

Supplementary Table 1. Summary of studies included in systematic review

First author, year	Population / Location	Histological method	NAFLD (n)	Control (n)	Study type	Candidate gene(s)
Hotta, 2010	Japanese	Sanyal, 2002[1] Matteoni, 1999[2] Teli, 1995[3] Brunt, 2001[4]	253	578	Association study	<i>PNPLA3</i>
Kawaguchi, 2012	Japanese	Matteoni, 1999[2] Brunt, 1999[5]	529	942	Association study	<i>PNPLA3</i>
Rotman, 2010	NASH CRN (US)	Brunt, 2009[6] Kleiner, 2005[7]	894 adult 223 paediatric	336 -	Association study	<i>PNPLA3</i>
Sookoian, 2009	Argentinian	Brunt, 1999[5] Kleiner, 2005[7]	172*	94	Association study	<i>PNPLA3</i>
Sookoian, 2011					Meta-analysis	<i>PNPLA3</i>
Speliotes, 2010	NASH CRN (US)	Kleiner, 2005[7]	592	1405	Association study	<i>PNPLA3</i>
Valenti, 2010a	Italian cohort/ UK cohort	Kleiner, 2005[7]	253 321	179 -	Association study	<i>PNPLA3</i>
Valenti, 2010b	Italian - Paediatrics	Kleiner, 2005[7]	149	0	Histological severity	<i>PNPLA3</i>
Zain, 2012	Malaysian	Brunt, 2011 [8] Kleiner, 2005[7]	144	198	Association study	<i>PNPLA3</i>
Corbin, 2013	NASH CRN (US)	Kleiner, 2005[7]	361	85	Association study	21 genes
Guichelaar, 2013	Obese	Kleiner, 2005[7]	144 obese	-	Histological severity	<i>PNPLA3</i>
Verrijken, 2013	Belgian - obese	Brunt, 2011[8] Kleiner, 2005[7]	470* obese	0	Histological severity	<i>PNPLA3</i> <i>APOC3</i>
Valenti, 2012	Italian	Kleiner, 2005[7]	257	337	Association study	<i>LPIN1</i>
Gawrieh, 2012	US	Kleiner, 2005[7]	212	62	Association study	<i>PPARG</i>
Rey, 2010	German	Kleiner, 2005[7]	263	259 Healthy 100 AFL	Association study	<i>PPARG</i>
Sahabkar, 2013					Meta-analysis	<i>PPARG</i>
Domenici, 2013	Brazilian	Brunt, 2010 [9] Brunt, 2011[8]	103	103	Association study	<i>PPARG</i> <i>PPARA</i>
Dongiovanni, 2010	Italian	Kleiner, 2005[7]	202	346	Association study	<i>PPARG</i> <i>PPARA</i>
Yoneda, 2008	Japanese	Matteoni, 1999[2] Teli, 1995[3]	115	441	Association study	<i>PPARGC1A</i>
Valenti, 2011	Italian cohort/ UK cohort	Kleiner, 2005[7]	758	316	Association study	<i>APOC3</i>
de Feo, 2012	Italian	Brunt, 1999[5]	310*	422	Association study	<i>APOE</i>
Musso, 2009	Italian	Brunt, 2001[4]	78*	156	Association study	<i>APOE</i>
Sazci, 2008	Turkish	Kleiner, 2005[7]	57	245	Association study	<i>APOE</i>
Musso, 2011	Italian	Brunt, 2001[4]	40	40	Association	<i>APOE</i>

					study	<i>OLR1</i> <i>MTP</i>
Gambino, 2007	Italian	Brunt, 2001[4]	29	29	Association study	<i>MTP</i>
Dong, 2007	Japanese	Brunt, 1999[5]	107	150 Healthy 100 HCV	Association study	<i>PEMT</i>
Carulli, 2009	Italian	Brunt, 2004[10]	114*	79	Association study	<i>MTP</i> <i>PC1</i> <i>IL6</i>
Oliviera, 2010	Brazilian	Kleiner, 2005[7]	139	141	Association study	<i>MTP</i> <i>GCLC</i>
Namikawa, 2004	Japanese	Brunt, 1999[5] Brunt, 2001[4]	63	150	Association study	<i>MTP</i> <i>SOD</i>
El-Koofy, 2010	Egyptian paediatrics	Kleiner, 2005[7]	76*	20	Association study	<i>MTP</i> <i>SOD2</i>
Musso, 2013a	Italian	Kleiner, 2005[7] Brunt, 2001[4]	127*	48	Longitudinal	<i>SREBFP2</i>
Musso, 2013b	Italian	Kleiner, 2005[7] Brunt, 2001[4]	161*	51	Longitudinal	<i>SREBPF1C</i>
Al-Serri, 2012	Italian cohort/ UK cohort	Brunt, 1999[5]	510	0	Histological severity	<i>SOD2</i>
Aller, 2010	Spanish	Brunt, 2001[4]	39	0	Histological severity	<i>UCP3</i>
Brun, 2006	Italian	Not described	28	52	Association study	<i>CD14</i> <i>TLR4</i>
Nozaki, 2004	Japanese	Brunt, 1999[5] Brunt, 2001[4]	63	100	Association study	<i>IL1B</i> <i>ADRB3</i>
Petta, 2012	Sicilian cohort	Kleiner, 2005[7]	165	0	Histological severity	<i>IL28B</i>
Akyildiz, 2010	Turkish	Kleiner, 2005[7]	91	104	Association study	<i>MIF</i>
Aller, 2010	Spanish	Brunt, 2001[4]	66	213	Association study	<i>TNF</i>
Chowdhury, 2013	Indian	Kleiner, 2005[7]	29	0	Association study	<i>TNF</i>
Hu, 2013	Chinese	Kleiner, 2005[7]	189*	138	Association study	<i>TNF</i>
Tokushige, 2007	Japanese	Neuschwander-Tetli, 2003[11] Brunt, 1999[5] Brunt, 2001[4] Kleiner, 2005[7]	102	100	Association study	<i>TNF</i>
Valenti, 2002	Italian	Sheth, 1997[12] Brunt, 2001[4]	99*	172	Association study	<i>TNF</i>
Yang, 2012	Korean - paediatric, obese	Brunt, 1999[5] Kleiner, 2005[7]	50	61	Association study	<i>TNF</i>
Wong, 2008	Chinese	Brunt, 1999[5]	79	40	Association study	<i>TNF</i> <i>ADIPOQ</i>
Gupta, 2012	Indian	Brunt, 2009[13] Kleiner, 2005[7]	137*	250	Association study	<i>ADIPOQ</i>
Tokushige, 2009	Japanese	Brunt, 1999[5] Brunt, 2001[4] Kleiner, 2005[7]	119	115	Association study	<i>ADIPOQ</i>
Aller, 2011	Spanish	Brunt, 2001[4]	76	0	Histological severity	<i>LEPR</i>
Swellam, 2012	Egyptian	Not described	90	30	Association study	<i>LEPR</i>

Zain, 2013	Malaysian	Brunt, 2011[8] Kleiner, 2005[7]	144	198	Association study	<i>LEPR</i>
Sookoian, 2007	Argentinian	Brunt, 1999[5]	136*	64	Association study	<i>CLOCK</i>
Miele, 2008	Italian cohort/ UK cohort	Brunt, 1999[5]	415	0	Histological severity	<i>KLF6</i>
Sazci, 2008	Turkish	Brunt, 1999[5] Kleiner, 2005[7] Brunt, 2004[10]	57	324	Association study	<i>MTFTR</i>
Serin, 2007	Turkish	Kleiner, 2005[7]	53	282	Association study	<i>MTFTR</i>
Assy, 2005	Israeli	Brunt, 1999[5]	30	10 Healthy 15 HCV	Association study	<i>MTHFR</i> <i>Prothrombin Factor V Leiden</i>
Sookoian, 2008	Argentinian	Brunt, 1999[5]	108*	55	Association study	<i>STAT3</i>
Deguti, 2003	Brazilian	Not described	32	0	Histological severity	<i>HFE</i>
Nelson, 2012	NASH CRN (US)	Kleiner, 2005[7]	786	0	Histological severity	<i>HFE</i>
Raszeja- Wyszomirska, 2010	Polish	Not described	62	0	Histological severity	<i>HFE</i>
Valenti, 2003	Italian	Sheth, 1997[12]	134*	291	Association study	<i>HFE</i>
Valenti, 2008	Italian	Kleiner, 2005[7]	587	184	Association study	<i>HFE</i>
Zamin, 2006	Brazilian	Brunt, 1999[5]	29	20 Healthy 20 HCV	Association study	<i>HFE</i>
Valenti, 2012b	Italian	Kleiner, 2005[7]	216	271	Association study	<i>TMPRSS6</i>
Zain, 2013	Malaysian	Brunt, 2011[8] Kleiner, 2005[7]	144	198	Association study	<i>AGTR1</i>
Yoneda, 2009	Japanese	Matteoni, 1999[2] Teli, 1995[3] Brunt, 2001[4]	167	435	Association study	<i>AT2</i>
Espino, 2011	Mexican	Kleiner, 2005[7]	29	21	Association study	<i>SERPINE1</i>
Dixon, 2003	Australia	Brunt, 1999[5] Lee, 1998 [14] Lee, 1995[15]	105	0	Histological severity	<i>TGFB1</i> <i>AT6</i>
Dongiovanni, 2010	Italian cohort/ UK cohort	Kleiner, 2005[7]	702	310	Association study	<i>ENPP1</i> <i>IRA1</i> <i>PC1</i>
Tan, 2013	Malaysian	Brunt, 1999[5] Kleiner, 2005[7]	144	198	Association study	<i>GCKR</i>
Aller, 2012	Caucasian (Spanish)	Brunt, 2001[4]	70	0	Histological severity	<i>CBR1</i>
Rossi, 2012	Italian - Paediatrics	Kleiner, 2005[7]	118	0	Histological severity	<i>CBR2</i>
Gorden, 2013	US	Kleiner, 2005[7]	748	344	Association study	<i>NCAN</i>
Lui, 2014	UK European	Bedossa, 2014[16]	349 725	265	Association study	<i>TM6SF2</i> <i>NCAN</i>
Dongiovanni, 2014	European	Kleiner, 2005[7]	1089	112	Association study	<i>TM6SF2</i>

Sookoian, 2014	Argentinian	Kleiner, 2005[7] Brunt, 2011[8]	226	135	Association study	<i>TM6SF2</i>
Oruc, 2009	Turkish	Not described	50	44	Association study	<i>SPINK1</i>
Iwata, 2011	UK	Brunt, 1999[5]	358	110 Control** 206 HCV	Association study	<i>ABCB11</i> <i>NRIH4</i>
Varela, 2008	Chilean	Not described	32	13	Association study	<i>CYP2E1</i>
Sookoian, 2010	Argentinian	Brunt, 1999[5]	188*	102	Association study	<i>NR1I2</i>
Aller, 2009	Spanish	Brunt, 2001[4]	30	0	Histological severity	<i>FABP2</i>
Auinger, 2010	Italian	Kleiner, 2005[7]	103	0	Histological severity	<i>SLC27A5</i>
Chalassni, 2010	NASH CRN (US)	Kleiner, 2005[7]	236	0	GWAS	
Kitamoto, 2013	Japanese	Brunt, 2001[4] Kleiner, 2005[7] Matteoni, 1999[2] Teli, 1995[3]	392	934	GWAS	
Speliotis, 2011	NASH CRN (US)	Kleiner, 2005[7]	592	1405	GWAS	
Vazquez-Chantada, 2013	Spanish European	Brunt, 1999[5] Kleiner, 2005[7]	69 451	217 303	GWAS	

N.B Association studies include case-control association and histological association

HCV: Chronic hepatitis C patients; AFL: alcoholic fatty liver patients

***Total NAFLD group, only partially histologically diagnosed**

****Control group undergoing resection for hepatic metastases of non-liver primary cancer**

Supplementary Table 2. Summary of candidate genes and polymorphisms included in systematic review

Gene symbol [17]	Description of encoded protein [18]	Polymorphisms [19]	Genomic alteration (g.) [20]	Type [19, 20]	Protein change [20]	Global MAF [19]
<i>ABCB11</i>	Membrane transporter, bile salt export	rs2287622	A>C, A>G, A>T	Missense	Val444Gly, Val444Ala, Val444Asp	A=0.40 59/884
<i>ABCB4</i>	Membrane transporter, may be involved in hepatic biliary phospholipid export	rs31672	C>T	Intron variant		C=0.33 88/738
<i>ADIPOQ</i>	Adiponectin, an adipocytokine	rs2241766	T>G	Synonymous		G=0.14 46/314
		rs17300539	G>A	Upstream gene variant		A=0.03 99/86
		rs1501299	G>T	Intron variant		T=0.32 00/696
		rs2241766	T>G	Synonymous		G=0.14 46/314
		rs266729	C>G	Upstream gene variant		G=0.25 07/546
<i>ADRB3</i>	G-protein coupled adrenergic receptor, involved in regulation of lipolysis and thermogenesis in adipose tissue	rs4994	A>G	Missense	Trp64Arg	G=0.10 01/218
<i>AGTR1</i>	Angiotensin II receptor, mediates cardiovascular effects of RAAS	rs772627	T>A	Intergenic variant		T=0.49 04/106 7
		rs3772622	T>C	Intron variant		C=0.36 82/802
		rs3772630	T>C	Intron variant		C=0.43 16/940
<i>APOC3</i>	VLDL component, inhibits hepatic lipase	rs2854116	C>T	Upstream gene variant		T=0.49 40/107 5
		rs2854117	T>C	Upstream gene variant		T=0.45 50/991
<i>APOE3</i>	Chylomicron component, mediates hepatic uptake and clearance	CM890009 (e3)	T>C	Missense	Arg160Cys	Not known
		rs429358 (e4)	T>C	Missense	Cys156Arg Pathogenic	C=0.14 92/324
<i>CHDH</i>	Enzyme choline dehydrogenase	rs4563403	C>T	3' variant		T=0.23 74/517
<i>Chromosome 7</i>		rs343064	C>T	Upstream variant		T=0.36 09/786
<i>CHUK</i>	Serine kinase involved in NF-kappa-B signalling	rs11591741	G>C	Intron variant		C=0.22 77/496
		rs11597086	A>C	Intron variant		C=0.22 27/484
<i>CLOCK</i>	Transcription factor involved in circadian rhythm regulation	rs6850524	C>G	Intron variant		C=0.42 93/935
		rs11932595	A>G	Intron variant		G=0.32 64/710
		rs1554483	C>G	Intron variant		G=0.38 66/841

		rs4580704	G>C	Intron variant		G=0.29 61/644
		rs4864548	G>A	Non-coding exon variant		A=0.38 61/840
		rs6843722	A>C	Intron variant		C=0.36 13/787
<i>CNR1</i>	GPCR in brain, mediates CNS effects of cannabis components	rs1049353	C>T	Synonymous		T=0.13 73/299
<i>CNR2</i>	GPCR in brain, mediates CNS effects of cannabis components	rs2501432	T>C	Missense	Gln63Arg	T=0.48 35/105 2
<i>COL13A1</i>	Nonfibrillar type collagen	rs1227756	G>A	Intron variant		A=0.39 16/853
<i>CPN1</i>	Plasma metallo-protease	rs11597390	G>A	Regulatory region variant		A=0.25 34/552
<i>CYP2E1</i>	Metabolic liver enzyme	rs6413432 (DraI)	T>A	Intron variant	Pathogenic - affects enzyme activity	A=0.15 47/336
		rs2031920 (RasI)	C>T	Upstream variant	Pathogenic - altered transcription	T=0.08 95/195
		rs3813867 (PstI)	G>C	Upstream variant	Pathogenic - altered transcription	C=0.10 06/219
<i>EFCAB4B</i>	Interacts with calcium in T lymphocytes, regulating the calcium release activating channel	Rs887304	T>C	3 prime UTR variant		T=0.15 43/336
<i>ENPP1</i>	Transmembrane glycoprotein, cleaves numerous substrates and involved in tissue calcification	rs1044498	A>C	Missense	Lys173Gln	C=0.29 25/636
<i>FABP2</i>	Intracellular protein involved in long chain fatty acid processing	rs1799883	T>G	Missense	ala54thr	T=0.25 21/548
<i>FATP5</i>	Involved in hepatic uptake of fatty acids and bile metabolism	rs56225452	C>T	Intron, downstream and upstream variant		T=0.16 21/352
<i>FDFT1</i>	Enzyme, in cholesterol biosynthesis pathway	rs2645424	A>G	Intron variant		G=0.46 65/101 5
<i>GCKR</i>	Inhibits glucokinase enzyme in the liver	rs780094	T>C	Intron variant		T=0.38 57/840
		rs1260326	T>C	Missense	Leu446Pro	T=0.38 48/838
<i>HFE</i>	Membrane protein, thought to have a role regulating iron absorption	rs1800562	G>A	Missense	Cys282Tyr	A=0.01 97/43
		rs1799945	C>G	Missense	His63Asp	G=0.08 36/181
<i>IFNL3</i> (<i>IL28B</i>)	Proinflammatory cytokine	rs8099917	T>G	Intron variant		G=0.13 82/300

		rs12979860	C>T	Intron variant		T=0.33 88/738
<i>IL1B</i>	Proinflammatory cytokine	rs16944	A>G	Upstream gene variant		A=0.46 51/101 3
<i>IL6</i>	Proinflammatory cytokine	rs1800795	C>G	Upstream gene variant		C=0.18 50/402
<i>IRS1</i>	Involved in pathways activated by insulin	rs1801278	C>A, C>T, C>G	Missense	Gly971Trp, Gly971Arg	T=0.05 37/116
<i>KLF6</i>	Tumour suppressing transcription factor	rs3750861	C>T	Intron variant		T=0.06 06/132
<i>LEPR</i>	Regulates fat metabolism	rs6700896	C>T	Intron variant		C=0.45 91/100 0
		rs1137100	A>G	Missense	Lys109Arg	G=0.38 52/839
		rs1137101	A>G	Missense	Gln223Arg	A=0.41 05/893
<i>LPIN1</i>	Required for adipocyte differentiation and transcriptional cofactor involved in lipid metabolism	rs13412852	C>T	Intron variant		T=0.24 61/535
<i>LTBP3</i>	Interacts with TGF-beta; possible role in TGF-beta translocation and targeting	Rs6591182	T>G	Missense	Val538Gly	G=0.43 16/940
<i>LYPLAL1</i>	Lysophospholipase enzyme activity	rs12137855	C>T	Downstream gene variant		T=0.16 48/358
<i>MIF</i>	Proinflammatory cytokine	rs755622	G>C	Upstream gene variant		C=0.27 23/592
<i>MTHFR</i>	Enzyme that catalyses reaction producing a co-substrate in homocysteine remethylation	rs7525338	C>T	Intron variant		T=0.01 61/35
<i>NCAN</i>	Proteoglycan, involved in cell adhesion and migration	Rs2228603	C>T	Missense	Pro92Ser	T=0.04 68/102
<i>NR1I2</i>	Ligand activated transcription factor, involved in cytochrome P450 CYP3A4 regulation	rs1248820	T>C	Upstream gene variant		C=0.42 15/918
		rs1054191	A>G	3 prime UTR variant		A=0.11 71/255
		rs2461823	A>G	Intron variant		T=0.38 71/842
		rs2472671	C>T	Intron variant		C=0.21 53/468
		rs3814055	C>T	Upstream variant, 5' UTR variant		T=0.32 42/706
		rs3814057	A>C	3 prime UTR variant		C=0.32 55/708
		rs6785049	G>A	Intron variant		A=0.44 44/967
		rs7643645	A>G	Intron variant		G=0.32 09/699
<i>PARVB</i>	Role in cytoskeleton and cell adhesion, binds actin	rs5764455	A>G	Intron variant		A=0.41 64/906
<i>PEMT</i>	Liver enzyme, catalyses production of	rs7946	C>T	Missense	Val175Met	T=0.46 14/100

	phosphatidylcholine required for VLDL secretion					5
		rs13342397	T>C	intron variant		C=0.10 19/221
		rs8068641	A>G	intron variant		G=0.21 58/469
		rs936108	C>T	intron variant		T=0.41 64/906
<i>PNPLA3</i>	Triglyceride lipase enzyme expressed by adipocytes	rs738409	C>G	Missense	Ile148Val	G=0.28 42/619
		rs2281135	G>A	intron variant		A=0.27 23/592
		rs2294918	A>G	Missense	Lys434Glu	A=0.22 96/499
<i>PPARA</i>	Transcription factor, stimulates fatty acid catabolism in the liver	rs1800206	C>G	Missense	Leu162Val	G=0.02 48/54
<i>PPARG</i>	Transcription factor, stimulates adipocyte differentiation and fatty acid storage	rs3856806	C>T	Synonymous		T=0.11 85/257
		rs1801282	C>G	Missense	Pro12Ala	G=0.06 61/143
<i>PPARGC1A</i>	Transcriptional coactivator, involved in energy metabolism	rs2290602	A>C	intron variant		Not known
<i>PPP1R3B</i>	Catalytic subunit of protein phosphatase-1 expressed in the liver; may be involved in glycogen synthesis regulation	Rs4240624	G>A	Intron variant		G=0.09 87/214
<i>SAMM50</i>	Component of the Sorting and Assembly Machinery in outer mitochondrial membrane	rs2143571	G>A	intron variant		A=0.32 19/701
<i>SLC2A1</i>	Glucose transporter	rs841856	G>T	Intron variant		T=0.19 05/415
		rs4658	C>G	3 prime UTR variant		G=0.36 18/788
<i>SLC44A1</i>	Fatty acid transporter	rs10820799	A>C	intron variant		C=0.12 40/270
<i>SOD2</i>	Mitochondrial protein, binds toxic superoxide products	rs4880	A>G	Missense	Val16Ala	G=0.37 05/806
<i>SPINK1</i>	Trypsin inhibiting enzyme, secreted by pancreatic acinar cells	rs17107315	T>C	Missense	N34S	C=0.00 60/13
<i>SREBF1</i>	Transcription factor, regulates LDL receptor and cholesterol biosynthesis genes	rs11868035	G>A	Splice region variant		A=0.46 92/102 2
<i>SREBF2</i>	Transcription factor, regulates cholesterol homeostasis	rs133291	C>T	intron variant		T=0.26 49/577
<i>STAT3</i>	Transcription activator, responds to cytokines and growth factors	rs9891119	A>C	Intron variant		C=0.37 14/809
		rs2293152	C>G	Intron variant		G=0.37 92/825
		rs6503695	T>C	Intron variant		C=0.33 15/722
<i>TCF7L2</i>	Transcription factor,	rs7903146	C>T	Intron variant		T=0.21

	role in glucose homeostasis, Wnt signalling pathway					81/475
<i>TM6SF2</i>	Transmembrane 6 superfamily member 2	rs58542926	C>T	Missense	Glu167Lys	T=0.06 67/334
<i>TPRSS6</i>	Protease, involved in liver matrix remodelling	rs855791	A>G	Missense	Val736Ala, reduced enzymatic activity	A=0.39 81/867
<i>TNF</i>	Proinflammatory cytokine	rs361525 (<i>TNFA</i>)	G>A	Upstream gene variant		A=0.05 05/110
		rs1800629 (<i>TNF2</i>)	G>A	Upstream gene variant		A=0.09 55/208
		rs1799964	T>C	Upstream gene variant		C=0.20 02/436
		rs1800630	C>A	Upstream gene variant		A=0.14 51/315
		rs1799724	C>T	Upstream gene variant		T=0.09 73/211
<i>UCP3</i>	Mitochondrial anion carrier protein	rs1800849	G>A	utr variant 5 prime		A=0.20 20/439

MAF: Minor allele frequency; RAAS: renin-angiotensin-aldosterone-system

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