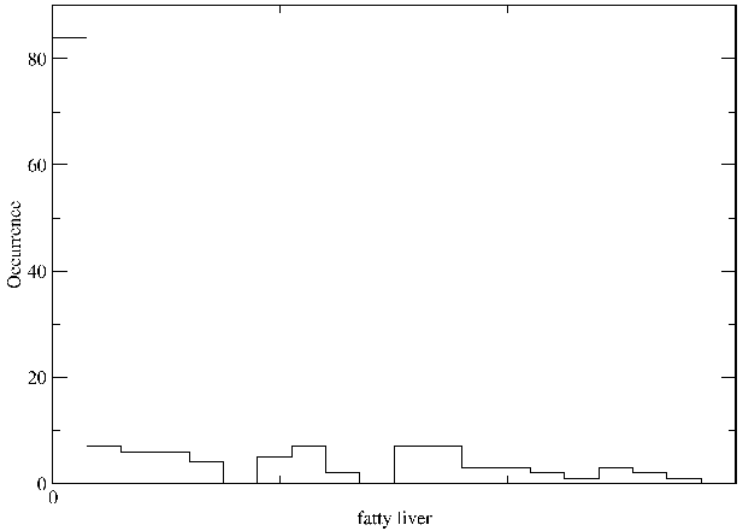
Balloon cells

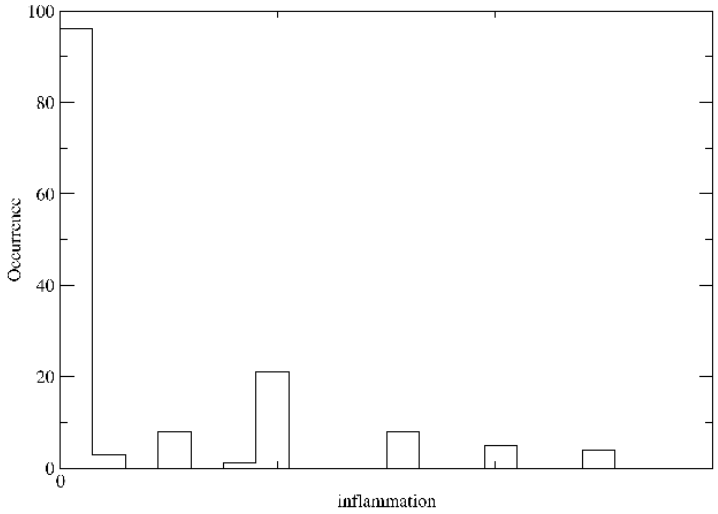
5 Dimensions

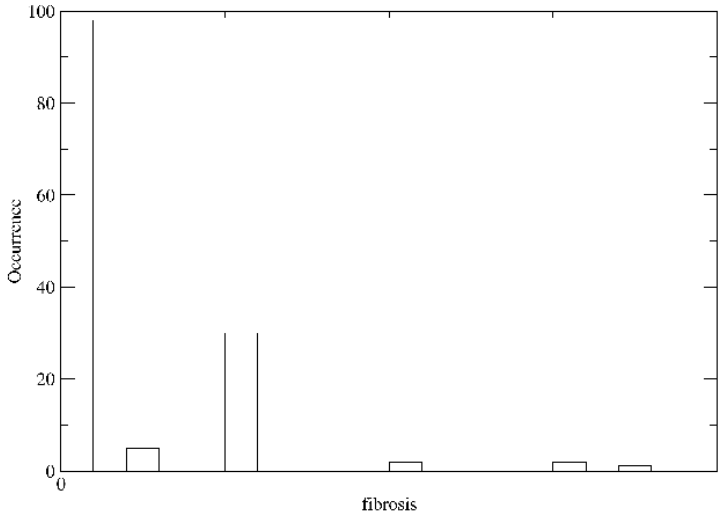
- BMI (quant.)
- Steatosis (quant.)
  - fat % measure (quant.)
  - Ballooning cells (qual.)
- Inflammation (qual.)
- Fibrosis (qual.)
- NAFLD consensus (average of steatosis, inflammation, fibrosis)

Histograms of parameters









Aim

Gene expression correlated with obesity and NASH

EITHER

- involved in disease mechanism
  - part of causal chain

OR

- consequence of disease
  - compensation
  - decompensation

Method

- For each phenomenological parameter
  - obesity
  - steatosis, inflammation, fibrosis
  - NAFLD consensus
- For each gene, compute
  - Correlation (r)
  - t-test (that non-zero correlation)
- Genes with maximal correlation |r|
- Split metabolic and non-metabolic genes

→ 10 ranked lists

Correlations among phenomenological parameters

	steatosis	inflammation	fibrosis	disease
obesity	0.62 $p=0$	0.2 $p=0.01$	0.15 $p=0.08$	0.37 $p<2.7\cdot10^{-6}$
steatosis	•	0.45 $p<1.1\cdot10^{-8}$	0.36 $p<1.2\cdot10^{-5}$	0.72 $p=0$
inflammation		•	0.55 $p<2.4\cdot10^{-12}$	0.87 $p=0$
fibrosis			•	0.76 $p=0$

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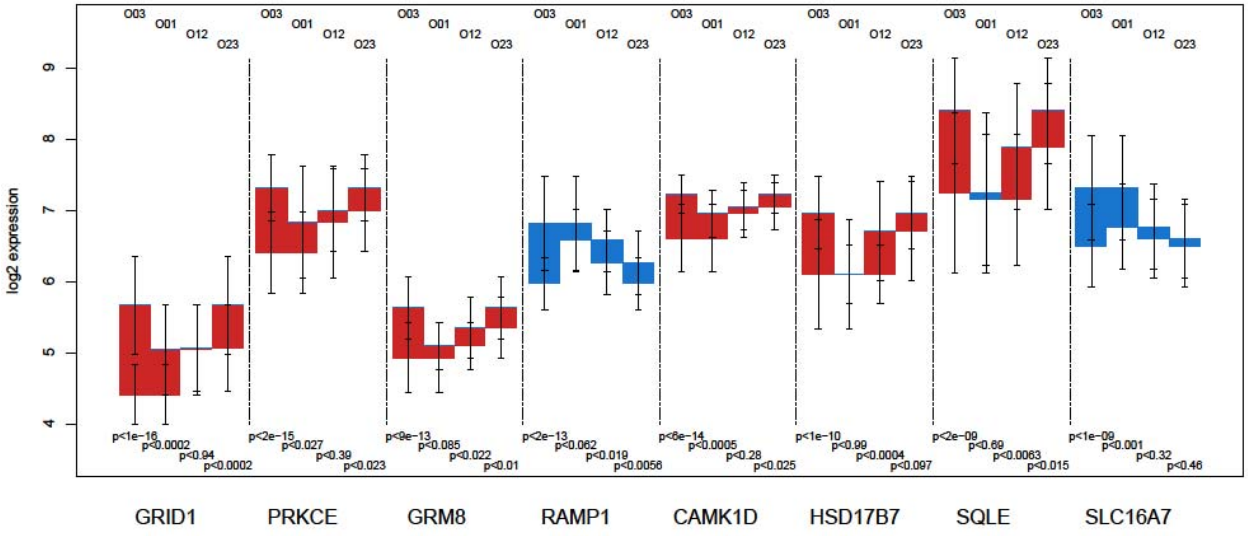
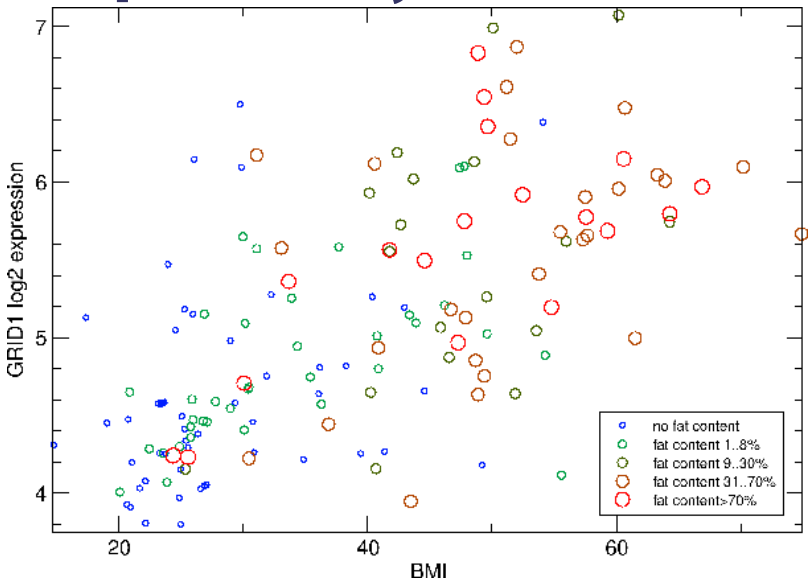
Obesity markers

Gene	r	p<	rank non-metabolic	rank total	
GRID1	0.66	0	1	1	glutamate receptor, ionotropic, delta 1
PRKCE	0.58	$4.4 \cdot 10^{-16}$	2	2	protein kinase C, epsilon
GRM8	0.57	$1.6 \cdot 10^{-15}$	3	3	glutamate receptor, metabotropic 8
RAMP1	-0.57	$2.2 \cdot 10^{-15}$	4	4	receptor (G protein-coupled) activity modifying protein 1
CAMK1D	0.56	$3.3 \cdot 10^{-15}$	5	5	calcium/calmodulin-dependent protein kinase ID
STAB2	0.55	$2.5 \cdot 10^{-14}$	6	6	stabilin 2

Gene	r	p<	rank metabolic	rank total	
HSD17B7	0.53	$3.8 \cdot 10^{-13}$	1	11	hydroxysteroid (17-beta) dehydrogenase 7
SQLE	0.5	$8.5 \cdot 10^{-12}$	2	21	squalene epoxidase
SLC16A7	-0.48	$9.5 \cdot 10^{-11}$	3	41	solute carrier family 16 (monocarboxylate transporter), member 7
COX7B	-0.47	$3.3 \cdot 10^{-10}$	4	50	
ABCB11	-0.46	$4.1 \cdot 10^{-10}$	5	56	
CA13	0.46	$6.3 \cdot 10^{-10}$	6	61	carbonic anhydrase XIII



GRID1, Glutamate receptor δ 1 subunit
Top obesity marker

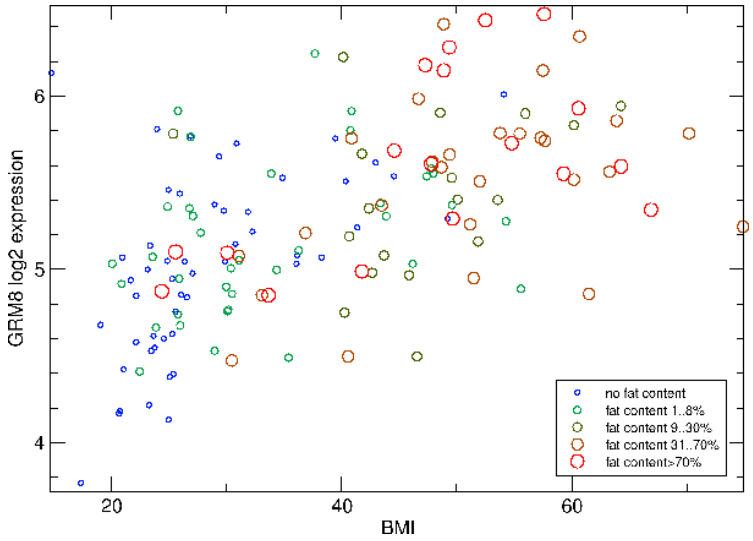


Factor	r	p<	rank metabolic	rank total
obesity	0.66	0	1	1
steatosis	0.48	$4.1 \cdot 10^{-10}$	20	20
inflammation	0.15	0.08	4571	4761
fibrosis	0.14	0.1	5283	5521
NAFLD	0.29	0.0003	713	758

- glutamate receptor ligand-gated ion channel
- fast excitatory synaptic transmission in CNS
- key role in synaptic plasticity
- association: GRID1 variants—increased risk of schizophrenia
- Protein not detected in liver (4 individuals, nextprot.org)

Glutamate receptor, metabotropic 8

GRM8, Obesity marker, non-metabolic



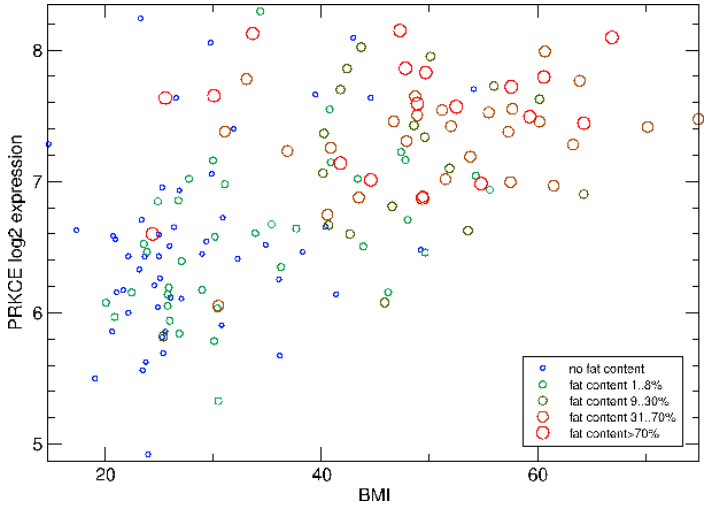
Factor	r	p<	rank metabolic	rank total
obesity	0.57	$1.6 \cdot 10^{-15}$	3	3
steatosis	0.43	$2.9 \cdot 10^{-8}$	56	61
inflammation	0.16	0.05	3387	3532
fibrosis	0.02	0.84	23864	24655
NAFLD	0.25	0.002	1253	1328

- G-protein coupled receptor for glutamate
- signaling inhibits adenylate cyclase activity
- reported in brain

also: RAMP1, receptor (G protein-coupled) activity modifying protein 1 (negatively correlated)

Protein kinase C, ε, PRKCE

Obesity marker, non-metabolic

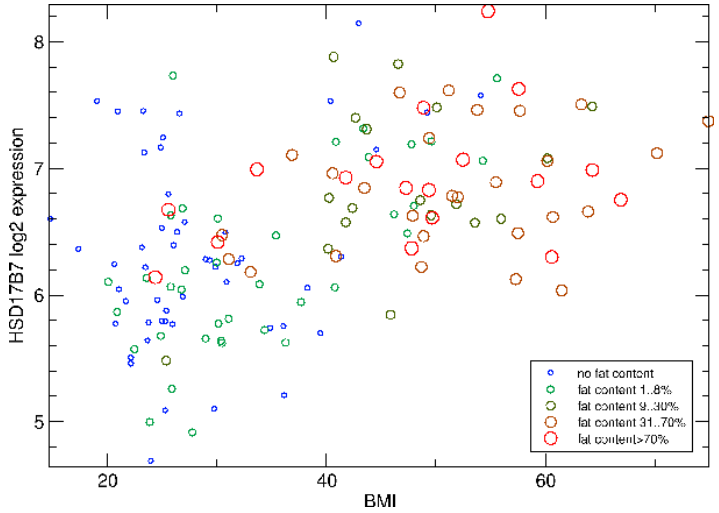


Factor	r	p<	rank metabolic	rank total
obesity	0.58	$4.4 \cdot 10^{-16}$	2	2
steatosis	0.54	$7.3 \cdot 10^{-13}$	3	3
inflammation	0.18	0.02	2254	2353
fibrosis	0.18	0.04	2988	3143
NAFLD	0.36	$7.2 \cdot 10^{-6}$	263	283

- phospholipid- and DAG-dependent serine/threonine-protein kinase
- wide range of functions
- contributes HGF-induced cell migration
- regulation of multiple cellular processes linked to cytoskeletal proteins

also: CAMK1D, calcium/calmodulin-dependent protein kinase ID

Hydroxysteroid (17-β) dehydrogenase 7
HSD17B7, obesity markers, metabolic

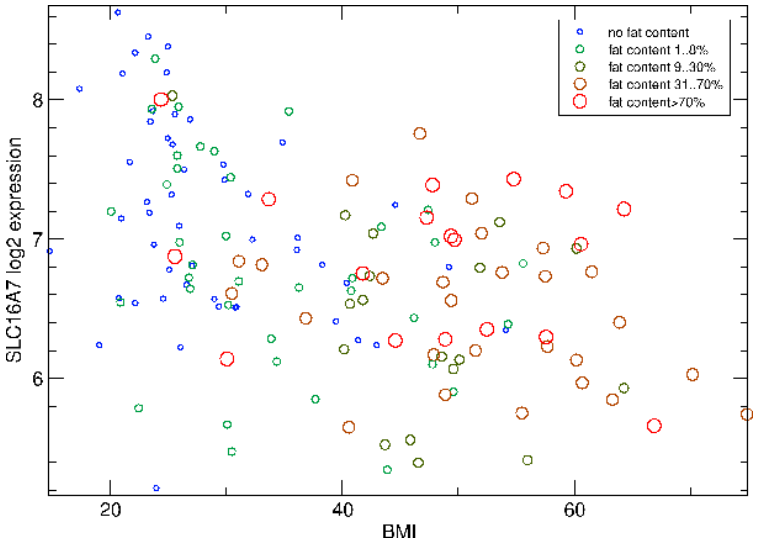


Factor	r	p<	rank metabolic	rank total
obesity	0.53	$3.8 \cdot 10^{-13}$	1	11
steatosis	0.36	$6.0 \cdot 10^{-6}$	20	297
inflammation	-0.03	0.75	743	23041
fibrosis	0.07	0.44	532	15561
NAFLD	0.12	0.13	321	8303

- HSD17B7: 3-keto-steroid reductase (17-beta-hydroxysteroid dehydrogenase 7, estradiol 17-beta-dehydrogenase 7)
- biosynthesis cholesterol, sex steroids

also: Squalene epoxidase SQLE

Monocarboxylate Transporter 2, SLC16A7, Obesity marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.48	$9.5 \cdot 10^{-11}$	3	41
steatosis	-0.2	0.01	171	4210
inflammation	0.13	0.11	231	6346
fibrosis	0.06	0.49	568	16921
NAFLD	0.01	0.89	842	26148

- rapid transport across the plasma membrane of many monocarboxylates
- highest affinity for pyruvate
- restricted expression in normal tissues, but widely expressed in cancer cells

Obesity markers

- Several receptors and signaling proteins correlate
  - Glutamate sensing increased
- Genes of cholesterol synthesis
  - Lipoprotein turnover
- Monocarboxylate transport, anti-correlate
  - less cancerous hepatocytes

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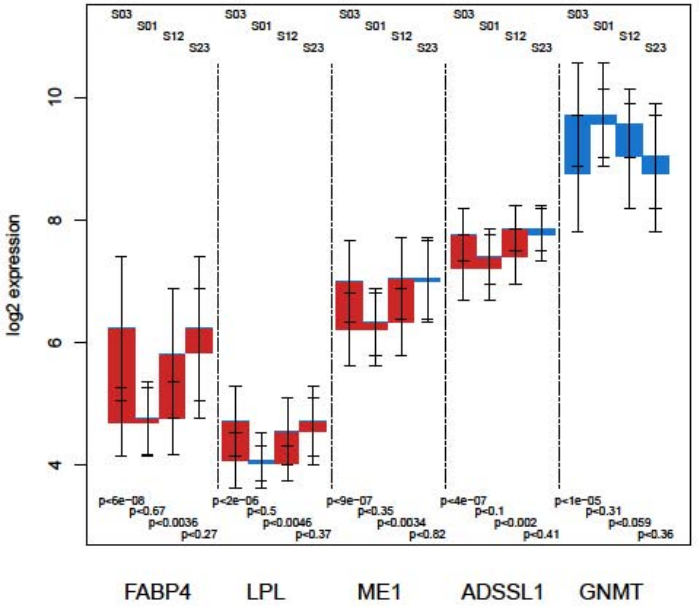
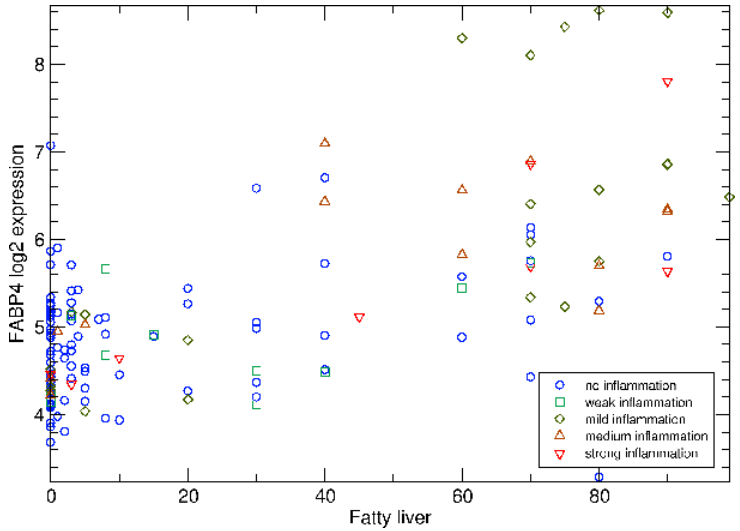
Steatosis markers

Gene	r	p<	rank non-metabolic	rank total	
FABP4	0.63	0	1	1	fatty acid binding protein 4, adipocyte
LPL	0.56	$9.8 \cdot 10^{-14}$	2	2	lipoprotein lipase
PRKCE	0.54	$7.3 \cdot 10^{-13}$	3	3	protein kinase C, epsilon
IGFBP2	-0.53	$1.6 \cdot 10^{-12}$	4	4	insulin-like growth factor binding protein 2, 36kDa
CAMK1D	0.52	$4.9 \cdot 10^{-12}$	5	5	calcium/calmodulin-dependent protein kinase ID
PRAMEF10	0.52	$7.5 \cdot 10^{-12}$	8	8	PRAME family member 10

Gene	r	p<	rank metabolic	rank total	
ME1	0.48	$6.1 \cdot 10^{-10}$	1	21	malic enzyme 1, NADP(+)-dependent, cytosolic
COL1A1	0.45	$5.2 \cdot 10^{-9}$	2	39	collagen, type I, alpha 1
ADSSL1	0.45	$9.6 \cdot 10^{-9}$	3	48	adenylosuccinate synthase like 1
COL1A2	0.44	$2.2 \cdot 10^{-8}$	4	56	collagen, type I, alpha 2
GNMT	-0.44	$2.2 \cdot 10^{-8}$	5	57	glycine N-methyltransferase
ABCB11	-0.42	$6.7 \cdot 10^{-8}$	6	78	



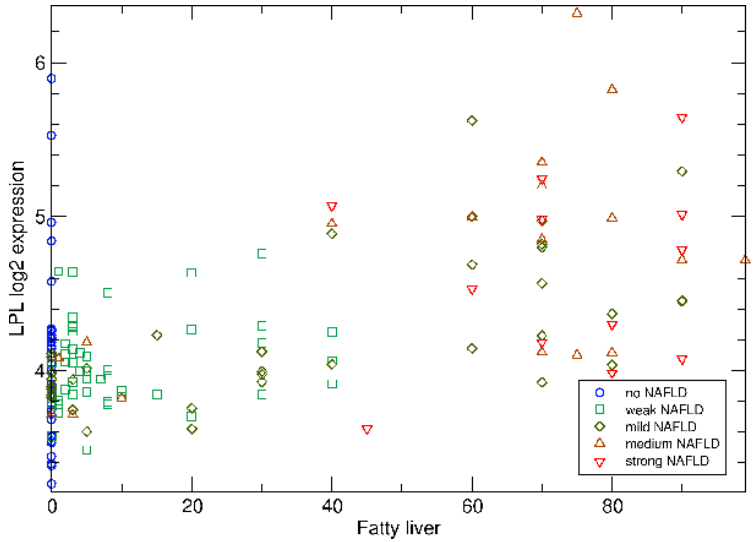
Fatty acid binding protein 4, adipocyte
FABP4, steatosis marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.43	$1.2{\cdot}10^{-8}$	115	122
steatosis	0.63	0	1	1
inflammation	0.37	$3.8{\cdot}10^{-6}$	97	102
fibrosis	0.38	$3.6{\cdot}10^{-6}$	155	174
NAFLD	0.57	$2.2{\cdot}10^{-14}$	2	2

- lipid transport in adipocytes

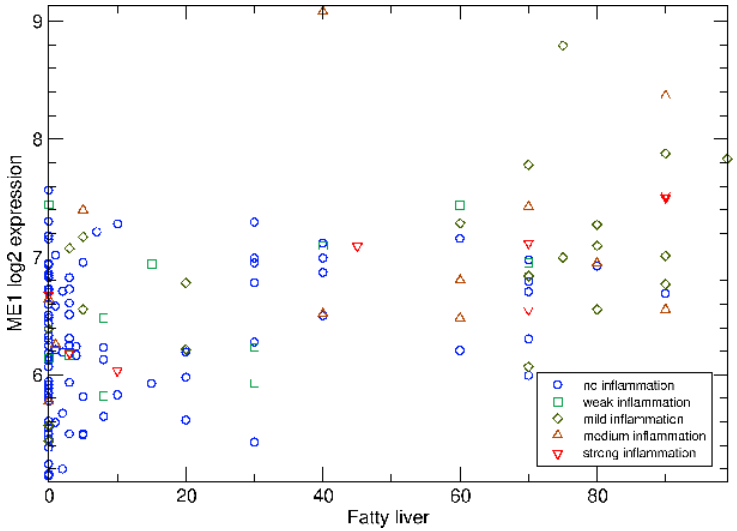
Lipoprotein lipase, LIPL, steatosis marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.32	$3.0 \cdot 10^{-5}$	1135	1180
steatosis	0.56	$9.8 \cdot 10^{-14}$	2	2
inflammation	0.24	0.003	857	896
fibrosis	0.24	0.01	1231	1309
NAFLD	0.43	$4.1 \cdot 10^{-8}$	91	101

- expressed in heart, muscle, and adipose tissue (cells utilizing) VLDL

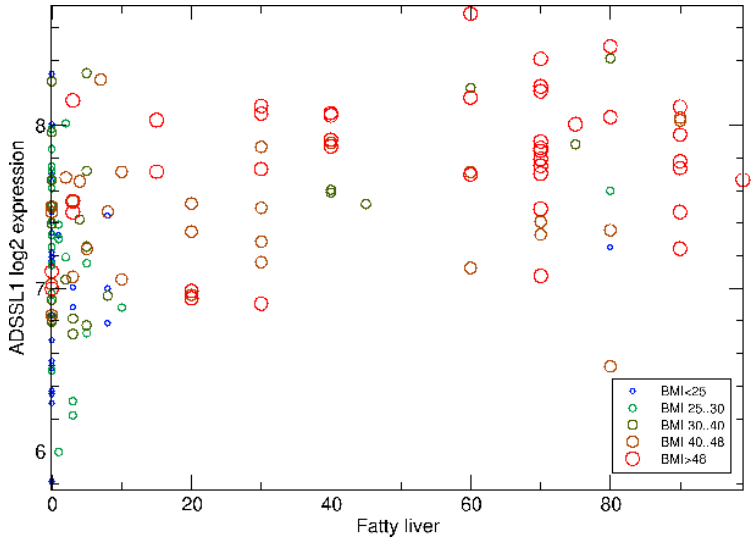
Malic enzyme 1, ME1, steatosis marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.37	$1.4 \cdot 10^{-6}$	24	506
steatosis	0.48	$6.1 \cdot 10^{-10}$	1	21
inflammation	0.34	$2.1 \cdot 10^{-5}$	8	173
fibrosis	0.38	$3.2 \cdot 10^{-6}$	18	169
NAFLD	0.48	$3.0 \cdot 10^{-10}$	4	37

- central metabolism enzyme, TCA

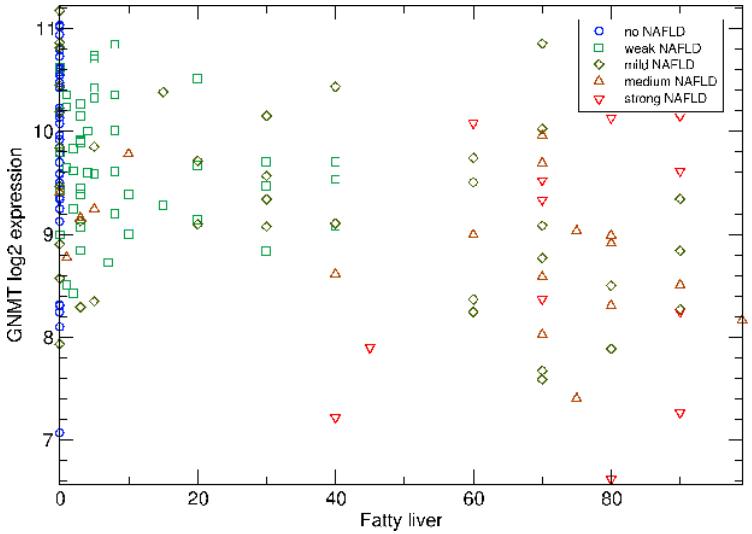
Adenylosuccinate synthase like 1, ADSSL1, steatosis marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.43	$7.9 \cdot 10^{-9}$	7	111
steatosis	0.45	$9.6 \cdot 10^{-9}$	3	48
inflammation	0.19	0.02	87	1953
fibrosis	0.13	0.12	260	6273
NAFLD	0.31	$9.9 \cdot 10^{-5}$	34	593

- normally found in muscle cells

Glycine N-methyltransferase, GNMT, steatosis marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.27	0.0004	92	2393
steatosis	-0.44	$2.2 \cdot 10^{-8}$	5	57
inflammation	-0.3	0.0002	17	414
fibrosis	-0.37	$6.8 \cdot 10^{-6}$	24	202
NAFLD	-0.45	$5.2 \cdot 10^{-9}$	6	65

- methylgroups
- Ahrens et al.: NASH accompanied by higher DNA methylation content

Steatosis markers

- Dedifferentiation
  - several genes noted in adipocytes
  - enzymes normally found in adipocytes, myocytes
- Methyl group supply
  - glycine methyltransferase
- Proteins extracellular matrix
  - Col1a1 Col1a2

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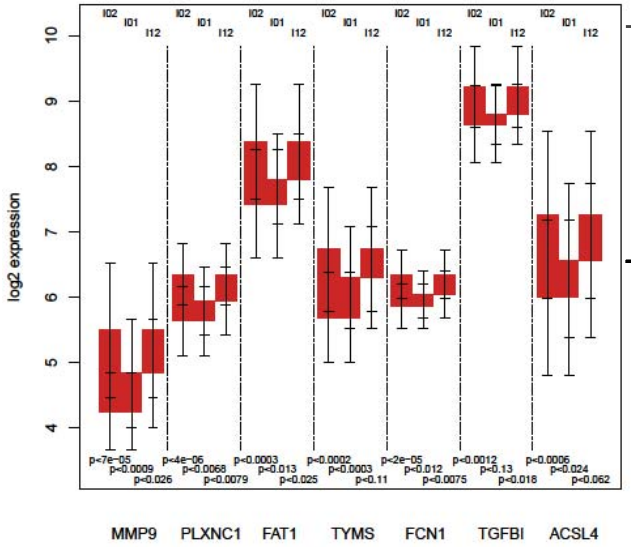
Inflammation marker, non-metabolic

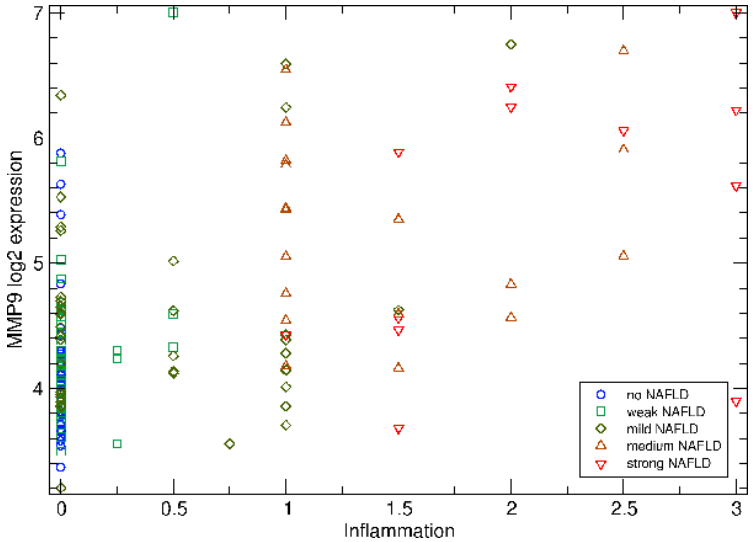


Gene	r	p<	rank non-metabolic	rank total	
MMP9	0.54	$1.3{\cdot}10^{-12}$	1	1	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
UBD	0.52	$1.4{\cdot}10^{-11}$	2	2	
PLXNC1	0.5	$4.9{\cdot}10^{-11}$	3	3	plexin C1
FAT1	0.47	$1.3{\cdot}10^{-9}$	4	4	FAT atypical cadherin 1
LAMA3	0.47	$1.4{\cdot}10^{-9}$	5	5	laminin, alpha 3
CXCL10	0.47	$1.7{\cdot}10^{-9}$	6	6	chemokine (C-X-C motif) ligand 10

Gene	r	p<	rank metabolic	rank total	
TYMS	0.46	$4.1{\cdot}10^{-9}$	1	12	thymidylate synthetase
FCN1	0.44	$1.2{\cdot}10^{-8}$	2	19	ficolin (collagen/fibrinogen domain containing) 1
TGFBI	0.42	$6.5{\cdot}10^{-8}$	3	31	transforming growth factor, beta-induced, 68kDa
ACSL4	0.38	$1.4{\cdot}10^{-6}$	4	72	acyl-CoA synthetase long-chain family member 4
ABCC4	0.37	$2.7{\cdot}10^{-6}$	5	86	ATP-binding cassette, sub-family C (CFTR/MRP), member 4
ACER3	0.35	$1.0{\cdot}10^{-5}$	6	129	

- qualitative parameter, lower r

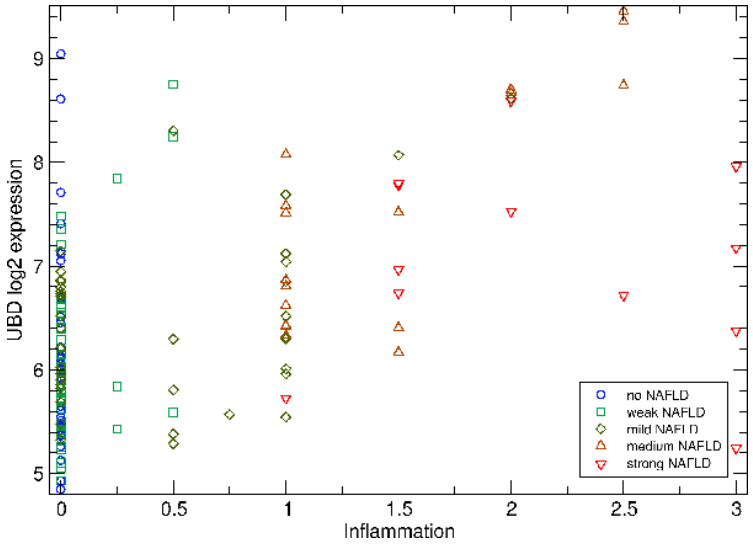
Matrix metallopeptidase 9, MMP9, inflammation marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.28	0.0004	2219	2310
steatosis	0.4	$3.8 \cdot 10^{-7}$	127	137
inflammation	0.54	$1.3 \cdot 10^{-12}$	1	1
fibrosis	0.17	0.04	3317	3482
NAFLD	0.48	$3.0 \cdot 10^{-10}$	35	39

- gelatinase B, 92kDa, type IV, collagenase
- degrades extracellular matrix

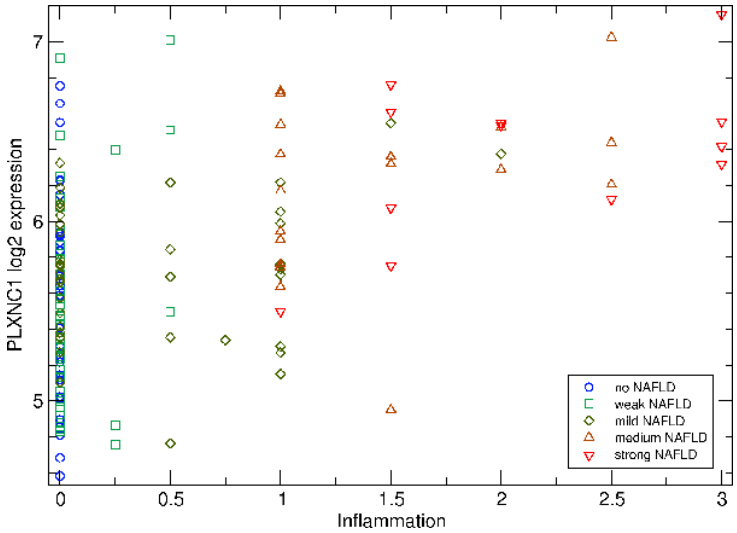
Ubiquitin D, UBD, inflammation marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.13	0.1	11683	12095
steatosis	0.13	0.1	9477	9829
inflammation	0.52	$1.4 \cdot 10^{-11}$	2	2
fibrosis	0.42	$2.5 \cdot 10^{-7}$	90	99
NAFLD	0.47	$1.5 \cdot 10^{-9}$	45	49

- attachement leads to rapid 26S proteasome degradation

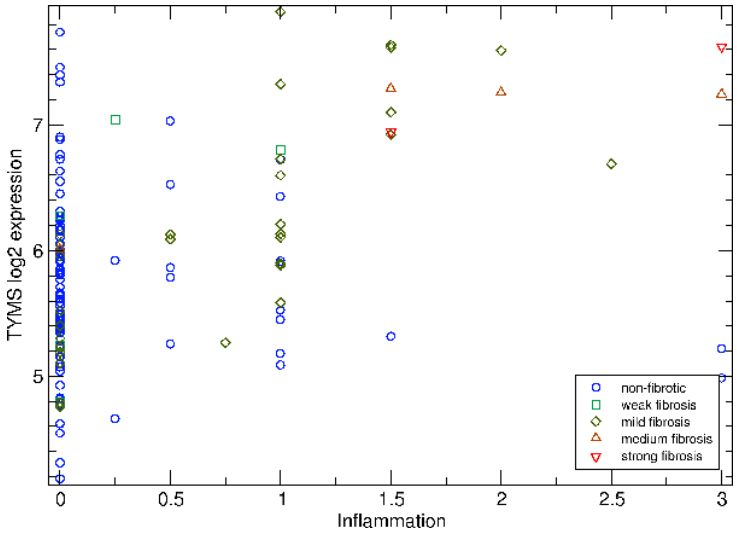
Plexin C1, PLXNC1, inflammation marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.13	0.09	11224	11624
steatosis	0.29	0.0004	1080	1144
inflammation	0.5	$4.9 \cdot 10^{-11}$	3	3
fibrosis	0.32	$9.8 \cdot 10^{-5}$	358	392
NAFLD	0.47	$1.2 \cdot 10^{-9}$	41	45

- receptor for SEMA7A, herpesvirus Sema protein, etc.
- binding triggers secretion of IL6 and IL8.
- rearrangement of the cytoskeleton

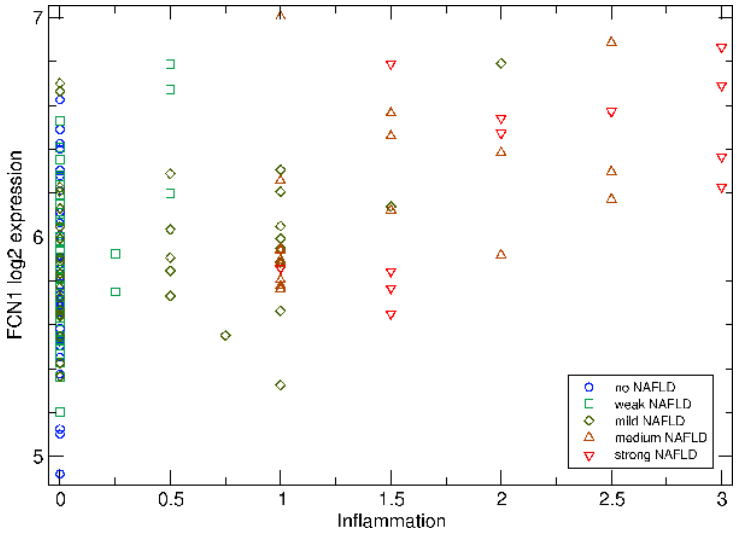
Thymidylate synthetase, TYMS, inflammation marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.09	0.23	532	16116
steatosis	0.25	0.002	94	2031
inflammation	0.46	$4.1 \cdot 10^{-9}$	1	12
fibrosis	0.41	$6.2 \cdot 10^{-7}$	12	120
NAFLD	0.49	$1.0 \cdot 10^{-10}$	2	27

- DNA replication and repair

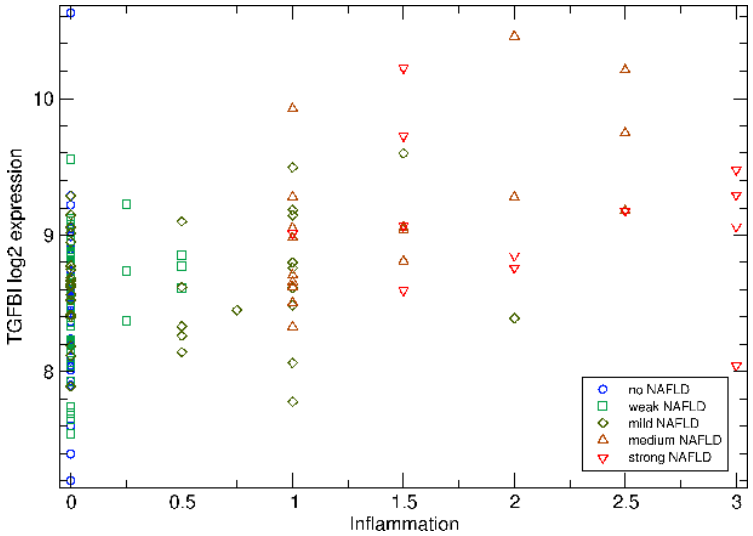
Ficolin 1, FCN1, inflammation marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.05	0.55	715	21898
steatosis	0.16	0.04	266	6987
inflammation	0.44	$1.2 \cdot 10^{-8}$	2	19
fibrosis	0.21	0.01	110	1872
NAFLD	0.35	$1.1 \cdot 10^{-5}$	21	307

- collagen/fibrinogen domain containing
- expressed in leukocytes
- plasma protein
- elastin binding

TGFβ-induced 68kDa protein, TGFBI, inflammation marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.07	0.35	610	18591
steatosis	0.21	0.01	159	3829
inflammation	0.42	$6.5 \cdot 10^{-8}$	3	31
fibrosis	0.35	$2.3 \cdot 10^{-5}$	27	282
NAFLD	0.43	$3.8 \cdot 10^{-8}$	10	99

- adhesion protein
- binds type I, II, IV collagens
- cartilage: endochondral bone formation

Inflammation marker

- Secreting interleukins
  - plexin C1: IL6 IL8 secretion
- Tissue reorganization
  - Protein degradation
  - Cellular polarization/migration
    - cadherin 1
  - Ficolin 1, plasma protein
  - Adhesion protein, TGFBI
- DNA replication
  - thymidylate synthase

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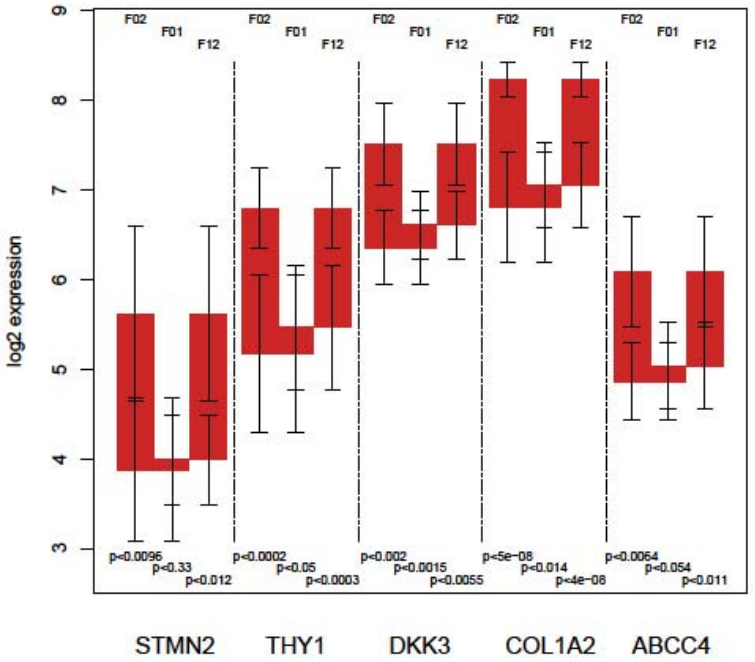
- Inflammation markers
- Fibrosis markers
- General disease markers

Fibrosis markers

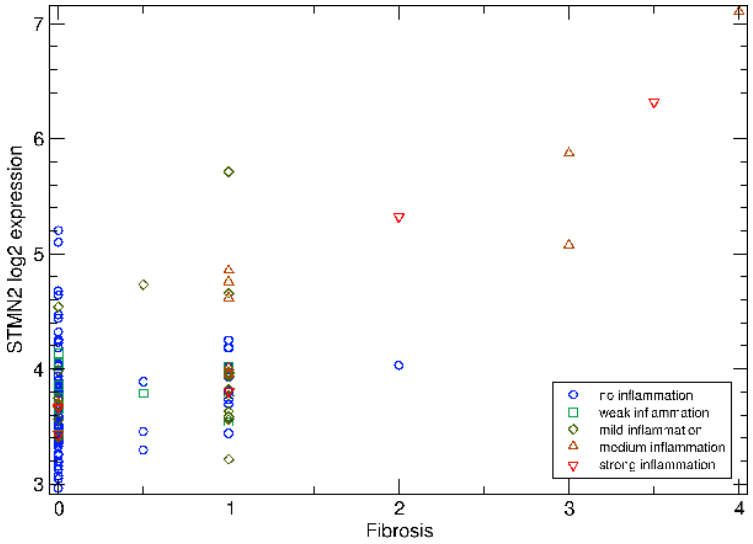
Gene	r	p<	rank non-metabolic	rank total	
STMN2	0.66	0	1	1	stathmin-like 2
THY1	0.58	$4.8 \cdot 10^{-14}$	2	2	Thy-1 cell surface antigen
DKK3	0.57	$2.2 \cdot 10^{-13}$	3	3	dickkopf WNT signaling pathway inhibitor 3
CFTR	0.56	$5.6 \cdot 10^{-13}$	4	4	cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)
AEBP1	0.56	$1.1 \cdot 10^{-12}$	5	5	AE binding protein 1
NFASC	0.53	$1.4 \cdot 10^{-11}$	6	7	neurofascin

Gene	r	p<	rank metabolic	rank total	
COL1A2	0.54	$7.0 \cdot 10^{-12}$	1	6	collagen, type I, alpha 2
COL1A1	0.5	$3.3 \cdot 10^{-10}$	2	23	collagen, type I, alpha 1
ABCC4	0.49	$8.1 \cdot 10^{-10}$	3	25	ATP-binding cassette, sub-family C (CFTR/MRP), member 4
COL4A2	0.49	$1.3 \cdot 10^{-9}$	4	27	collagen, type IV, alpha 2
CA12	0.47	$4.6 \cdot 10^{-9}$	5	41	carbonic anhydrase XII
COL3A1	0.46	$1.2 \cdot 10^{-8}$	6	52	collagen, type III, alpha 1

- high r despite qualitative



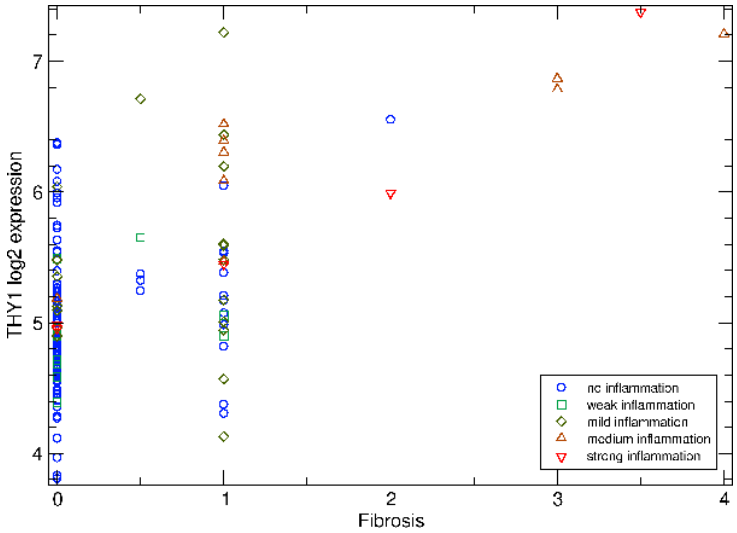
Stathmin-like 2, STMN2, fibrosis marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.04	0.59	21733	22459
steatosis	0.29	0.0004	1088	1152
inflammation	0.43	$4.9 \cdot 10^{-8}$	27	29
fibrosis	0.66	0	1	1
NAFLD	0.58	$9.1 \cdot 10^{-15}$	1	1

- Superior cervical ganglion-10
- neuronal growth-associated protein
  - regulator of microtubule stability
- involved in osteogenesis

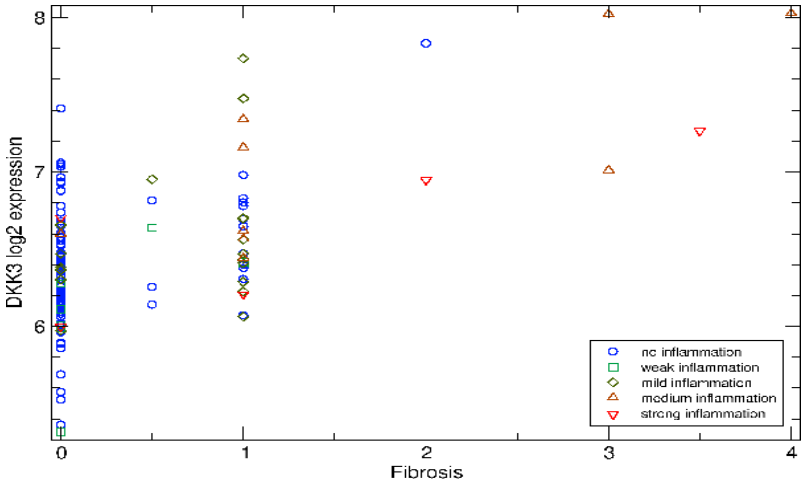
Thy-1 cell surface antigen, THY1, fibrosis marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.02	0.81	24740	25570
steatosis	0.33	$3.5 \cdot 10^{-5}$	474	504
inflammation	0.42	$1.0 \cdot 10^{-7}$	31	34
fibrosis	0.58	$4.8 \cdot 10^{-14}$	2	2
NAFLD	0.55	$1.6 \cdot 10^{-13}$	4	4

- cell-cell or cell-ligand interactions during synaptogenesis

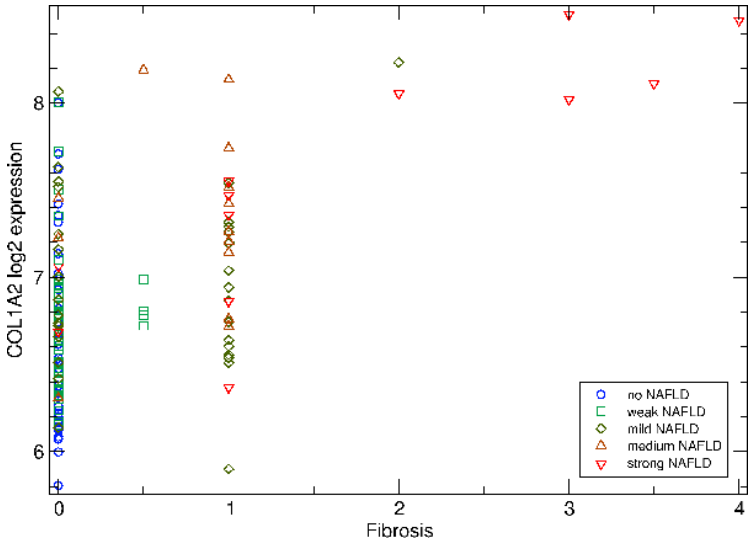
Dickkopf homolog 3, DKK, Fibrosis marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.04	0.62	22204	22942
steatosis	0.28	0.0004	1127	1191
inflammation	0.21	0.01	1529	1606
fibrosis	0.57	$2.2 \cdot 10^{-13}$	3	3
NAFLD	0.41	$1.3 \cdot 10^{-7}$	118	131

- Antagonizes canonical Wnt signaling by inhibiting LRP5/6 interaction with Wnt
- Dkks implicated in
  - adult bone formation
  - bone disease
  - cancer
  - Alzheimer disease

Collagen, type I, alpha 2, COL1A2, fibrosis marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.16	0.04	326	8932
steatosis	0.44	$2.2 \cdot 10^{-8}$	4	56
inflammation	0.27	0.001	23	576
fibrosis	0.54	$7.0 \cdot 10^{-12}$	1	6
NAFLD	0.49	$1.8 \cdot 10^{-10}$	3	31

- component of the extracellular matrix
- mostly found in skin, tendon, bone

Fibrosis markers

- Tissue modeling
  - STMN2, Superior cervical ganglion10, microtubule stability
  - Thy1 cell surface antigen
  - Collagen: Col1a2, 1a1,4a2,3a1
  - Bone formation: STMN2, DKK3
- Loss of liver organization
  - DKK3, antagonist of Wnt signaling

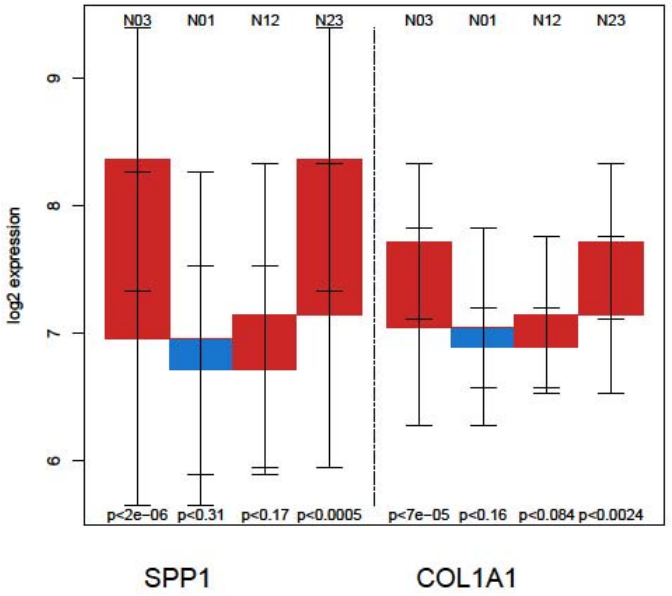
Outline

- Introduction
- Obesity markers
- Steatosis markers
- Inflammation markers
- Fibrosis markers
- General disease markers

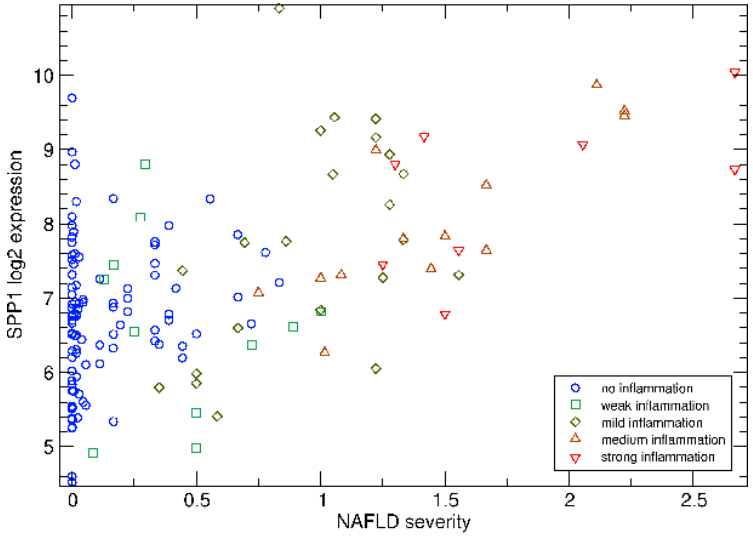
NAFLD progression marker, non-metabolic

Gene	r	p<	rank non-metabolic	rank total	
STMN2	0.58	$9.1 \cdot 10^{-15}$	1	1	stathmin-like 2
FABP4	0.57	$2.2 \cdot 10^{-14}$	2	2	fatty acid binding protein 4, adipocyte
SPP1	0.57	$3.1 \cdot 10^{-14}$	3	3	secreted phosphoprotein 1
THY1	0.55	$1.6 \cdot 10^{-13}$	4	4	Thy-1 cell surface antigen
FAT1	0.54	$8.2 \cdot 10^{-13}$	5	5	FAT atypical cadherin 1
DNAJC12	-0.53	$2.1 \cdot 10^{-12}$	6	6	DnaJ (Hsp40) homolog, subfamily C, member 12

Gene	r	p<	rank metabolic	rank total	
COL1A1	0.53	$3.2 \cdot 10^{-12}$	1	8	collagen, type I, alpha 1
TYMS	0.49	$1.0 \cdot 10^{-10}$	2	27	thymidylate synthetase
COL1A2	0.49	$1.8 \cdot 10^{-10}$	3	31	collagen, type I, alpha 2
ME1	0.48	$3.0 \cdot 10^{-10}$	4	37	malic enzyme 1, NADP(+)-dependent, cytosolic
COL4A2	0.46	$3.6 \cdot 10^{-9}$	5	58	collagen, type IV, alpha 2
GNMT	-0.45	$5.2 \cdot 10^{-9}$	6	65	glycine N-methyltransferase



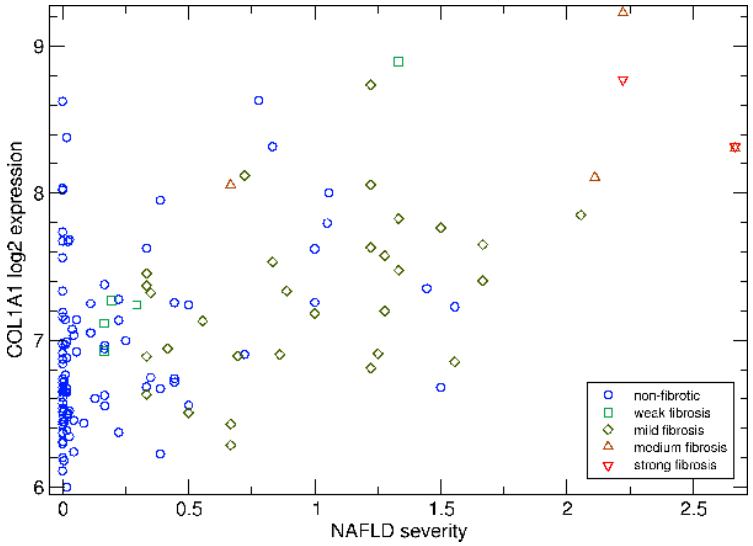
Secreted phosphoprotein 1, SPP1, NAFLD progression marker, non-metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.11	0.17	13971	14452
steatosis	0.42	$6.2 \cdot 10^{-8}$	70	75
inflammation	0.45	$8.7 \cdot 10^{-9}$	15	16
fibrosis	0.46	$9.1 \cdot 10^{-9}$	43	48
NAFLD	0.57	$3.1 \cdot 10^{-14}$	3	3

- Osteopontin/Immunoglobulin Alpha 1
- attachment of osteoclasts to the mineralized bone matrix
- binds hydroxyapatite
- cytokine that up-regulates expression of interferon-γ and IL-12.

Collagen, type I, alpha 1, COL1A1, NAFLD progression marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.12	0.12	434	12828
steatosis	0.45	$5.2{\cdot}10^{-9}$	2	39
inflammation	0.33	$4.5{\cdot}10^{-5}$	9	246
fibrosis	0.5	$3.3{\cdot}10^{-10}$	2	23
NAFLD	0.53	$3.2{\cdot}10^{-12}$	1	8

- main component of the extracellular matrix

General disease markers

- Tissue remodelling
  - Osteoporin SPP1, osteoclast attachment
- Extracellular matrix
  - Col1a1

Outlook

- Finer classification of proteins
  - receptor/enzyme/transporter/structural/signaling/secretion
- Experimental validation
  - layer of protein
  - secretion products
  - secondary products (plexin → IL6,IL8)
  - macroscopic

Take-home message

- Obesity markers
  - glutamate sensing
  - cholesterol
- Steatosis markers
  - “hepatocytes become adipocytes”
  - methylation
- Inflammation markers
  - Tissue reorganization
  - DNA replication
- Fibrosis markers
  - Loss of liver organization
  - “liver becomes bone”
- General disease markers
  - Osteoporin & Collagen 1a1

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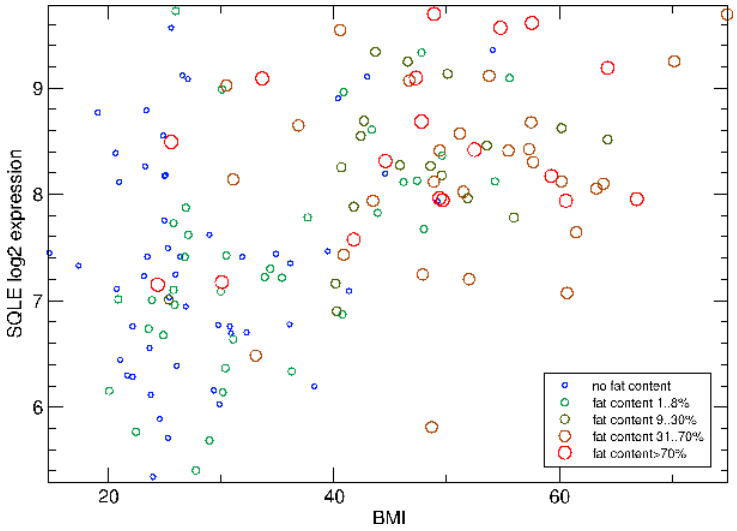
  - Dresden/Kiel


virtual liver
network
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Squalene epoxidase SQLE

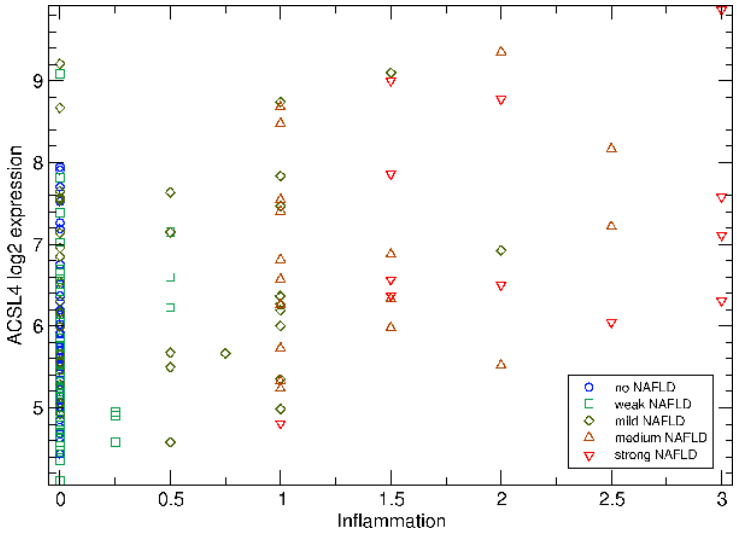
Obesity marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.5	$8.5 \cdot 10^{-12}$	2	21
steatosis	0.39	$7.8 \cdot 10^{-7}$	12	160
inflammation	0.12	0.14	254	7330
fibrosis	0.13	0.14	280	6920
NAFLD	0.24	0.003	91	1490

- cholesterol synthesis

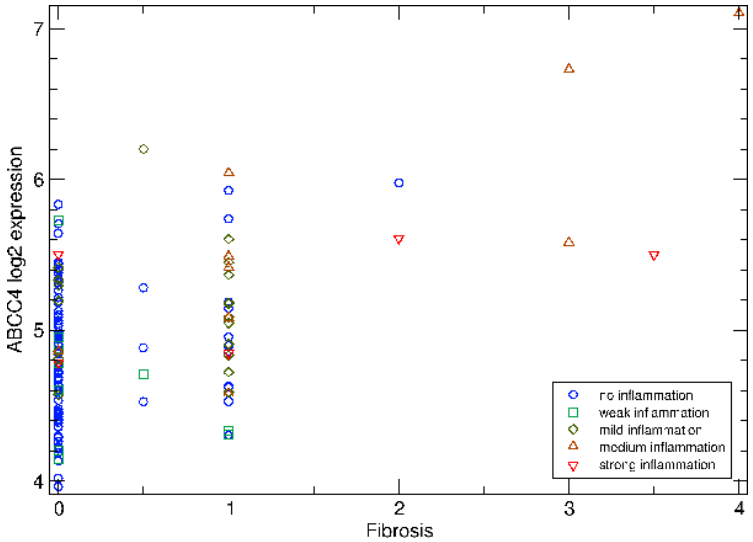
Acyl-CoA synthetase long-chain family member 4, ACSL4, inflammation marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	0.17	0.03	291	7908
steatosis	0.3	0.0001	48	830
inflammation	0.38	$1.4 \cdot 10^{-6}$	4	72
fibrosis	0.37	$7.4 \cdot 10^{-6}$	25	205
NAFLD	0.43	$3.6 \cdot 10^{-8}$	9	96

- Mental Retardation, X-Linked 63.
- synthesis of cellular lipids
- degradation via beta-oxidation.
- Preferentially uses arachidonate and eicosapentaenoate

ATP-binding cassette, sub-family C (CFTR/MRP), member 4, ABCC4, fibrosis marker, metabolic



Factor	r	p<	rank metabolic	rank total
obesity	-0.01	0.94	878	27290
steatosis	0.16	0.05	281	7420
inflammation	0.37	$2.7 \cdot 10^{-6}$	5	86
fibrosis	0.49	$8.1 \cdot 10^{-10}$	3	25
NAFLD	0.42	$5.4 \cdot 10^{-8}$	13	108

- MRP/CMOAT-Related ABC Transporter
- organic anion pump
- relevant to cellular detoxification.