Figure S1. Continued.

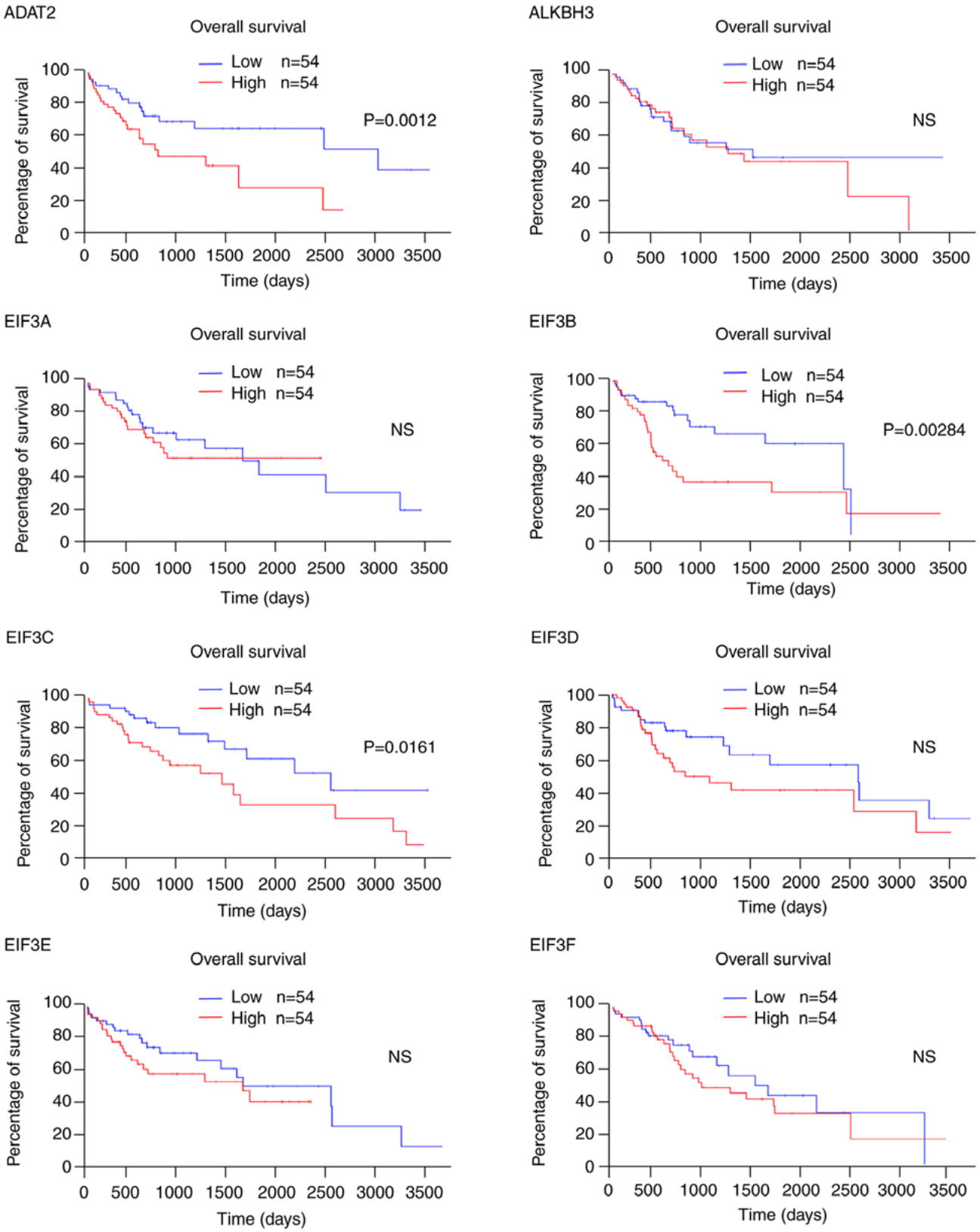

Figure S1. Continued.

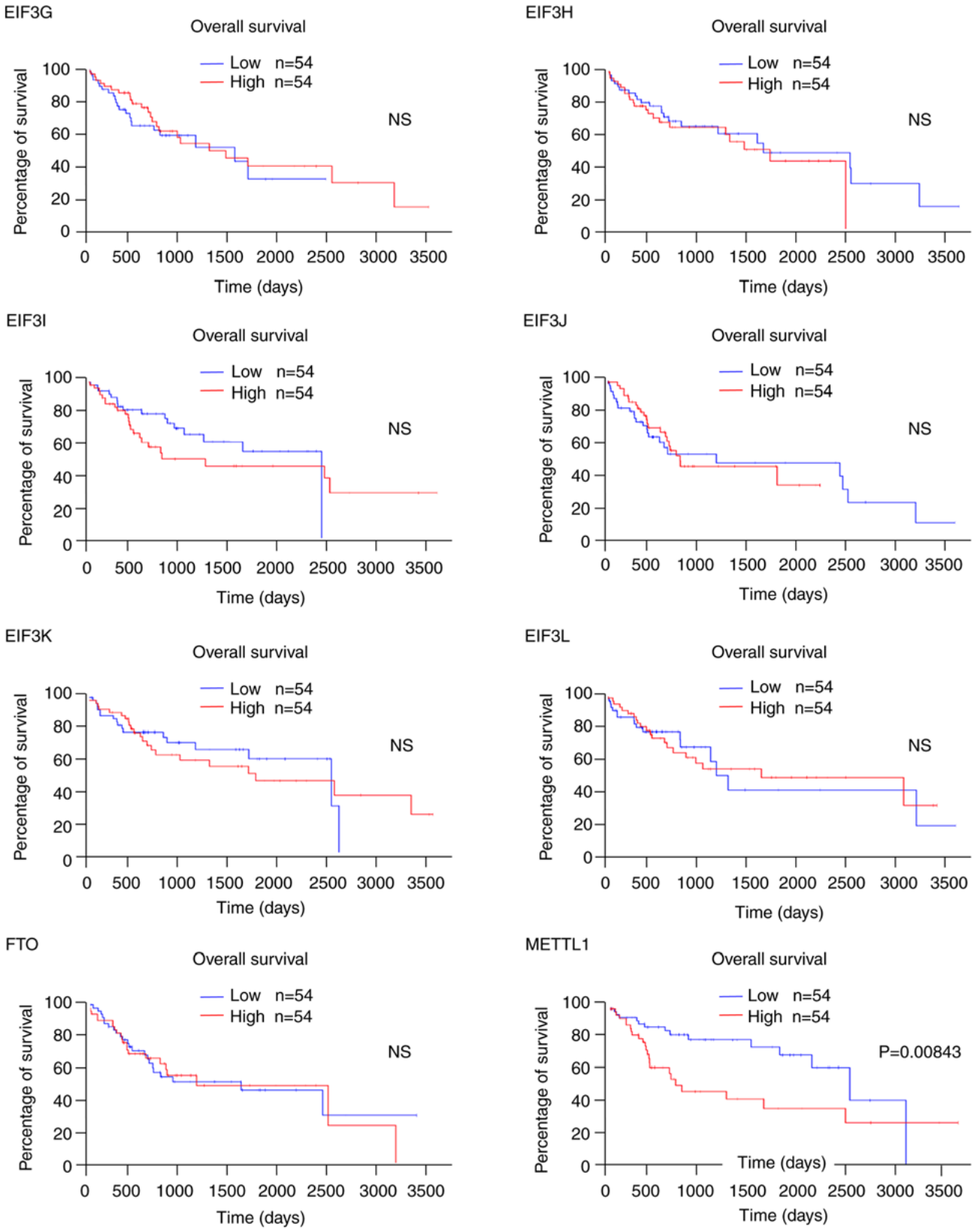

Figure S1. Continued.

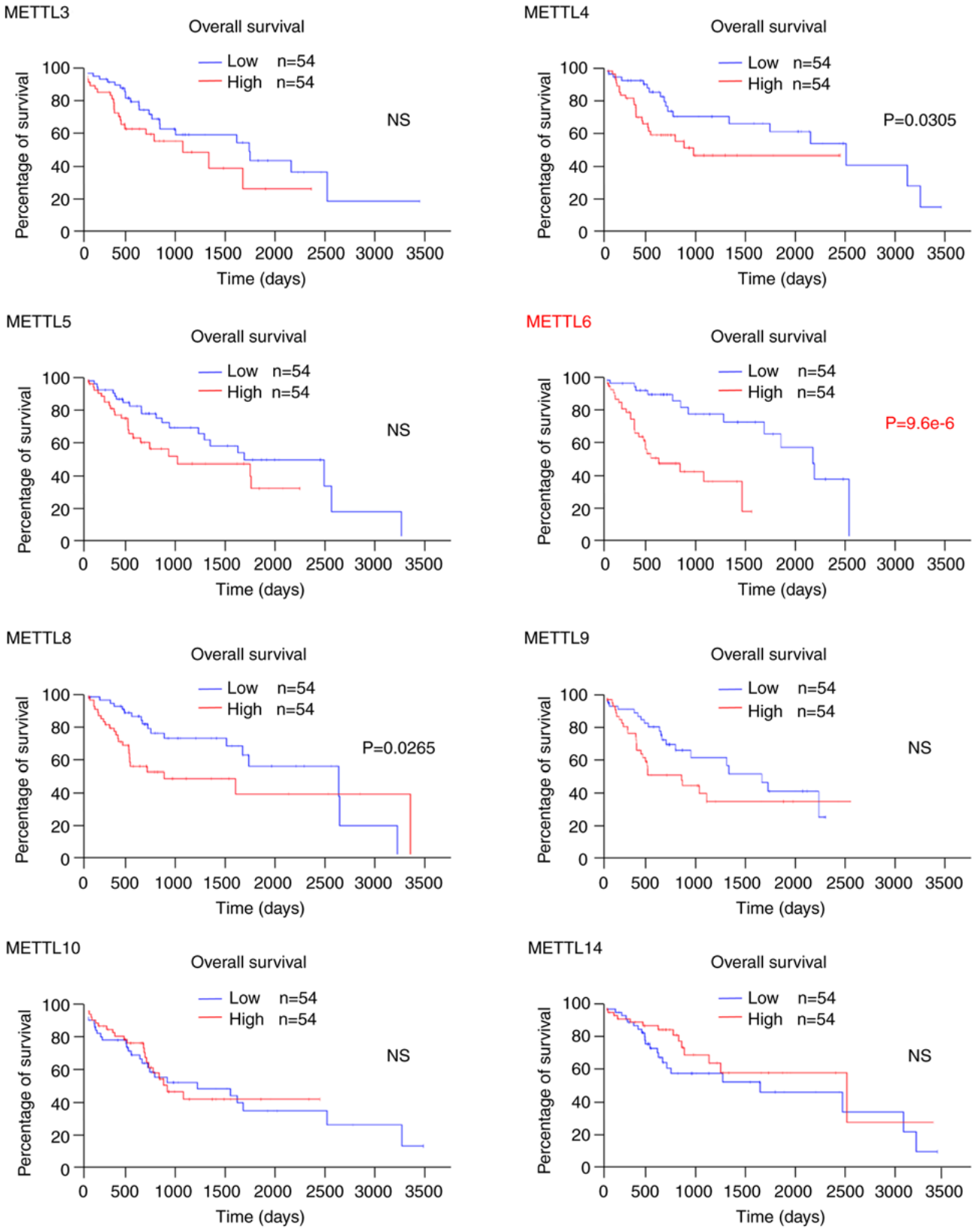

Figure S1. Screening of RNA modification enzymes in HCC using OncoLnc. The overall survival rate in patients with HCC based on high and low *METTL6* mRNA levels. The group cut-off value is based on the quartile. HCC, hepatocellular carcinoma; METTL6, methyltransferase-like 6.

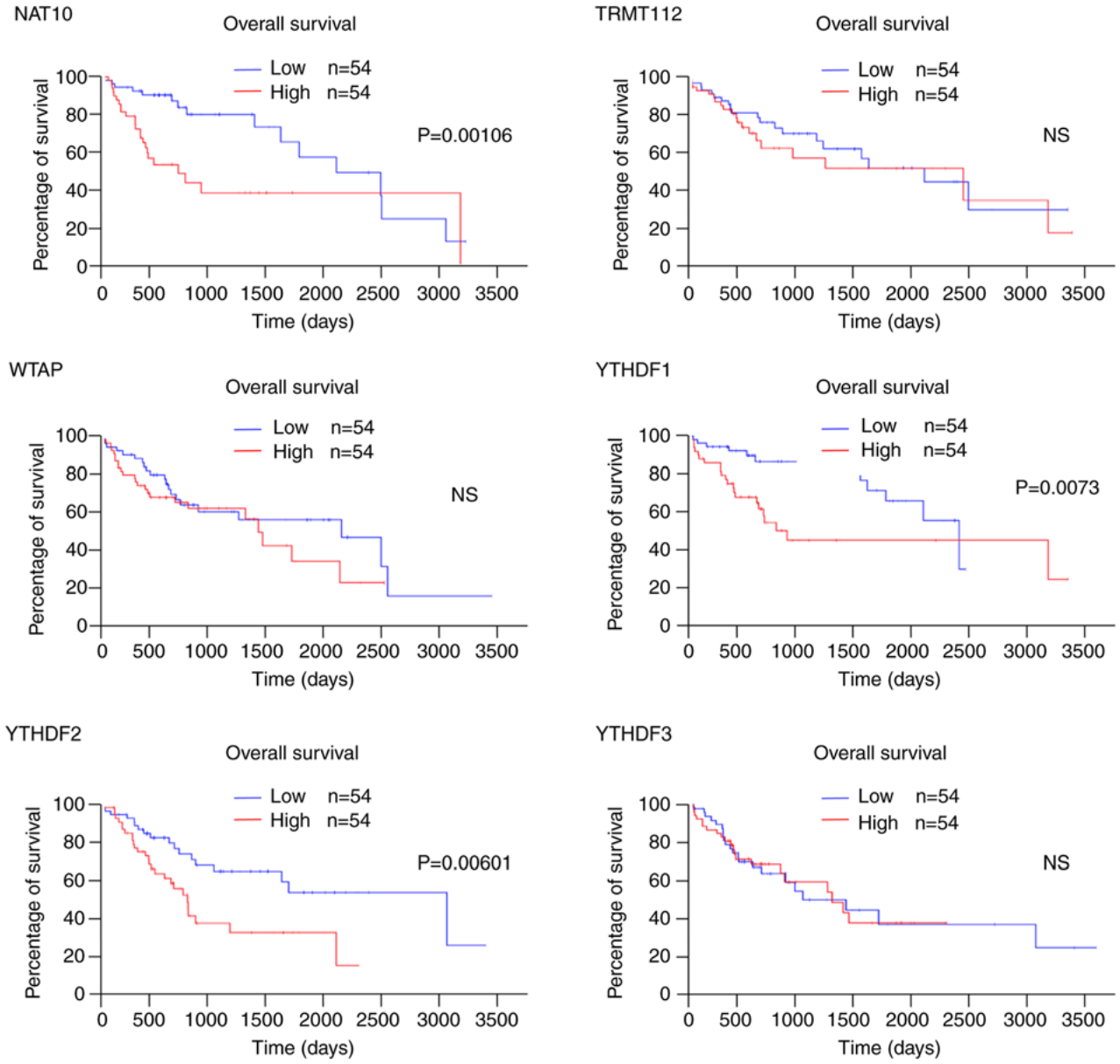

Figure S2. (A) Western blot analysis shows METTL6 expression in different HCC cell lines. (B) Western blot analysis of cell adhesion-associated proteins ITGA1, SPON1 and CLDN14 in SNU-423 and SNU-475 cell lines before and after METTL6 knockout. (C) ChIP-seq analysis of cell adhesion genes *ITGA1*, *CLDN14*, and *SPON1* in SNU-475 METTL6 knockout cells. The chromatin binding activity of H3K27ac and transcription factor CTCF binding affinity between control and METTL6 knockout cells. All data are presented as means ± standard deviation of at least three independent experiments; **P<0.01; ***P<0.001; NS as non-significant. HCC, hepatocellular carcinoma. METTL6, methyltransferase-like 6; ITGA1, integrin α-1/β-1; CLDN14, claudin-14 molecules; SPON1, spondin1.

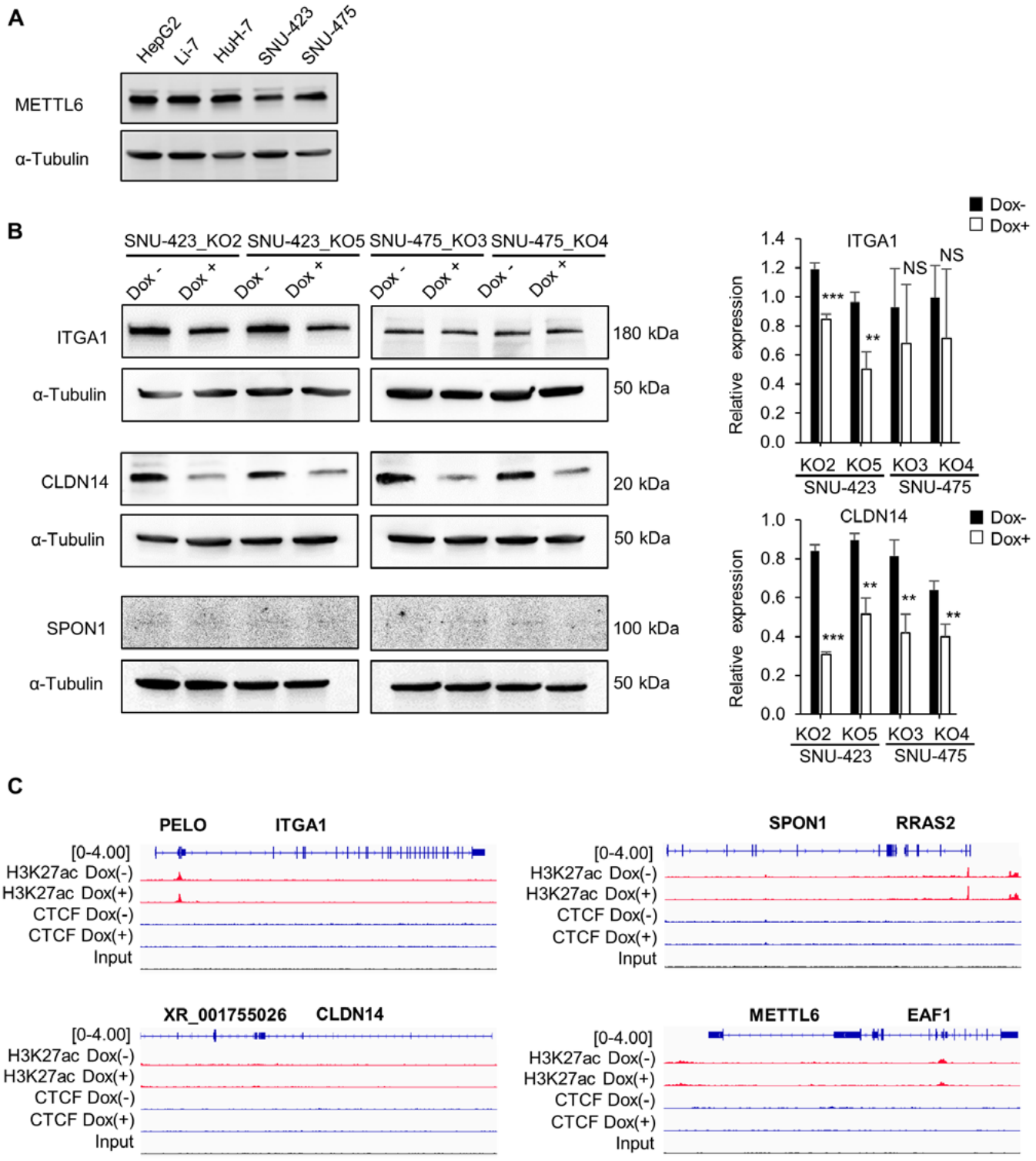

Table SI. Information of the certified cell lines.

Name	Origin	Certification institution	Tested method	DNA profile or characteristics
SNU-423	Human hepatocellular carcinoma	ATCC	STR	Amelogenin: X,Y CSF1PO: 11,12 D13S317: 10,13 D16S539: 9 D5S818: 10 D7S820: 12 THO1: 6,9 TPOX: 8 vWA: 15
SNU-475	Human hepatocellular carcinoma	ATCC	STR	Amelogenin: X,Y CSF1PO: 11,12 D13S317: 8,11 D16S539: 12 D5S818: 10,13 D7S820: 7,12 THO1: 7,9 TPOX: 8,9 vWA: 14
HepG2	Human hepatocellular carcinoma	RBRC	STR	Amelogenin: X,Y CSF1PO: 10,11 D13S317: 9,13 D16S539: 12,13 D5S818: 11,12 D7S820: 10 F13A01: 5,7 F13B: 6,10 FESFPS: 11 LPL: 10,11 THO1: 9 TPOX: 8,9 vWA: 17
Huh-7	Human hepatocellular carcinoma	RBRC	STR	D5S818:12 D13S317:10,11 D7S820:11 D16S539:10 VWA:16,18 TH01:7 Amelogenin:X TPOX:8,11 CSF1PO:10.3
Li-7	Human hepatocellular carcinoma	RBRC	STR	Amelogenin: X CSF1PO: 12 D13S317: 11 D16S539: 9 D5S818: 9,11 D7S820: 10,11 THO1: 7 TPOX: 8,11 vWA: 16.19

ATCC, American Type Culture Collection; RBRC, RIKEN BioResource Research Center.

Table SII. Screening of the RNA modification enzymes in hepatocellular carcinoma (HCC) using GEPIA.

RNA-modification enzymes	Name	mRNA expression in HCC	HCC prognostic	Previous studies in HCC	Authors, year (Refs.)
ADAR1	Adenosine deaminase RNA specific	Significantly upregulated	NS	ADAR1 enhanced HCC metastasis by promoting tumor cells adherence to ECM via increasing ITGA2 expression	Yu *et al*, 2019 (1)
ADAR2	Adenosine deaminase RNA specific B1	NS	NS		
ADAT1	Adenosine deaminase tRNA specific 1	NS	NS		
ADAT2	Adenosine deaminase tRNA specific 2	NS	Log rank P=0.013 higher expression with worse outcome		
ADAT3	Adenosine deaminase tRNA specific 3	NS	NS		
ALKBH1	alkB homolog 1, tRNA methyltransferase	NS	Log rank P=0.0091 higher expression with worse outcome	Expression level of *ALKBH1* is increased in HCC tissues	Ma *et al*, 2019 (2)
ALKBH5	alkB homolog 5, tRNA methyltransferase	NS	NS		
ALKBH8	alkB homolog 8, tRNA methyltransferase	NS	NS		
CTU1	Cytosolic thiouridylase subunit 1	NS	NS		
DNMT2	DIMT2 rRNA methyltransferase and ribosome maturation factor	NS	NS		
EIF2A	Eukaryotic translation initiation factor 2 subunit A	NS	Log rank P=0.026 high expression with worse outcome		
EIF3A	Eukaryotic translation initiation factor 3 subunit A	NS	NS		
EIF3B	Eukaryotic translation initiation factor 3 subunit B	Significantly upregulated	Log rank P=0.0078 higher expression with worse outcome	EIF3B was upregulated in HCV-associated HCC	Golob-Schwarzl *et al*, 2017 (3)
EIF3C	Eukaryotic translation initiation factor 3 subunit C	NS	NS	EIF3C promotes HCC cell proliferation *in vitro* as well as tumorigenicity *in vivo*	Li *et al*, 2017 (4)
EIF3E	Eukaryotic translation initiation factor 3 subunit E	Significantly upregulated	NS	EIF3E are required for HCC cell proliferation and normal protein biogenesis *in vivo* and *in vitro*	Sadato *et al*, 2018 (5)

Table SII. Continued.

RNA-modification enzymes	Name	mRNA expression in HCC	HCC prognostic	Previous studies in HCC	Authors, year (Refs.)
EIF3H	Eukaryotic translation initiation factor 3 subunit H	Significantly upregulated	Log rank P=0.047 higher expression with worse outcome	EIF3H is involved in HCC progression, and EIF3H may be a potentially valuable biomarker for HCC	Zhu *et al*, 2016 (6)
EIF3I	Eukaryotic translation initiation factor 3 subunit I	NS	Log rank P=0.015 higher expression with worse outcome	Overexpression of EIF3I in HCC is oncogenic and is a surrogate marker and therapeutic target for treatment with Akt1 inhibitors.	Wang *et al*, 2013 (7)
ELP1	Elongator acetyltransferase complex subunit 1	NS	NS		
ELP3	Elongator acetyltransferase complex subunit 3	NS	NS	Overexpression of ELP3 or ELP4 promotes the migration and invasion of HCC cells, which was abolished when either ELP3 or ELP4 was silenced	Xu *et al*, 2018 (8)
ELP4	Elongator acetyltransferase complex subunit 4	NS	NS	Overexpression of ELP3 or ELP4 promoted the migration and invasion of HCC cells, which was abolished when either ELP3 or ELP4 was silenced	Xu *et al*, 2018 (8)
EMG1	EMG1 N1-specific pseudouridine methyltransferase	NS	Log rank P=0.015 higher expression with worse outcome		
FTO	FTOα-ketoglutarate dependent dioxygenase	NS	Not statistically significant		
FTSJ3	FtsJ RNA 2'-O-methyltransferase 3	Significantly upregulated	Log rank P=0.02 higher expression with worse outcome		
GTPBP3	GTP binding protein 3, mitochondrial	Significantly upregulated	NS		
IGF2BP1	Insulin like growth factor 2 mRNA binding protein 1	NS	NS	IGF2BP1 promotes SRF-dependent transcription in cancer in an m6A- and miRNA-dependent manner (HCC)	Muller *et al*, 2019 (9)
KIAA1456/TRM9L	tRNA methyltransferase 9B (putative)	NS	NS	No significant differences between recurrence-free survival and KIAA1456 (P=0.564) in HCC	Peng *et al*, 2014 (10)
METTL1	Methyltransferase like 1	Significantly upregulated	Log rank P=0.00037 higher expression with worse outcome	METTL1 overexpression is correlated with poor prognosis and promotes hepatocellular carcinoma via PTEN	Tian *et al*, 2019 (11)

Table SII. Continued.

RNA-modification enzymes	Name	mRNA expression in HCC	HCC prognostic	Previous studies in HCC	Authors, year (Refs.)
METTL14	Methyltransferase like 14	NS	NS	METTL14 downregulation acts as an adverse prognosis factor for recurrence-free survival of HCC and is significantly associated with tumor metastasis *in vitro* and *in vivo*	Ma *et al*, 2017 (12)
METTL3	Methyltransferase like 3	Significantly upregulated	Log rank P=0.0021 higher expression with worse outcome	METTL3 is frequently upregulated in human HCC and contributes to HCC progression. METTL3 represses SOCS2 expression in HCC through an m6A-YTHDF2-dependent mechanism	Chen *et al*, 2018 (13)
METTL5	Methyltransferase like 5	Significantly upregulated	Log rank P=0.00026 higher expression with worse outcome		
METTL6	Methyltransferase like 6	Significantly upregulated	expression with worse outcome	Log rank P=0.0022 higher	
MOD5		NS	NS		
MRM2	Mitochondrial rRNA methyltransferase 2	NS	Log rank P=0.0059 higher expression with worse outcome		
MTO1	Mitochondrial tRNA translation optimization 1	NS	NS		
NAT10	N-acetyltransferase 10	NS	Log rank P=0.00076 higher expression with worse outcome	Loss of nucleolar localization of NAT10 promotes cell migration and invasion in HCC	Tan *et al*, 2018 (14)
NEP1		NS	Log rank P=0.015 higher expression with worse outcome		
NML		NS	Log rank P=4.1e-05 higher expression with worse outcome		
NOP2	N-acetyltransferase 10	Significantly upregulated	NS		
NSUN1	NOP2/Sun RNA methyltransferase 1	Significantly upregulated	NS		
NSUN2	NOP2/Sun RNA methyltransferase 2	NS	NS		

Table SII. Continued.

RNA-modification enzymes	Name	mRNA expression in HCC	HCC prognostic	Previous studies in HCC	Authors, year (Refs.)
NSUN3	NOP2/Sun RNA methyltransferase 3	NS	NS		
NSUN4	NOP2/Sun RNA methyltransferase 4	NS	NS		
NSUN5	NOP2/Sun RNA methyltransferase 5	Significantly upregulated	NS		
NSUN6	NOP2/Sun RNA methyltransferase 6	NS	NS		
TRDMT1	tRNA aspartic acid methyltransferase 1	NS	NS		
TRMT10C	tRNA methyltransferase 10C, mitochondrial RNase P subunit	NS	Log rank P=0.0066 higher expression with worse outcome		
TRMT11	tRNA methyltransferase 11 homolog	NS	NS		
TRMT112	tRNA methyltransferase subunit 11-2	Significantly upregulated	Log rank P=0.0025 higher expression with worse outcome		
TRMT13	tRNA methyltransferase subunit 13	NS	NS		
TRMT2A	tRNA methyltransferase 2 homolog A	Significantly upregulated	Log rank P=0.0049 higher expression with worse outcome		
TRMT2B	tRNA methyltransferase 2 homolog B	NS	NS		
TRMT6	tRNA methyltransferase 6	NS	Log rank P=0.0016 higher expression with worse outcome		
EIF3H	Eukaryotic translation	Significantly	Log rank	EIF3H is involved in HCC	Zhu *et al*, 2016 (6)
TRMT7	tRNA methyltransferase 7	Significantly upregulated	Log rank P=0.00017 higher expression with worse outcome		

Table SII. Continued.

RNA-modification enzymes	Name	mRNA expression in HCC	HCC prognostic	Previous studies in HCC	Authors, year (Refs.)
TRMU	tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase	Significantly upregulated	Log rank P=0.0027 higher expression with worse outcome		
WDR4	WD repeat domain 4	Significantly upregulated	Log rank P=0.00022 higher expression with worse outcome	METTL1/WDR4 COMPLEX related to poor prognosis and promotes HCC	Tian *et al*, 2019 (11)
WTAP	WT1 associated protein	NS	Log rank P=0.0053 higher expression with worse outcome	WTAP facilitates progression of HCC via m6A-HuR-dependent epigenetic silencing of ETS1	Chen *et al*, 2019 (15)
YTHDC2	YTH domain containing 2	NS	NS		
YTHDF1	YTH N6-methyladenosine RNA binding protein 1	NS	Log rank P=0.0013 higher expression with worse outcome	m6A reader YTHDF1 drives hypoxia-induced autophagy and malignancy of HCC by promoting ATG2A and ATG14 translation	Li *et al*, 2021 (16)
YTHDF2	YTH N6-methyladenosine RNA binding protein 2	NS	Log rank P=0.0068 higher expression with worse outcome	YTHDF2 suppresses cell proliferation and growth via destabilizing the EGFR mRNA in HCC	Zhong *et al*, 2019 (17)
YTHDF3	YTH N6-methyladenosine RNA binding protein 3	NS	NS		

A list of 60 RNA modification enzymes and their mRNA expression levels, prognostic role in HCC, and previous related studies are shown. The group cut-off value are based on the median level. GEPIA, Gene Expression Profiling Interactive Analysis; HCC, hepatocellular carcinoma; NS, not significant.

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