

Supplementary Materials

Exploring key genes in NAFLD linked to glutamine metabolism: a comprehensive analysis combining multi-omics, machine learning and SHAP

Changan Chen BM¹, Wenfeng Liu BM², Yongtao Lan BM², Fuxiong Li MMed³, Xiaoman Li BM⁴

¹*Department of Gastroenterology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China*

²*The First School of Clinical Medicine, Guangdong Medical University, Zhanjiang, China*

³*School of Basic Medicine, Guangdong Medical University, Zhanjiang, China*

⁴*Department of Endocrinology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China*

Corresponding Author:

Dr Xiaoman Li, Department of Endocrinology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, 524001, China. Affiliated Hospital of Guangdong Medical University, No. 57, Renmin Avenue South, Xia Shan District, Zhanjiang, Guangdong, 524001, China.

Tel.: (+86) 13763004575.

Email: l_man@gdmu.edu.cn

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Supplementary Table 1. finngen_R10_NAFLD and 1400metabolites MR results

Outcome	Exposure	Method	b	se	p
NAFLD	Cysteine-glutathione disulfide levels	IVW	-0.215	0.066	0.001
NAFLD	Taurochenodeoxycholate levels	IVW	0.266	0.083	0.001
NAFLD	Plasma free asparagine levels	IVW	-0.164	0.053	0.002
NAFLD	X-11444 levels	IVW	0.189	0.064	0.003
NAFLD	3-hydroxyisobutyrate to adenosine 5'-diphosphate (ADP) ratio	IVW	0.156	0.055	0.004
NAFLD	Glycerophosphorylcholine (GPC) levels	IVW	0.197	0.072	0.006
NAFLD	5alpha-androstan-3beta,17beta-diol disulfate levels	IVW	0.146	0.053	0.006
NAFLD	X-24728 levels	IVW	0.186	0.069	0.007
NAFLD	1-stearoyl-GPG (18:0) levels	IVW	0.172	0.064	0.007
NAFLD	X-12851 levels	IVW	0.207	0.078	0.008
NAFLD	Inosine levels	IVW	0.178	0.067	0.008
NAFLD	Carnitine to ergothioneine ratio	IVW	0.179	0.068	0.008
NAFLD	X-24241 levels	IVW	0.201	0.077	0.009
NAFLD	Malate levels	IVW	0.243	0.094	0.010
NAFLD	X-25790 levels	IVW	-0.281	0.110	0.010
NAFLD	Serine to alpha-tocopherol ratio	IVW	0.231	0.091	0.011
NAFLD	Adenosine 5'-diphosphate (ADP) to flavin adenine dinucleotide (FAD) ratio	IVW	0.135	0.053	0.012
NAFLD	Inosine to EDTA ratio	IVW	0.150	0.059	0.012
NAFLD	N-acetyl-aspartyl-glutamate (naag) levels	IVW	-0.051	0.020	0.012
NAFLD	Catechol glucuronide levels	IVW	-0.196	0.079	0.013
NAFLD	Carnitine C18:2 levels	IVW	0.149	0.060	0.013
NAFLD	1-oleoyl-GPG (18:1) levels	IVW	0.135	0.055	0.013
NAFLD	Linoleoyl ethanolamide levels	IVW	-0.161	0.065	0.013
NAFLD	Glutamine to alanine ratio	IVW	-0.175	0.072	0.015
NAFLD	tryptophan to tyrosine ratio	IVW	0.194	0.080	0.016
NAFLD	Histidine to asparagine ratio	IVW	0.122	0.051	0.016
NAFLD	X-25433 levels	IVW	0.139	0.058	0.016
NAFLD	X-21829 levels	IVW	0.149	0.063	0.017
NAFLD	5-methylthioadenosine (mta) levels	IVW	-0.187	0.079	0.018
NAFLD	X-12127 levels	IVW	-0.143	0.060	0.018
NAFLD	Ornithine to glutamate ratio	IVW	-0.229	0.097	0.018
NAFLD	1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6) levels	IVW	-0.260	0.110	0.018
NAFLD	Decadienedioic acid (C10:2-DC) levels	IVW	0.091	0.039	0.019
NAFLD	N2,N5-diacetylornithine levels	IVW	-0.132	0.056	0.019
NAFLD	Alpha-ketoglutarate levels	IVW	0.163	0.069	0.019
NAFLD	X-11299 levels	IVW	0.219	0.093	0.019
NAFLD	Metabolonic lactone sulfate levels	IVW	0.094	0.040	0.019
NAFLD	Creatine to carnitine ratio	IVW	0.193	0.082	0.019
NAFLD	N-acetyl-isoputrescine levels	IVW	0.116	0.050	0.020
NAFLD	X-26111 levels	IVW	0.167	0.072	0.020
NAFLD	Methionine sulfoxide levels	IVW	-0.176	0.076	0.021
NAFLD	3-indoleglyoxylic acid levels	IVW	-0.150	0.066	0.022
NAFLD	Dihydroferulic acid sulfate levels	IVW	0.138	0.061	0.023
NAFLD	Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] levels	IVW	-0.194	0.086	0.023
NAFLD	phosphate to asparagine ratio	IVW	0.131	0.058	0.023
NAFLD	Adenosine 5'-diphosphate (ADP) to arginine ratio	IVW	-0.161	0.072	0.025
NAFLD	Alpha-tocopherol levels	IVW	-0.237	0.106	0.025
NAFLD	Palmitoylcholine levels	IVW	0.182	0.082	0.026
NAFLD	X-25172 levels	IVW	0.172	0.078	0.026
NAFLD	X-21467 levels	IVW	0.107	0.048	0.027
NAFLD	X-21285 levels	IVW	-0.149	0.068	0.028
NAFLD	2,4-di-tert-butylphenol levels	IVW	0.178	0.081	0.028
NAFLD	Pyrraline levels	IVW	0.196	0.089	0.028
NAFLD	Serine to threonine ratio	IVW	0.124	0.057	0.030
NAFLD	X-23782 levels	IVW	0.207	0.095	0.030

Supplementary Table 1. finngen_R10_NAFLD and 1400metabolites MR results (cont.)

Outcome	Exposure	Method	b	se	<i>p</i>
NAFLD	Alanine to asparagine ratio	IVW	0.134	0.062	0.030
NAFLD	X-12100 levels	IVW	0.210	0.097	0.031
NAFLD	Glycine levels	IVW	0.095	0.044	0.032
NAFLD	Creatinine levels	IVW	-0.191	0.089	0.032
NAFLD	Pro-hydroxy-pro levels	IVW	-0.190	0.089	0.032
NAFLD	5alpha-pregnan-3beta,20alpha-diol disulfate levels	IVW	0.126	0.059	0.034
NAFLD	11beta-hydroxyandrosterone glucuronide levels	IVW	0.136	0.064	0.035
NAFLD	X-17325 levels	IVW	0.156	0.074	0.035
NAFLD	Phosphate to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	IVW	0.236	0.113	0.037
NAFLD	Cortisol levels (plasma)	IVW	0.171	0.082	0.037
NAFLD	Dihydroferulate levels	IVW	0.271	0.130	0.037
NAFLD	Branched-chain, straight-chain, or cyclopropyl 10:1 fatty acid (1) levels	IVW	-0.226	0.110	0.039
NAFLD	S-methylcysteine sulfoxide levels	IVW	-0.185	0.090	0.039
NAFLD	X-21471 levels	IVW	0.111	0.054	0.041
NAFLD	Glycerol 3-phosphate levels	IVW	0.132	0.064	0.041
NAFLD	X-21607 levels	IVW	0.121	0.059	0.041
NAFLD	1-methyl-4-imidazoleacetate levels	IVW	0.131	0.064	0.041
NAFLD	X-25420 levels	IVW	-0.209	0.103	0.043
NAFLD	Myo-inositol levels	IVW	0.194	0.096	0.043
NAFLD	Threonate levels	IVW	0.158	0.078	0.044
NAFLD	N-stearoyl-sphinganine (d18:0/18:0) levels	IVW	0.222	0.110	0.044
NAFLD	Retinol (Vitamin A) levels	IVW	-0.141	0.070	0.045
NAFLD	Gamma-glutamylleucine levels	IVW	0.198	0.099	0.046
NAFLD	Tricosanoyl sphingomyelin (d18:1/23:0) levels	IVW	0.157	0.079	0.048
NAFLD	Glycine to pyridoxal ratio	IVW	0.137	0.069	0.048
NAFLD	Argininate levels	IVW	0.140	0.071	0.049
NAFLD	Pseudouridine levels	IVW	0.175	0.089	0.050
NAFLD	Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [1] ratio	IVW	0.261	0.133	0.050
NAFLD	Glycocholate levels	IVW	0.113	0.058	0.050

Supplementary Table 2. ebi-a-GCST90091033 and 1400metabolites MR results

Outcome	Exposure	Method	b	se	p
NAFLD	X-21285 levels	IVW	-0.139	0.038	<0.001
NAFLD	Pregnenetriol sulfate levels	IVW	0.135	0.041	0.001
NAFLD	X-19141 levels	IVW	0.111	0.034	0.001
NAFLD	X-24337 levels	IVW	-0.109	0.035	0.002
NAFLD	Glucose to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio	IVW	-0.152	0.050	0.002
NAFLD	1-palmitoyl-2-oleoyl-gpc (16:0/18:1) levels	IVW	-0.152	0.050	0.002
NAFLD	1-palmitoyl-2-linoleoyl-GPI (16:0/18:2) levels	IVW	0.119	0.039	0.003
NAFLD	Sphingadienine levels	IVW	-0.157	0.053	0.003
NAFLD	Ximenoylcarnitine (C26:1) levels	IVW	0.108	0.036	0.003
NAFLD	X-07765 levels	IVW	-0.140	0.048	0.004
NAFLD	Glutamine to alanine ratio	IVW	-0.144	0.049	0.004
NAFLD	Branched-chain, straight-chain, or cyclopropyl 10:1 fatty acid (1) levels	IVW	-0.189	0.067	0.005
NAFLD	X-26109 levels	IVW	0.058	0.021	0.005
NAFLD	X-24344 levels	IVW	-0.166	0.059	0.005
NAFLD	Deoxycholate levels	IVW	-0.164	0.062	0.008
NAFLD	Adenosine 5'-diphosphate (ADP) to mannose ratio	IVW	0.107	0.041	0.009
NAFLD	Caffeine to paraxanthine ratio	IVW	0.125	0.049	0.010
NAFLD	Glutamine levels	IVW	-0.102	0.040	0.010
NAFLD	X-16397 levels	IVW	-0.165	0.064	0.010
NAFLD	Dihydroorotate levels	IVW	0.078	0.031	0.012
NAFLD	Bilirubin degradation product, C17H18N2O4 (1) levels	IVW	0.079	0.032	0.014
NAFLD	Isovalerylcarnitine (C5) levels	IVW	-0.100	0.041	0.015
NAFLD	X-17690 levels	IVW	-0.099	0.041	0.015
NAFLD	X-12127 levels	IVW	-0.096	0.039	0.015
NAFLD	1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (p-16:0/18:2) levels	IVW	0.106	0.043	0.015
NAFLD	X-18913 levels	IVW	0.120	0.050	0.016
NAFLD	Phenyllactate (PLA) levels in elite athletes	IVW	-0.102	0.042	0.016
NAFLD	X-25422 levels	IVW	0.102	0.043	0.017
NAFLD	Gamma-glutamylalanine levels	IVW	0.149	0.062	0.017
NAFLD	Adenosine 3',5'-cyclic monophosphate (cAMP) to adenosine 5'-monophosphate (AMP) ratio	IVW	-0.160	0.067	0.017
NAFLD	Imidazole lactate levels	IVW	-0.061	0.026	0.017
NAFLD	X-24565 levels	IVW	-0.095	0.042	0.022
NAFLD	Arabitol/xylitol levels	IVW	0.130	0.057	0.022
NAFLD	Perfluorooctanoate (PFOA) levels	IVW	-0.136	0.060	0.023
NAFLD	Cholesterol to taurocholate ratio	IVW	-0.109	0.048	0.024
NAFLD	9-hydroxystearate levels	IVW	-0.107	0.048	0.024
NAFLD	Alpha-ketobutyrate to 3-methyl-2-oxovalerate ratio	IVW	-0.141	0.063	0.025
NAFLD	Adenosine 5'-diphosphate (ADP) to glycerol ratio	IVW	0.088	0.039	0.025
NAFLD	Andro steroid monosulfate C19H28O6S (1) levels	IVW	-0.062	0.028	0.025
NAFLD	4-cholesten-3-one levels	IVW	-0.114	0.051	0.025
NAFLD	Iminodiacetate (IDA) levels	IVW	0.128	0.058	0.026
NAFLD	5alpha-pregnan-3beta,20alpha-diol disulfate levels	IVW	-0.074	0.033	0.026
NAFLD	Glycerol to palmitoylcarnitine (C16) ratio	IVW	-0.122	0.055	0.027
NAFLD	Ursodeoxycholate levels	IVW	-0.127	0.057	0.027
NAFLD	S-methylcysteine sulfoxide levels	IVW	-0.123	0.056	0.027
NAFLD	Xanthurenate levels	IVW	0.098	0.045	0.029
NAFLD	Bilirubin (Z,Z) to etiocholanolone glucuronide ratio	IVW	0.067	0.031	0.030
NAFLD	2'-deoxyuridine levels	IVW	0.082	0.038	0.030
NAFLD	1-stearoyl-2-linoleoyl-GPI (18:0/18:2) levels	IVW	0.097	0.045	0.031
NAFLD	Taurine to cysteine ratio	IVW	0.128	0.060	0.032

Supplementary Table 2. ebi-a-GCST90091033 and 1400metabolites MR results

Outcome	Exposure	Method	b	se	<i>p</i>
NAFLD	Alpha-ketoglutarate to alanine ratio	IVW	0.109	0.051	0.032
NAFLD	X-18887 levels	IVW	-0.120	0.056	0.033
NAFLD	(R)-3-hydroxybutyrylcarnitine levels	IVW	-0.111	0.052	0.034
NAFLD	Trans-urocanate levels	IVW	-0.079	0.037	0.036
NAFLD	Phosphate to sulfate ratio	IVW	-0.112	0.054	0.039
NAFLD	Dopamine 3-o-sulfate levels	IVW	0.118	0.057	0.039
NAFLD	Bilirubin (E,Z or Z,E) levels	IVW	0.060	0.029	0.040
NAFLD	Adenosine 5'-monophosphate (AMP) to flavin adenine dinucleotide (FAD) ratio	IVW	-0.093	0.045	0.040
NAFLD	X-21467 levels	IVW	0.071	0.035	0.040
NAFLD	Adenosine 5'-diphosphate (ADP) to aspartate ratio	IVW	0.072	0.035	0.041
NAFLD	1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6) levels	IVW	-0.141	0.069	0.042
NAFLD	Gluconate levels	IVW	0.094	0.047	0.043
NAFLD	Nisinate (24:6n3) levels	IVW	-0.079	0.039	0.043
NAFLD	Phosphate to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	IVW	-0.122	0.061	0.045
NAFLD	21-hydroxypregnenolone disulfate levels	IVW	0.074	0.037	0.045
NAFLD	Adenosine 5'-diphosphate (ADP) to glucose ratio	IVW	0.092	0.046	0.045
NAFLD	N-acetylmethionine levels	IVW	0.142	0.071	0.046
NAFLD	Lignoceroylcarnitine (C24) levels	IVW	0.067	0.034	0.049