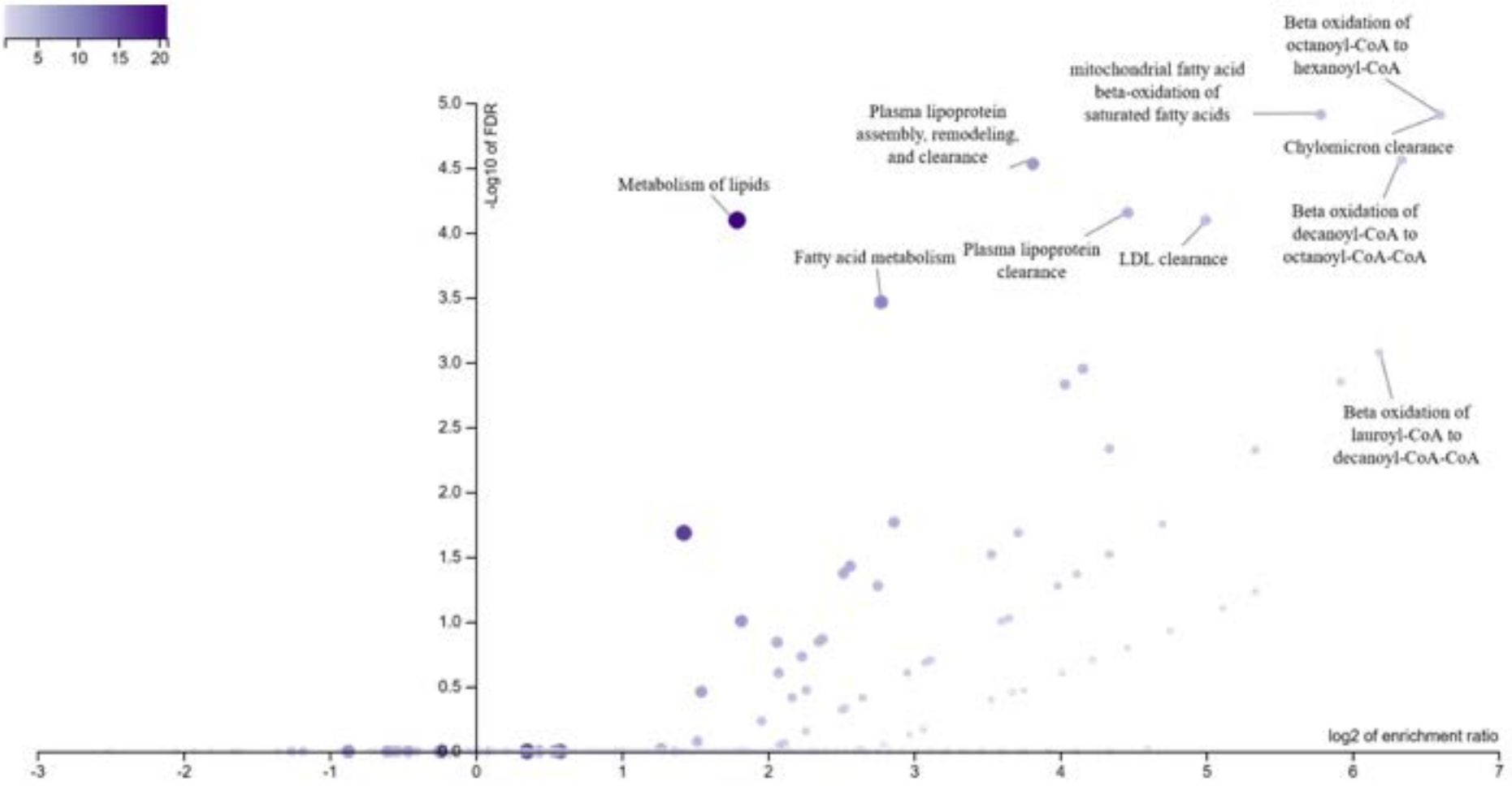
Supplemental Methods

Reactome pathways

Genes related to a taxonomic identifier (Homo sapiens: tax id = 9606) were used exclusively and without literature extension by orthology. To integrate these genes/proteins into molecular pathways of NAFLD, we used the overrepresentation test provided by the PANTHER resource using as input list ('reference' list) the terms retrieved from data mining. We identified 344 Reactome pathways enriched with NAFLD-terms with *p* values that ranged from 4.92E-2 to 5.43E-76. We used WebGestalt (WEB-based Gene SeTAnaLysis Toolkit) functional enrichment analysis (99) available at http://webgestalt.org/.

Reactome pathway of the list of genes causing monogeneic disorders associated with liver steatosis



Supplemental Figure 1

Reactome pathway analysis of genes causing monogenic disorders with hepatic steatosis.

Enrichment method: ORA (over-representation analysis). Enrichment Categories: pathway_Reactome (data source: https://www.reactome.org/ and http://www.geneontology.org. Reference list: list of genes associated with fatty infiltration of liver, Fatty liver, Steatosis, Liver steatosis" (HP:0001397). Cross References: *SNOMEDCT_US:197321007, UMLS:C2711227, SNOMEDCT_US:442191002, MSH:D005234* in the Human Phenotype Ontology (https://hpo.jax.org/ . Organism: Homo sapiens. FDR Method: Benjamini-Hochberg. The size and color of the dot is proportional to the number of overlapping (for ORA) or leading edge genes (for GSEA) of the category. ORA was performed by the WebGestalt (WEB-based Gene SeTAnaLysis Toolkit) functional enrichment analysis web tool available at http://www.webgestalt.org/.

Supplemental Table 1: Hereditary disorders associated with hepatic steatosis.

DISEASE ID	ASSOCIATED DISEASE NAME	GENE ID
ORPHA:254346	19p13.12 microdeletion syndrome	-
ORPHA:1606	1p36 deletion syndrome	GABRD
		RERE
		PRDM16
		SKI
OMIM:610198	3-methylglutaconic aciduria, Type V	DNAJC19
OMIM:231530	3-hydroxyacyl-coA dehydrogenase deficiency	HADH *
OMIM:210200	3-methylcrotonyl-coA carboxylase 1 deficiency	MCCC1
ORPHA:445038	3-methylglutaconic aciduria type 7	CLPB
ORPHA:79086	Acquired generalized lipodystrophy	-
ORPHA:79087	Acquired partial lipodystrophy	LMNB2
ORPHA:99901	Acyl-coA dehydrogenase 9 deficiency	ACAD9
OMIM:201450	Acyl-coA dehydrogenase, medium-chain deficiency	ACADM
OMIM:201475	Acyl-coA dehydrogenase, very long-chain deficiency	ACADVL
OMIM:300270	Adrenomyodystrophy	-
ORPHA:977	Adrenomyodystrophy	-
ORPHA:139507	African iron overload	-
ORPHA:79085	Akt2-related familial partial lipodystrophy	AKT2 *
ORPHA:404454	Alacrimia-choreoathetosis-liver dysfunction syndrome	NGLY1
ORPHA:64	Alström syndrome	ALMS1 *
OMIM:203800	Alström syndrome	ALMS1 *
OMIM:243910	Arima syndrome	-
ORPHA:91	Aromatase deficiency	CYP19A1 *
ORPHA:79474	Atypical Werner syndrome	LMNA
ORPHA:2137	Autoimmune hepatitis	-

ORPHA:369840	Autosomal recessive limb-girdle muscular dystrophy Type 2	TRAPPC11
ORPHA:280365	Autosomal semi-dominant severe lipodystrophic laminopathy	LMNA
ORPHA:528	Berardinelli-Seip congenital lipodystrophy	BSCL2
		CAV1
		CAVIN1
		AGPAT2
		PPARG *
OMIM:615119	Cardioencephalomyopathy, fatal infantile, due to cytochrome C oxidase deficiency 2	COX15
OMIM:212140	Carnitine deficiency, systemic primary	SLC22A5
OMIM:255120	Carnitine palmitoyltransferase I deficiency	CPT1A *
OMIM:600649	Carnitine palmitoyltransferase II deficiency, infantile	CPT2 *
OMIM:608836	Carnitine palmitoyltransferase II deficiency, lethal neonatal	CPT2 *
OMIM:275630	Chanarin-Dorfman syndrome	ABHD5 *
OMIM:618400	Charcot-Marie-Tooth disease, axonal, type 2ee	MPV17
ORPHA:71	Chylomicron retention Disease	SAR1B
ORPHA:435651	Cidec-related familial partial lipodystrophy	CIDEC *
ORPHA:247585	Citrullinemia type Ii	SLC25A13*
OMIM:603471	Citrullinemia, type Ii, adult-onset	SLC25A13*
OMIM:614922	Combined oxidative phosphorylation deficiency 11	RMND1
OMIM:614924	Combined oxidative phosphorylation deficiency 12	EARS2
OMIM:615395	Combined oxidative phosphorylation deficiency 16	MRPL44
OMIM:615595	Combined oxidative phosphorylation deficiency 19	LYRM4
OMIM:615918	Combined oxidative phosphorylation deficiency 21	TARS2
OMIM:616672	Combined oxidative phosphorylation deficiency 27	CARS2
OMIM:617872	Combined oxidative phosphorylation deficiency 34	MRPS7
OMIM:212065	Congenital disorder of glycosylation, type Ia	PMM2

OMIM:614576	Congenital disorder of glycosylation, type Iil	COG6
OMIM:616829	Congenital disorder of glycosylation, type Iip	TMEM199
OMIM:614921	Congenital disorder of glycosylation, type It	PGM1
OMIM:261515	D-bifunctional protein deficiency	HSD17B4
ORPHA:300536	DDOST-CDG (Developmental delay, hypotonia, strabismus and hepatic dysfunction	DDOST
ORPHA:66634	Dilated cardiomyopathy with ataxia	DNAJC19
ORPHA:412	Dysbetalipoproteinemia	APOE *
ORPHA:444490	Familial chylomicronemia syndrome	-
ORPHA:2348	Familial partial lipodystrophy, Dunnigan type	LMNA
ORPHA:79084	Familial partial lipodystrophy, Köbberling type	LMNA
OMIM:613282	Fatty liver disease, nonalcoholic, susceptibility to, 1	-
OMIM:613387	Fatty liver disease, nonalcoholic, susceptibility to, 2	-
OMIM:229600	Fructose intolerance, hereditary	ALDOB *
ORPHA:348	Fructose-1,6-bisphosphatase deficiency	FBP1 *
ORPHA:264580	Glycogen storage disease due to liver phosphorylase kinase deficiency	PHKG2
		PHKA2
ORPHA:53693	Gracile syndrome	BCS1L
OMIM:617093	Growth retardation, impaired intellectual development, hypotonia and hepatopath	ARS1
ORPHA:139491	Hemochromatosis type 4	SLC40A1 *
ORPHA:93111	Hnf1b-related autosomal dominant tubulointerstitial kidney disease	HNF4A *
		HNF1B *
OMIM:236200	Homocystinuria due to cystathionine beta-synthase deficiency	CBS *
ORPHA:391665	Homozygous familial hypercholesterolemia	LDLRAP1 *
		LDLR *
		PCSK9 *
		APOB *
		ABCG8 *

		ABCG5 *
ORPHA:740	Hutchinson-Gilford progeria syndrome	LMNA *
		ZMPSTE24
ORPHA:209902	Hypercholesterolemia due to cholesterol 7alpha-hydroxylase deficiency	
ORPHA:71212	Hyperinsulinism due to short chain 3-hydroxylacyl-coA dehydrogenase deficiency	HADH
OMIM:614300	Hypermethioninemia due to adenosine kinase deficiency	ADK
OMIM:614480	Hypertriglyceridemia, transient infantile	GPD1 *
OMIM:300972	Immunodeficiency 47	ATP6AP1
ORPHA:52430	Inclusion body myopathy with Paget disease of bone and frontotemporal dementia	HNRNPA2B1
		HNRNPA1
		VCP
OMIM:615438	Infantile liver failure syndrome 1	LARS1
OMIM:615486	Interstitial lung and liver disease	MARS1
OMIM:220111	Leigh syndrome, French Canadian type	LRPPRC
ORPHA:435660	LIPE-related familial partial lipodystrophy	LIPE *
ORPHA:156156	Lipoatrophy with diabetes, leukomelanodermic papules, liver steatosis, and hypertrophic cardiomyopathy	-
OMIM:608594	Lipodystrophy, congenital generalized, type 1	AGPAT2 *
OMIM:269700	Lipodystrophy, congenital generalized, type 2	BSCL2
OMIM:612526	Lipodystrophy, congenital generalized, type 3	CAV1 *
OMIM:613327	Lipodystrophy, congenital generalized, type 4	CAVIN1
OMIM:151660	Lipodystrophy, familial partial, type 2	LMNA
OMIM:604367	Lipodystrophy, familial partial type 3	PPARG
OMIM:613877	Lipodystrophy, familial partial type 4	PLIN1 *
OMIM:615238	Lipodystrophy, familial partial, type 5	CIDEC
OMIM:615980	Lipodystrophy, familial partial, type 6	LIPE
OMIM:613070	Liver failure, infantile, transient	TRMU

ORPHA:99900	Long chain acyl-coA dehydrogenase deficiency	-
ORPHA:275761	Lysosomal acid lipase deficiency	-
OMIM:278000	Lysosomal acid lipase deficiency	LIPA *
OMIM:615381	Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome	POLD1
ORPHA:42	Medium chain acyl-coA dehydrogenase deficiency	ACADM
ORPHA:436182	Microcephalic primordial dwarfism-insulin resistance Syndrome	NSMCE2
		XRCC4
OMIM:611126	Mitochondrial complex I deficiency due to Acad9 deficiency	ACAD9
OMIM:618234	Mitochondrial complex I deficiency, nuclear type 11	NDUFAF1
OMIM:124000	Mitochondrial complex III deficiency, nuclear type 1	BCS1L
OMIM:617156	Mitochondrial DNA depletion syndrome 15 (hepatocerebral Type)	TFAM
OMIM:251880	Mitochondrial DNA depletion syndrome 3 (hepatocerebral Type)	DGUOK *
OMIM:203700	Mitochondrial DNA depletion syndrome 4a (Alpers Type)	POLG
ORPHA:298	Mitochondrial neurogastrointestinal encephalomyopathy	POLG
		RRM2B
		TYMP
ORPHA:746	Mitochondrial trifunctional protein deficiency	HADHA
		HADHB
ORPHA:96168	Monosomy 13q34	-
ORPHA:99226	Monosomy X	-
OMIM:615703	Morbid obesity and spermatogenic failure	CEP19
ORPHA:99228	Mosaic monosomy X	-
OMIM:617303	Mucopolysaccharidosis-plus syndrome	VPS33A
OMIM:231680	Multiple acyl-coA dehydrogenase deficiency	ETFB
		ETFA
		ETFDH

OMIM:615356	Muscular dystrophy, limb-girdle, autosomal Recessive 18	TRAPPC11
OMIM:256810	Navajo neurohepatopathy	MPV17
ORPHA:247598	Neonatal intrahepatic cholestasis due To citrin deficiency	SLC25A13
OMIM:616263	Neurologic, endocrine and pancreatic disease, multisystem, infantile-onset	PTRH2
ORPHA:98907	Neutral lipid storage disease with ichthyosis	ABHD5
OMIM:610717	Neutral lipid storage disease with myopathy	PNPLA2 *
ORPHA:98908	Neutral lipid storage myopathy	PNPLA2
ORPHA:436271	Non-progressive predominantly posterior cavitating leukoencephalopathy with peripheral neuropathy	COA8
OMIM:601466	Patent ductus venosus	-
OMIM:264470	Peroxisomal acyl-coA oxidase deficiency	ACOX1
OMIM:261650	Phosphoenolpyruvate carboxykinase 2, mitochondrial	PCK2 *
OMIM:261680	Phosphoenolpyruvate carboxykinase deficiency, cytosolic	PCK1 *
ORPHA:280356	Plin1-related familial partial lipodystrophy	PLIN1
ORPHA:101330	Porphyria cutanea tarda	-
ORPHA:79083	Pparg-related familial partial lipodystrophy	PPARG
ORPHA:90970	Primary lipodystrophy	-
ORPHA:2959	Progeria-short stature-pigmented nevi syndrome	-
OMIM:613658	Rajab interstitial lung disease with brain calcifications	FARSB
OMIM:617253	Seckel syndrome 10	NSMCE2
ORPHA:363400	Severe neurodegenerative syndrome with lipodystrophy	BSCL2 *
ORPHA:465508	Symptomatic Form of hemochromatosis type 1	HFE *
ORPHA:881	Turner syndrome	-
ORPHA:99413	Turner syndrome due to structural X chromosome anomalies	-
OMIM:228100	Visceral steatosis, congenital	-
ORPHA:3455	Wiedemann-Rautenstrauch syndrome	POLR3A

ORPHA:905	Wilson disease	ATP7B

This search was performed using The Human Phenotype Ontology (https://hpo.jax.org/) database, which contains 3,000 terms and over 156,000 annotations to hereditary diseases. We searched for disease terms:"Fatty infiltration of liver, Fatty liver, Steatosis, Liver steatosis" Hepatic steatosis HP:0001397. Cross References: *SNOMEDCT_US:197321007, UMLS:C2711227, SNOMEDCT_US:442191002, MSH:D005234.* Source of disease ID: Orphanet, DECIPHER, and OMIM. * The list includes genes associated with the pathogenesis of NAFLD identified in previous human studies and are included in the enrichment analysis.