

Supplementary Figure 1 TM6SF2 is upregulated in *in vitro* and *in vivo* models of nonalcoholic fatty liver disease. A: Protein levels of TM6SF2 in response to palmitic acid (150 μ M) treatment in two cell lines; B: Protein (left) and mRNA levels (right) of TM6SF2 in the liver of mice fed with normal chow diet or high-fat diet at the indicated time points. ^c*P* < 0.001.



Supplementary Figure 2 Overexpression of TM6SF2 improved hepatic lipid accumulation. A: TM6SF2-knockdown L02 cells were restored with the expression of wild type TM6SF2. Protein levels of TM6SF2 were assessed by immunoblotting; B: Representative nile red staining (top) and quantification of lipid accumulation (bottom) of L02 cells were shown. Scale bars: 50 µm; C: TM6SF2-knockdown L02 cells were restored with the expression of wild type TM6SF2 or empty vector. Left, intracellular TG levels in cells were examined after palmitic acid (PA) (150 µM) treatment for 24 h (n = 3). Right, the reconstituted cells were incubated with PA (150 µM) for 24 h and then the cellular viability analysis was performed (n = 5). ^bP < 0.01; ^cP < 0.001.



Supplementary Figure 3 Knockdown of TM6SF2 promotes high-fat diet-induced inflammation in liver. A-C: Mice were injected with AAV-shNC and AAV-shTm6sf2 viruses *via* the tail vein and fed a high-fat diet or normal chow diet for 16 wk (n = 5 mice per group). The serum concentrations of inflammatory cytokines (A), hepatic mRNA levels of inflammation-related genes (B) and serum levels of ALT and AST (C) were shown; D: Representative images of immunofluorescent staining (left) and their quantification (right) were shown (8 fields of each mouse were examined). Scale bar: 50 µm. ^aP < 0.05; ^bP < 0.01; ^cP < 0.001. NS: Not significant.



Supplementary Figure 4 Hepatic TM6SF2 deficiency increases de novo lipogenesis. A and B: Levels of fasting blood glucose and plasma insulin (A) were examined and the glucose tolerance test and insulin tolerance test test (B) were also performed in the indicated mice during normal chow diet or high-fat diet feeding; C: The effect of starvation or hypoxia condition on CD36 and FABP1 protein expression was determined in TM6SF2-knockdown cells with or without palmitic acid treatment. NS: Not significant.

Antibodies	Source	Identifier
Mouse anti-TM6SF2 (1:1500)	Abcam	Cat#ab169629
Mouse anti-Beta-tubulin	Proteintech	Cat#10094-1-AP
(1:10000)		
Rabbit anti-SREBP-1c (1:500)	Proteintech	Cat#66875-1-Ig
Rabbit anti-p-ACC (1:1000)	ABclonal	Cat#AP0298
Rabbit anti-ACC (1:1000)	ABclonal	Cat#A15606
Rabbit anti-SCD-1 (1:1000)	ABclonal	Cat#A16429
Rabbit anti-FASN (1:500)	ABclonal	Cat#A0461
Rabbit anti-LaminA/C (1:1500)	ABclonal	Cat#A19524
Rabbit anti-PPAR-alpha (1:1500)	ABclonal	Cat#A6697
Rabbit anti-CPT1a (1:500)	ABclonal	Cat#A5307
Rabbit anti-ACOX1 (1:500)	ABclonal	Cat#A8091
Rabbit anti-CD36 (1:1500)	ABclonal	Cat#A5792
Rabbit anti-FABP1 (1:1000)	ABclonal	Cat#A5311
Chemicals, Reagent or Resource	Source	Identifier
Palmitic acid	Sigma-Aldrich	Cat#P0500
Glucose	Sigma-Aldrich	Cat#G8270
Novolin R	Novo Nordisk	N/A
Mouse and Rabbit Specific	Abcam	Cat#ab236466.
HRP/DAB IHC Detection Kit -		
Micro-polymer		
Oil Red O	Solarbio	Cat#O8010
Hematoxylin and Eosin Staining	Beyotime	Cat# C0105M
Kit		
High-Fat (60 kal%) Purfied	Dyets	Cat#HF60
Rodent Diet		

Supplementary Table 1 The information of materials used in this study

Normal chow dietResearch DietsCat# D12450BNile redSolarbioCat#N8440Antifade PolyvinylpyrrolidoneBeyotimeCat#P0123Mounting MediumBeyotimeCat#P0013BSDS-PACE: Sample LoadingBeyotimeCat#P00151Buffer, 5XBeyotimeCat#P00171BCA Protein Assay KitBeyotimeCat#P00111Triglyceride assay kitNanjing JianchengCat#A1110-11AspartateaminotransferaseNanjing JianchengCat#C009-2-1Assay KitVVCat#A009-2-1Alanine aminotransferaseNanjing JianchengCat#A10875B-Hydroxybutyrate(beta-HB)AbcamCat#a1808765AssayNanjing JianchengCat#A1042-2-1Assay KitVCat#A1042-2-1KitVVCat#A11416Monseterified Free fatty acidsNanjing JianchengCat#A1042-2-1Assay KitAbcamCat#A1042-2-1Assay KitVVVMonseterified Free fatty acidsNanjing JianchengCat#A114716KitMouse malonyl-CoA ELISA test KitAbcamCat#A1042-2-1Mouse IL-Iß ELISA test KitAbcamCat#ab208348Mouse IL-Iß ELISA test KitAbcamCat#ab208348Mouse CL1_2 ELISA test KitGelatinsCat#JICA94Mouse CL1_2 ELISA test KitGelatinsCat#JICA94Mouse CL1_2 ELISA test KitGelatinsCat#JICA94Mouse CL2_ELISA test KitGelatinsCat#JICA94-000Mouse CL2_LISA			
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FAO Substrate		
Blood Glucose Meter	Yuwell	Cat#590
MK-4074	MedChemExpress	Cat#HY-107709
GW7647	MedChemExpress	Cat#HY-13861
Etomoxir (Eto)	MedChemExpress	Cat#HY-50202
PrimeScript TM RT Master Mix	Takara Biotechnology	Cat#RR036A
(Perfect Real Time)		
Hieff® qPCR SYBR Green	Yeasen	Cat#11201ES08
Master Mix (No Rox)		
Enhanced Chemiluminescent	NCM Biotech	Cat#P10100
C57BL/6	GemPharmatech Co.,Ltd	N/A
Oligonucleotides		
Human TM6SF2	F:	N/A
	5'-GCATTGATGAGCGCCCTAAT	
	C-3′	
	R:	
	5'-AGTGGGTCATAGGAGACCTC	
	G-3′	
Human ACTB	F:	N/A
	5'-CATGTACGTTGCTATCCAGGC	
	-3′	
	R	
	5'-CTCCTTAATGTCACGCACGAT	
	-3′	
Mouse <i>Tm6sf</i> 2	F:	N/A
	5'-GATCACCTACGACCCTCTCTA	
	TG-3'	
	R:	

	5'-TGGAGTGCAATGACAAGGTC	
	C-3′	
Mouse Actb	F:	N/A
	5'-GGCTGTATTCCCCTCCATCG-3	
	1	
	R	
	5'-CCAGTTGGTAACAATGCCAT	
	GT-3'	
Mouse <i>Tnf</i>	F:	N/A
	5'-CAGGCGGTGCCTATGTCTC-3'	
	R:	
	5'-CGATCACCCCGAAGTTCAGT	
	AG-3'	
Mouse <i>ll6</i>	F:	N/A
	5'-CTGCAAGAGACTTCCATCCA	
	G-3'	
	R:	
	5'-AGTGGTATAGACAGGTCTGT	
	TGG-3'	
Mouse <i>ll1b</i>	F:	N/A
	5'-GAAATGCCACCTTTTGACAG	
	TG-3'	
	R:	
	5'-TGGATGCTCTCATCAGGACA	
	G-3'	
Mouse Ccl2	F:	N/A
	5'-TAAAAACCTGGATCGGAACC	
	AAA-3'	
	R:	

	5'-GCATTAGCTTCAGATTTACGG	
	GT-3'	
Mouse Cxcl10	F:	N/A
	5'-CCAAGTGCTGCCGTCATTTTC	
	-3′	
	R:	
	5'-GGCTCGCAGGGATGATTTCA	
	A-3'	
Mouse Col1a1	F:	N/A
	5'-GCTCCTCTTAGGGGCCACT-3'	
	R:	
	5'-ATTGGGGACCCTTAGGCCAT-	
	3'	
Mouse Srebf1	F:	N/A
	5'-TGACCCGGCTATTCCGTGA-3'	
	R:	
	CTGGGCTGAGCAATACAGTTC-3	
	,	
Mouse Fasn	F:	N/A
	5'-GGAGGTGGTGATAGCCGGTA	
	T-3′	
	R:	
	5'-TGGGTAATCCATAGAGCCCA	
	G-3′	
Mouse Scd1	F:	N/A
	5'-TTCTTGCGATACACTCTGGTG	
	C-3′	
	R:	
	5'-CGGGATTGAATGTTCTTGTCG	

	T-3′	
Mouse Acaca	F:	N/A
	5'-CTCCCGATTCATAATTGGGTC	
	TG-3'	
	R:	
	5'-TCGACCTTGTTTTACTAGGTG	
	C-3′	
Mouse <i>Hmgcr</i>	F:	N/A
	5'-TGTTCACCGGCAACAACAAG	
	A-3'	
	R:	
	5'-CCGCGTTATCGTCAGGATGA-	
	3'	
Mouse Cd36	F:	N/A
	5'-ATGGGCTGTGATCGGAACTG-	
	3'	
	R:	
	5'-TTTGCCACGTCATCTGGGTTT-	
	3'	
Mouse Slc27a1	F:	N/A
	5'-CTGGGACTTCCGTGGACCT-3'	
	R:	
	5'-TCTTGCAGACGATACGCAGA	
	A-3'	
Mouse <i>Fabp1</i>	F:	N/A
	5'-ATGAACTTCTCCGGCAAGTA	
	CC-3′	
	R:	
	5'-GGTCCTCGGGCAGACCTAT-3'	

Mouse <i>Ppara</i>	F:	N/A
	5'-AACATCGAGTGTCGAATATG	
	TGG-3'	
	R:	
	5'-CCGAATAGTTCGCCGAAAGA	
	A-3′	
Mouse <i>Cpt1a</i>	F:	N/A
	5'-TGGCATCATCACTGGTGTGTT	
	-3′	
	R:	
	GTCTAGGGTCCGATTGATCTTT	
	G-3′	
Mouse Acox1	F:	N/A
	5'-TAACTTCCTCACTCGAAGCC	
	A-3′	
	R:	
	5'-AGTTCCATGACCCATCTCTGT	
	C-3′	
Mouse Acadl	F:	N/A
	5'-TTTCCTCGGAGCATGACATTT	
	T-3'	
	R:	
	5'-GCCAGCTTTTTCCCAGACCT-3	
	,	
Mouse Acadm	F:	N/A
	5'-AACACAACACTCGAAAGCG	
	G-3′	
	R:	
	5'-TTCTGCTGTTCCGTCAACTCA-	

AAV-shTm6sf2	GCACAGCACATGGCATCTT	CA	N/A
sh-TM6SF2	TGACCTGGCCCTTGTCATAT	А	N/A
The sequences of shRNAs			
	3'		
	GCAAACCTGGAAGGGTCAAAC-		
	R:	5'-	
	TTCCCTGATGGACGCTCTTTA-3'		
Mouse <i>Cyp4a10</i>	F:	5'-	N/A
	3′		

GEO series	Contributors	Overall design
GSE130970	Hoang SA, Oseini A, Feaver	6 cases are histologically normal,
	RE, Cole BK <i>et al</i>	and 72 cover the full spectrum of
		nonalcoholic fatty liver disease
		(activity score 0-6, fibrosis stage 0-4)
GSE48452	Ahrens M, Ammerpohl O, von	73 samples of human liver grouped
	Schönfels W, Kolarova J et al	into Control = 14, Healthy obese =
		27, Steatosis = 14 and NASH = 18
GSE83452	Lefebvre P, Lalloyer F, Baugé	Microarray data were obtained for
	E, Pawlak M et al	152 patients at baseline (44 no
		NASH, 104 NASH, 4 undefined)
		and 79 patients (54 no NASH, 22
		NASH, 3 undefined) at 1 yr
		follow-up [38 diet restriction (Diet),
		41 bariatric surgeries]
GSE89632	Arendt BM, Comelli EM, Ma	Cross-sectional study, including
	DW, Lou W et al	patients with non-alcoholic fatty
		liver disease (25 SS, 23 NASH) and
		24 healthy living liver donors as HC

Supplementary Table 2 The information of Gene Expression Omnibus series cited in this study