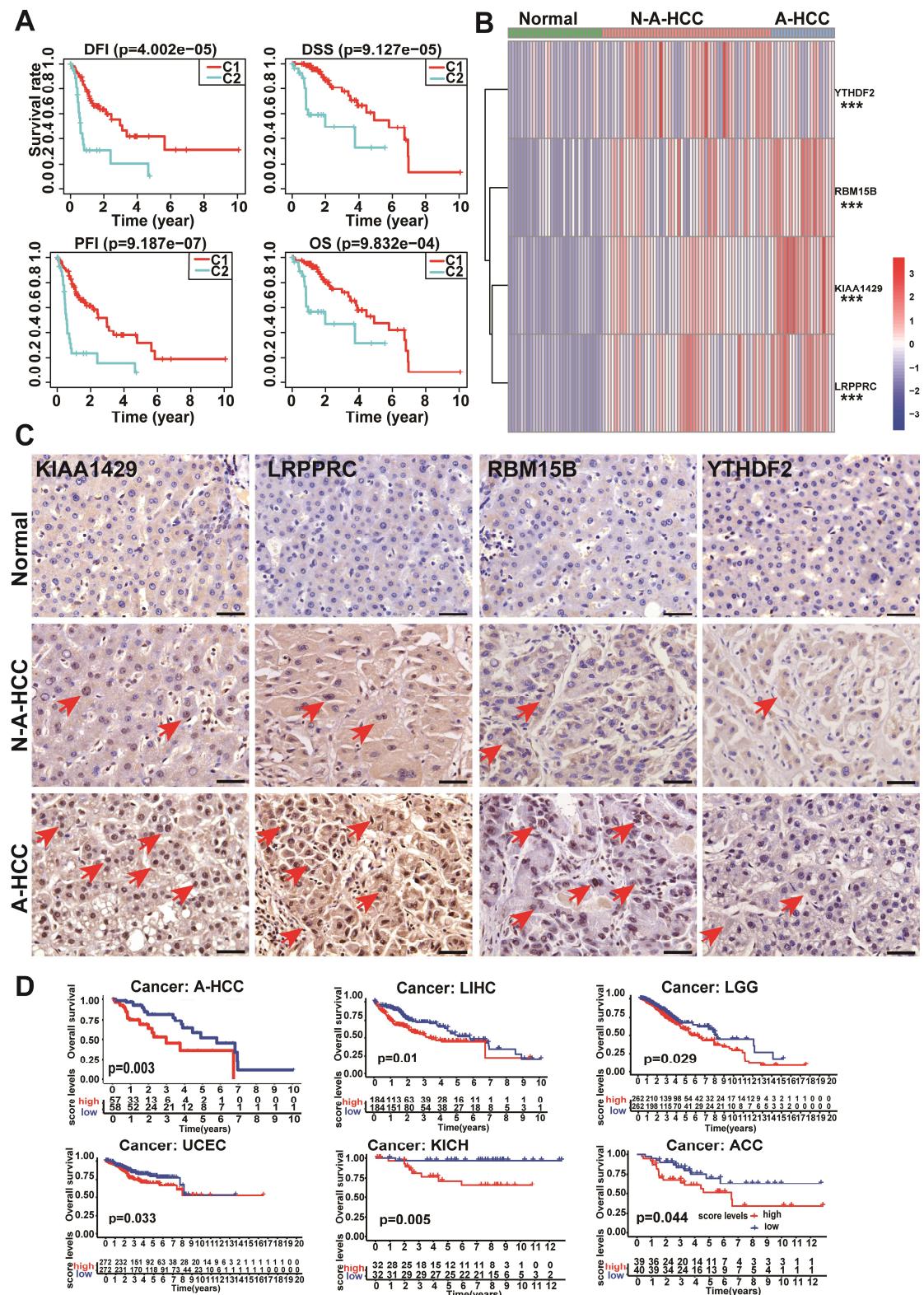


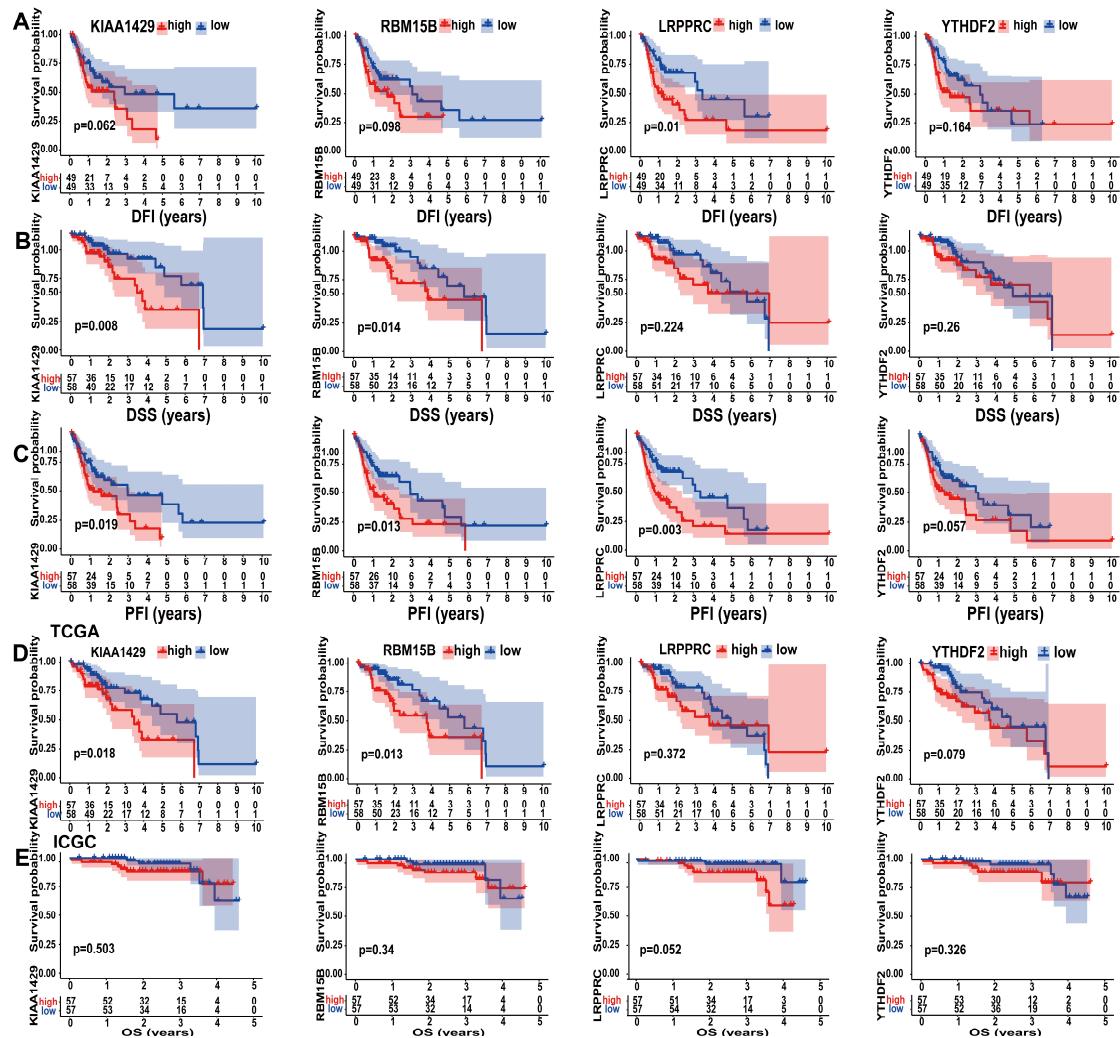
## Supplementary Material



### **Figure S1. External applicability of the m6A model**

(A) Figure 3G different survival intervals (DFI/DSS/PFI/OS) of patients in two clusters.

(B-C) The qRT-PCR expression (B) and immunohistochemical staining(C) of KIAA1429/LRPPRC/RBM15B/YTHDF2 in clinical patients of three groups was observed: Normal (n = 31), N-A-HCC (no history of alcohol consumption n = 56), and A-HCC (n = 21).  
(D) The m6A model was predictive of multiple tumour survival: A-HCC ( $P=0.003$ ). Liver hepatocellular carcinoma (LIHC,  $P=0.01$ ), Lower Grade Glioma (LGG,  $P=0.029$ ), Uterine Corpus Endometrial Carcinoma (UCEC,  $P=0.033$ ) KIDNEY Chromophobe (KICH,  $P=0.005$ ) and Arenal cortical Carcinoma (ACC,  $P=0.044$ ).



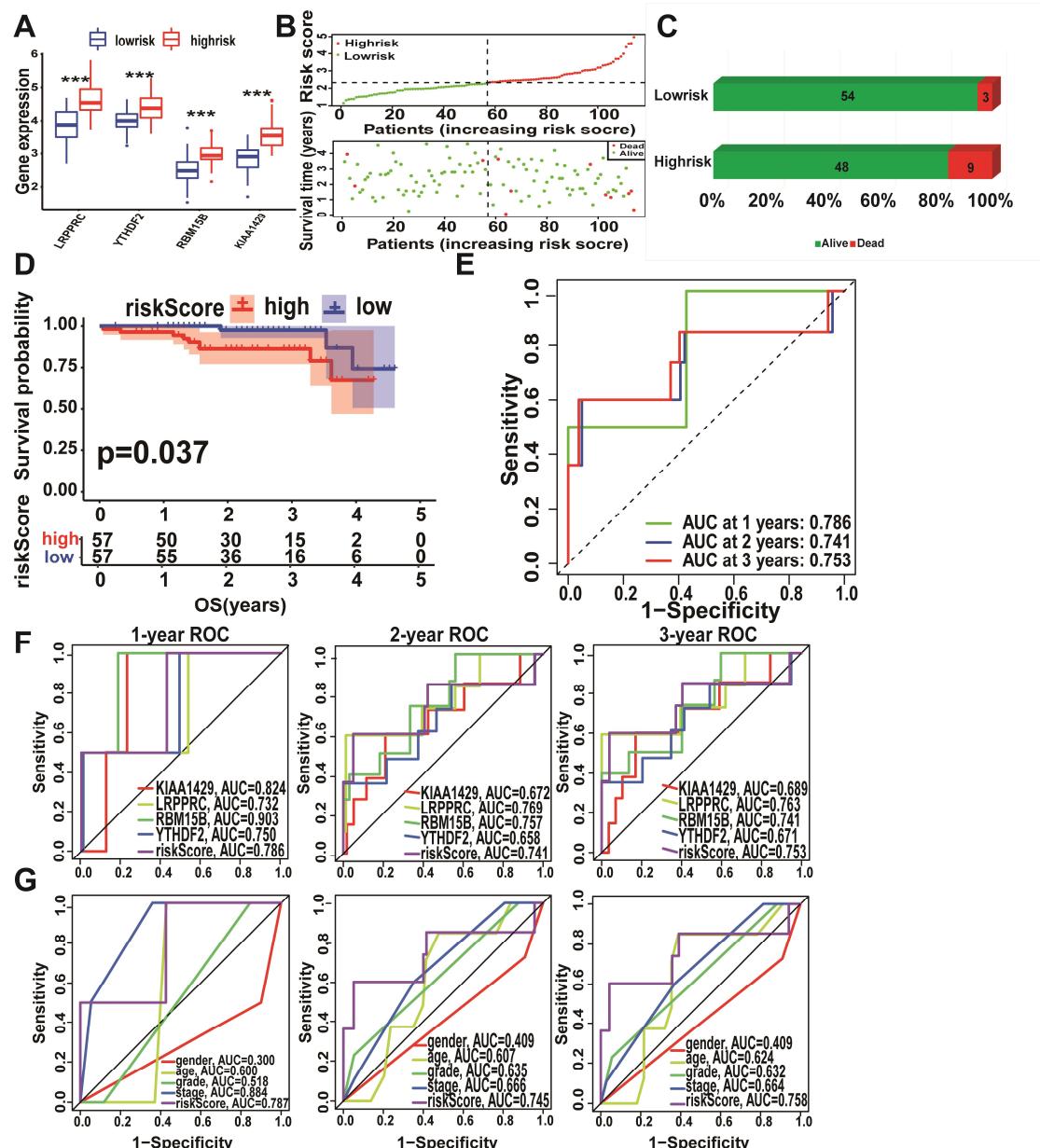
**Figure S2. Kaplan–Meier analysis of different survival times in the TCGA-A-HCC cohort**

(A) Different factors (*KIAA1429*, *LRPPRC*, *RBM15B*, and *YTHDF2*) of Kaplan–Meier analysis for disease-free interval (DFI);

(B) Different factors (*KIAA1429*, *LRPPRC*, *RBM15B*, and *YTHDF2*) of Kaplan–Meier analysis for disease-specific survival (DSS);

(C) Different factors (*KIAA1429*, *LRPPRC*, *RBM15B*, and *YTHDF2*) of Kaplan–Meier analysis for progression-free survival (PFI);

(D/E) Different factors (*KIAA1429*, *LRPPRC*, *RBM15B*, and *YTHDF2*) of Kaplan–Meier analysis for overall survival (OS) in TCGA (D)/ICGC (E) databases.



**Figure S3. Performance of the m6A-risk model in predicting A-HCC patient survival in ICGC databases.**

(A) Boxplots showing four m6A-related gene expression profiles in high-risk and low-risk subtypes.

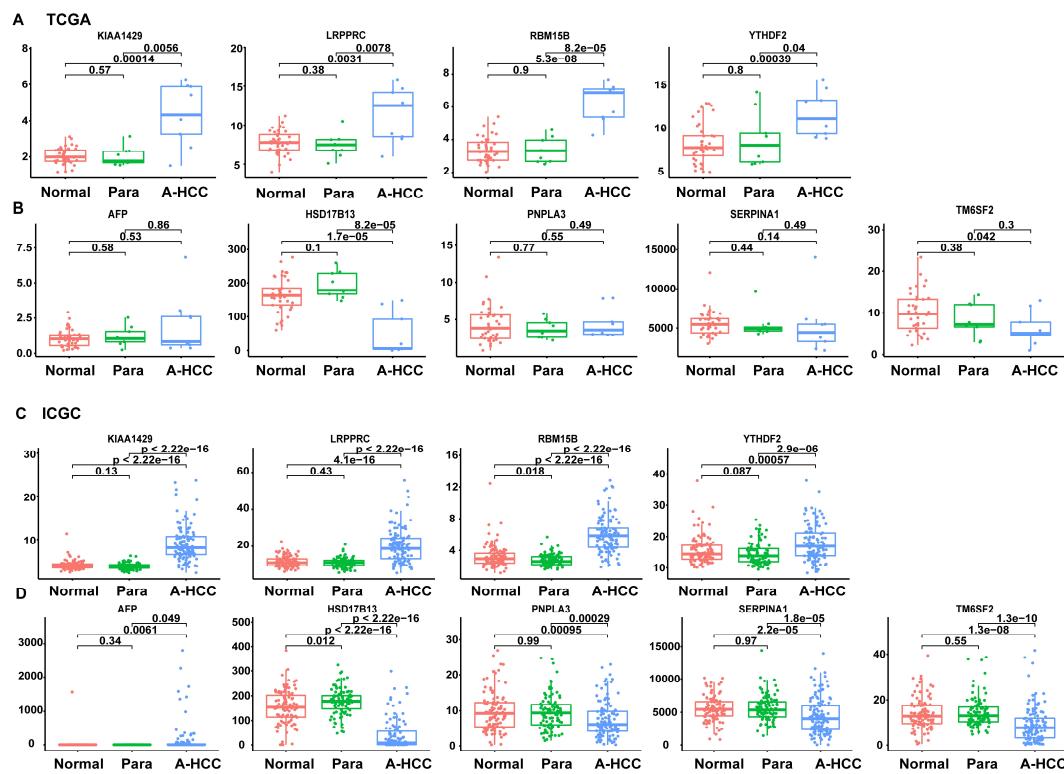
(B) Patient status distribution in the high-risk and low-risk subtypes.

(C) Mortality rates of the high-risk and low-risk subtypes.

(D) Overall survival curves for A-HCC patients.

(E-G) ROC curves of TCGA cohort: ROC curves showing the predictive accuracy of model

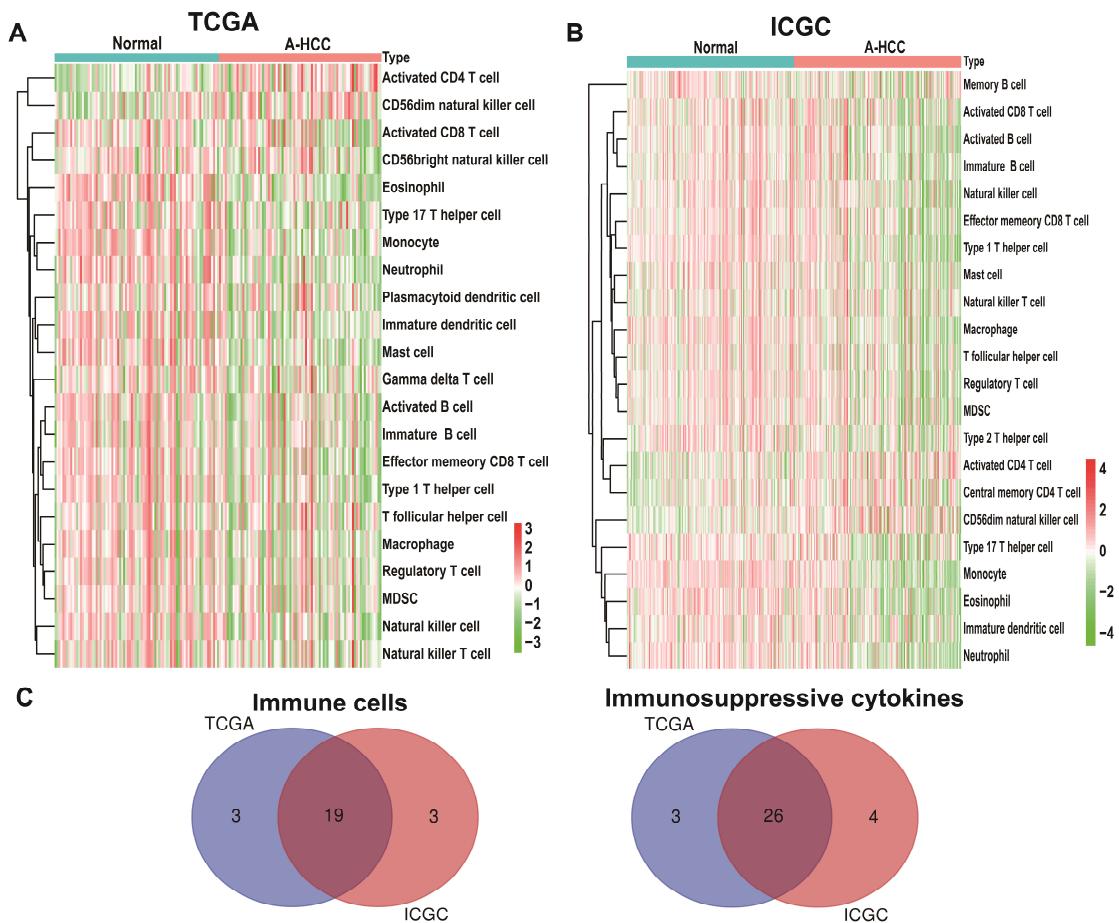
(E)/model-related genes (F)/different clinical characteristics and time (1/2/3 year) (G).



**Figure S4. Difference among normal individuals and paracarcinoma (para) and A-HCC patients**

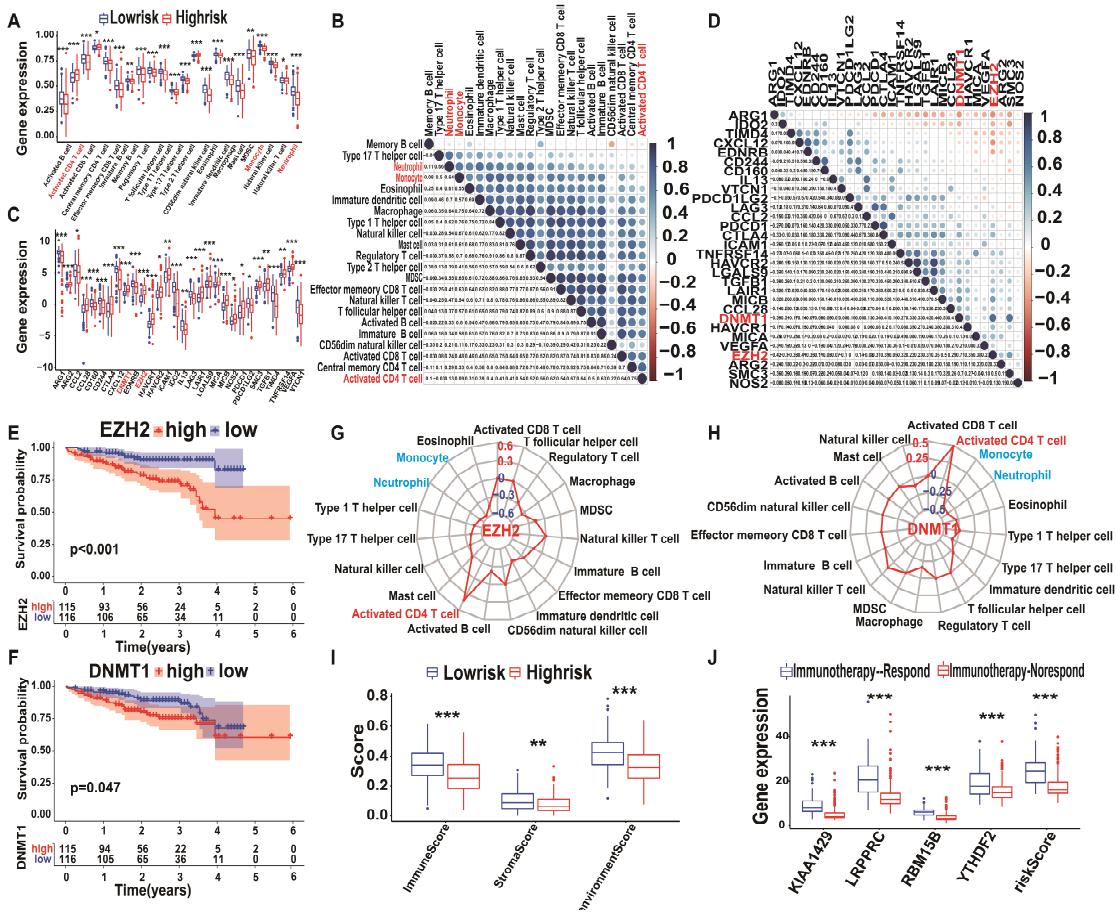
(A-B) Boxplots showing difference of model-related genes (A)/validated predictors (B) in TCGA databases.

(C-D) Boxplots showing difference of model-related genes (C)/validated predictors (D) in ICGC databases.



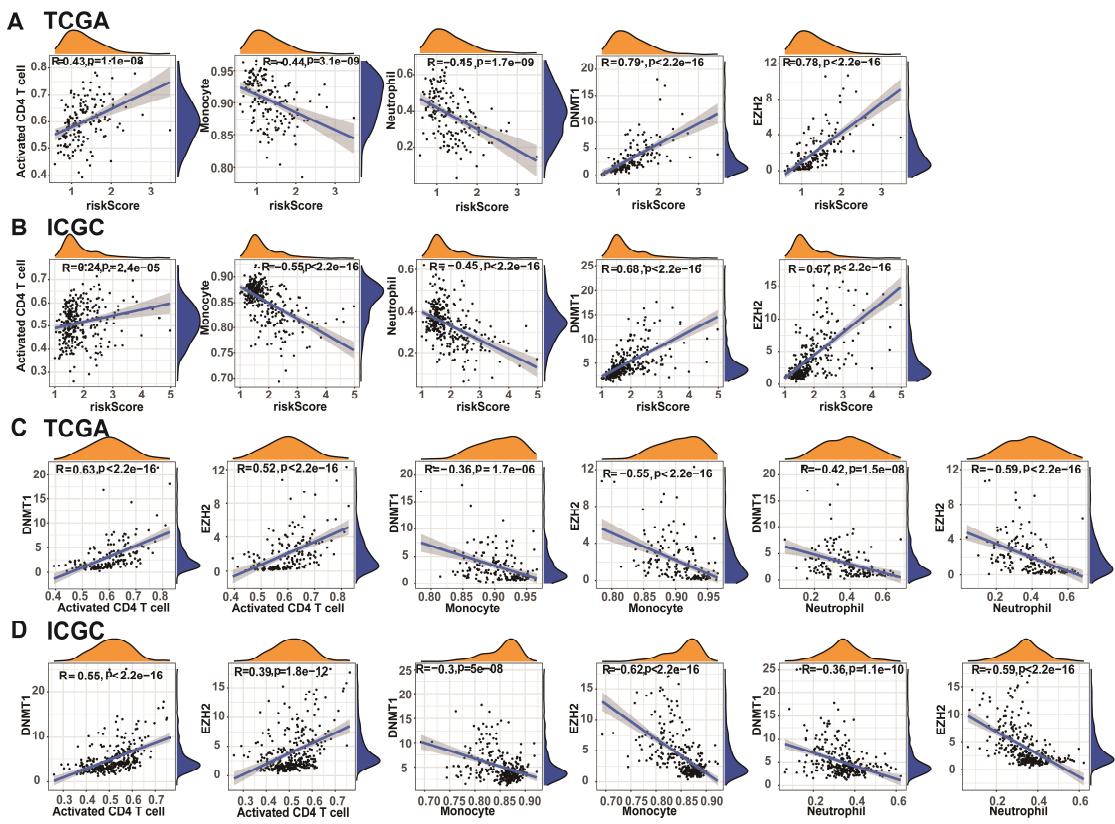
**Figure S5. Immune microenvironment prediction**

- (A) Relative proportion of immune cell infiltration in all TCGA-A-HCC patients.
- (B) Relative proportion of immune cell infiltration in all ICGC-A-HCC patients.
- (C) Venn diagram of overlapping immune cells and immunosuppressive cytokines between TCGA and ICGC databases.



**Figure S6. Immune landscape and immunotherapy prediction between low and high m6A-risk A-HCC patients in ICGC databases.**

- (A) Boxplot visualizing the difference of immune cell infiltration among different risk subtypes from ICGC-A-HCC. \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .
- (B) Correlation analysis of immune cells from ICGC-A-HCC.
- (C) Boxplot visualizing the different expression of immunosuppressive cytokines among different risk subtypes from ICGC-A-LIHC. \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .
- (D) Correlation analysis of immunosuppressive cytokines from ICGC-A-HCC.
- (E-F) Kaplan–Meier analysis of DNMT1 (E) and EZH2 (F) for OS between different risk subtypes.
- (G-H) Radar map showing relationship between immune cells and DNMT1 (G)/EZH2 (H).
- (I) Boxplot of the relationship between ImmuneScore StromaScore ImmuneScore/StromaScore-MicroenvironmentScore.
- (J) Boxplot showing risk scores and four hub genes (KIAA1429, LRPPRC, RBM15B, and YTHDF2) between the immunotherapy non-response and immunotherapy response groups.



**Figure S7. Correlation between risk scores, immune cells, and immunosuppressive cytokines**

(A-B) Diagram showing the correlation between risk scores and activated CD4+ T cell/monocyte/neutrophil/DNMT1/EZH2 (from left to right) in TCGA (A) and ICGC (B) databases.

(C-D) Diagram showing the correlation between immune cells (Activated CD4+ T cell/monocyte/neutrophil) and immunosuppressive cytokines (DNMT1/EZH2) in TCGA (C) and ICGC (D) databases.



**Figure S8. Prediction of drug sensitivity for A-HCC patients**

**Table 1 Clinicopathological factors and the number of patients for two types of hepatocellular carcinoma, and normal subjects involved in this study**

Characteristic	Category	N-A-HCC	A-HCC	Normal
		Total	Number of subjects	Number of subjects
Gender	Female	21	7	12
	Male	35	14	19
Age(years)	<65	26	9	23
	≥65	30	12	8
Stage	I	23	5	
	II	15	7	
	III	18	9	
Grade	1	16	2	
	2	8	5	
	3	13	6	
	4	19	8	
Status	Alive	52	18	31
	Dead	4	3	0

**Table 2 Primers included in the RT-qPCR assay.**

Primer	5'→3' Sequence
Dnmt1-F	AGGCGGCTAAAGATTGGAA
Dnmt1-R	GCAGAAATTCTGTCAAGAGATTC
EZH2-F	TGCAGTTGCTTCAGTACCCATAAT
EZH2-R	ATCCCCGTGTACTTCCCATCATAAT
KIAA1429-F	CTTGGCAAGTGGCTTGAACC
KIAA1429-R	ACGTAAGGCAGTGGTAAGGC
LRPPRC-F	AGCCTGCTCCTGTGAGAAAG
LRPPRC-R	TCCCAGATCTTGTGAGCAAA
RBM15B-F	GAGAACCACTCCAGTGAAGGG
RBM15B-R	GCTGACTGGAGGTACTGCTG
YTHDF2-F	TAGCCAAC TGCGACACATTG
YTHDF2-R	CACGACCTTGACGTTCCCTT
GAPDH-F	CCCACTCCTCCACCTTGAC
GAPDH-R	TCCTCTTGCTCTTGCTGG

**Table 3 Characters of ALD-HCC patients in TCGA**

Characteristic	Category	Number of patients
Gender	Female	14
	Male	103
Age(years)	<65	64
	≥65	53
Stage	I	55
	II	21
	III	31
Grade	1	18
	2	58
	3	39
	4	2
Status	Alive	79
	Dead	38
	Mild	20
Adjacent tissue inflammation	Severe	5
	Other	92
	0-2	27
Fibrosis	3-4	9
	5-6	16
	Other	65

**Table 4 Characters of ALD-HCC patients in ICGA**

Characteristic	Category	Number of patients
Gender	Female	13
	Male	101
Age(years)	<65	47
	≥65	67
Grade	I	16
	II	83
	III	12
Stage	1	20
	2	50
	3	36
Status	4	8
	Alive	102
	Dead	12
fibrosis	0-2	52
	3-4	62
Tumor venous Infiltration	Yes	34
	No	77

**Table 5 UnivariateCox Analysis**

gene	HR	z	pvalue
YTHDF2	4.528899	3.333443	0.000858
KIAA1429	2.865334	2.913846	0.00357
YTHDF1	3.147081	2.719835	0.006531
RBM15B	2.61164	2.599653	0.009332
LRPPRC	2.296597	2.488739	0.01282
RBM15	2.598275	2.410586	0.015927
YTHDF3	1.935591	2.105286	0.035266
HNRNPC	1.789915	1.745728	0.080858
WTAP	1.528766	1.308472	0.190713
IGF2BP1	1.21253	1.269264	0.204347
METTL3	1.475177	1.185321	0.235891
HNRNPA2B1	1.335914	0.952523	0.340832
YTHDC1	1.361391	0.840087	0.400859
ELAVL1	1.397328	0.821852	0.411161
ALKBH5	0.793244	-0.76873	0.442053
CBLL1	1.233887	0.675424	0.499406
FTO	0.78936	-0.5728	0.566777
ZC3H13	0.880681	-0.54288	0.587214
METTL14	1.171621	0.410549	0.681403
YTHDC2	0.936664	-0.19145	0.848171
FMR1	1.005043	0.021778	0.982625

**Table 6 Clinical survival in both subtypes(C1/C2)**

Type	C1					C2				
DFI	Time (y)	Paients (n)	Survival	SE	95% CI	Paients (n)	Survival	SE	95% CI	
DFI	1	50	0.774	0.0515	0.679-0.882	8	0.308	0.095	0.1685-0.564	
	3	12	0.509	0.0837	0.368-0.702	3	0.206	0.1051	0.0754-0.56	
	5	10	0.416	0.0905	0.272-0.637	2	0.103	0.0897	0.0186-0.569	
DSS	1	79	0.987	0.0126	0.963-1	15	0.591	0.1001	0.424-0.824	
	3	24	0.777	0.0663	0.6569- 0.918	6	0.493	0.1227	0.302-0.803	
	5	10	0.548	0.1014	0.3815- 0.788	3	0.328	0.1571	0.129-0.839	
PFI	1	59	0.764	0.0474	0.677-0.863	7	0.2352	0.0837	0.1172-0.472	
	3	14	0.451	0.0769	0.3225- 0.629	3	0.1568	0.0849	0.0543-0.453	
	5	6	0.318	0.0878	0.1848- 0.546	2	0.0784	0.0698	0.0137-0.449	
OS	1	79	0.9519	0.0235	0.9071- 0.999	15	0.568	0.0988	0.404-0.798	
	3	24	0.7181	0.0666	0.5987- 0.861	6	0.473	0.1193	0.288-0.776	
	5	10	0.4787	0.0943	0.3254- 0.704	3	0.315	0.1513	0.123-0.808	

**Table 7 GSEA analysis**

NAME	TCGA				ICGC		
	SIZE	ES	NES	NOM p-val	SIZE	ES	NES
G2M_CHECKPOINT	195	0.773925	1.872758	<0.001	190	0.722994	2.002184
PI3K_AKT_MTOR_SIGNALING	105	0.654883	1.894131	<0.001	104	0.536363	1.941547
PROTEIN_SECRETION	96	0.70774	1.958296	<0.001	95	0.641883	2.105106
UNFOLDED_PROTEIN_RESPONSE	110	0.646417	1.91497	<0.001	106	0.584688	1.963052
MYC_TARGETS_V1	196	0.711536	1.799156	0.001996	193	0.722594	1.949364
E2F_TARGETS	198	0.752525	1.788301	0.003976	194	0.756297	2.03516
MTORC1_SIGNALING	196	0.590905	1.851324	0.004016	194	0.601345	2.022227
DNA_REPAIR	149	0.625902	1.837142	<0.001	141	0.562544	1.937359
MITOTIC_SPINDLE	198	0.762504	1.998572	<0.001	197	0.576724	1.898549
ANDROGEN_RESPONSE	98	0.511055	1.651018	0.00616	96	0.446966	1.724436
HEME_METABOLISM	193	0.533672	1.821891	<0.001	191	0.373494	1.591133
GLYCOLYSIS	197	0.507472	1.772849	0.002092	197	0.443539	1.760442
SPERMATOGENESIS	133	0.522367	1.701034	0.004132	131	0.44227	1.576259
UV_RESPONSE_UP	156	0.497127	1.693498	0.002045	152	0.352935	1.485076
WNT_BETA_CATENIN_SIGNALING	42	0.684786	1.79914	<0.001	42	0.46991	1.579675

**Table 8 Relationship between DNMT1/EZH2 and immune cells in TCGA/ICGC database**

Immune Cell	EZH2		DNMT1	
	ICGC	TCGA	ICGC	TCGA
Activated CD4 T cell	0.41	0.49	0.49	0.56
Monocyte	-0.56	-0.45	-0.35	-0.39
Neutrophil	-0.52	-0.44	-0.38	-0.36
Activated CD8 T cell	0	-0.17	0	0
Eosinophil	-0.44	-0.51	-0.29	-0.33
Type 1 T helper cell	-0.46	-0.42	-0.25	-0.18
Type 17 T helper cell	-0.41	-0.31	-0.33	-0.2
Natural killer cell	-0.35	-0.35	-0.11	0
Mast cell	-0.26	-0.48	0	-0.31
Activated B cell	-0.22	-0.25	0	0
CD56dim natural killer cell	0	0.22	0	0.27
Immature dendritic cell	-0.34	-0.38	-0.21	-0.17
Effector memory CD8 T cell	-0.24	-0.35	0	0
Immature B cell	-0.17	-0.22	0	0
Natural killer T cell	0	-0.2	0.12	0
MDSC	-0.17	-0.18	0	0
Macrophage	-0.36	-0.24	-0.16	0
Regulatory T cell	-0.27	-0.22	0	0
T follicular helper cell	0	0	0	0

**Table 9 m6A regulatory gene and associated pathway**

Gene_Na me	Locus	Trans_Type	p_value	Pathway
ABCA3	chr16:23258 82-2390736	protein_coding	0.02551 92	Regulation of activated PAK- 2p34 by proteasome mediated degradation;Metabolism of proteins;Surfactant metabolism; Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds
	chr16:23258 82-2390747	protein_coding	0.01005 88	
	chr16:23733 40-2379725	protein_coding	0.49683 46	
ACTA2	chr10:90694 831- 90712530	protein_coding	0.67518 24	Actin Nucleation by ARP- WASP Complex;PAK Pathway;VEGF Pathway; fMLP
	chr10:90701 542- 90751096	protein_coding	0.00146 77	Pathway;Sertoli-Sertoli Cell Junction Dynamics

	chr10:90701		0.02246	
	542-	protein_coding	29	
	90751045			
	chr19:42470		0.04956	
	734-	protein_coding	27	
	42498428			
	chr19:42470		0.00408	Cardiac conduction;Aldosterone synthesis and secretion;cGMP-PKG signaling pathway;Salivary secretion;Aldosterone-regulated
	773-	protein_coding	96	
ATP1A3	42497619			
	chr19:42470		0.44222	sodium reabsorption
	736-	protein_coding	72	
	42498412			
	chr19:42470		0.55168	
	736-	protein_coding	58	
	42498231			
	chr5:409093		0.00445	Immune response Lectin induced complement
	54-40983041		36	
C7	chr5:409364	processed_transcript	0.49551	pathway;Complement Pathway; Complement and coagulation cascades; Creation of C4 and C2 activators;Innate Immune System
	40-40937589		84	
CEND1	chr11:78710		0.00135	DNA Damage;Neuroscience
	4-790123	protein_coding	29	
	chr19:82742		0.03338	
	37-8327305	protein_coding	34	
	chr19:82741		0.03951	
	97-8327305	protein_coding	57	
	chr19:82899		0.55542	
	11-8321559	protein_coding	78	
	chr19:82742		0.71507	Sphingolipid
	55-8327305	protein_coding	72	metabolism;Metabolism;Sphing
CERS4	chr19:82742		0.20698	olipid signaling pathway
	40-8327305	protein_coding	62	
	chr19:82745		0.56448	
	18-8316055	protein_coding	67	
	chr19:82742		0.99288	
	10-8320608	protein_coding	41	
	chr19:82742	processed_transcript	0.44080	
	67-8327305		55	
COL13A1	chr10:71561		0.00115	Collagen chain
	688-	protein_coding	21	trimerization;Integrin
	71718904			Pathway;ERK Signaling;

	chr10:71561				Degradation of the extracellular matrix;Phospholipase-C Pathway
	688-71718904	protein_coding	0.0336758		
	chr10:71561				
	874-71718489	protein_coding	0.6720126		
	chr10:71690				
	209-71718683	protein_coding	0.4893448		
	chr10:71637				
	052-71639183	processed_transcript	0.1142819		
	chr10:71703				
	881-71724031	processed_transcript	0.4189301		
	chr10:71562				
	180-71718457	protein_coding	0.5290397		
	chr10:71561				
	874-71718489	protein_coding	0.7242527		
	chr11:76863				
	31-7694732	protein_coding	0.0227442		
	chr11:76904				
	36-7698453	protein_coding	0.8202211		
	chr11:76863				
	31-7694703	protein_coding	0.2063338	O2/CO2 exchange in erythrocytes;Amino sugar and nucleotide sugar	
	chr11:76897				
CYB5R2	43-7695449	protein_coding	0.7598926	nucleotide sugar metabolism;PAK Pathway;	
	chr11:76863				
	35-7690548	processed_transcript	0.5220367	Metabolism;Cytochrome P450 - arranged by substrate type	
	chr11:76863				
	35-7695439	protein_coding	0.3905512		
	chr11:76863				
	65-7688991	processed_transcript	0.0006005		
	chr2:716938				
	32-71913778	protein_coding	0.164561		
	chr2:716938				
DYSF	32-71913778	protein_coding	0.5256073	Cardiac conduction;Smooth Muscle Contraction	
	chr2:716808				
	52-71913778	protein_coding	0.4226497		
	chr2:716938				
	32-71913778	protein_coding	0.177521		

	chr2:716938	protein_coding	0.16410	
	32-71913778		3	
	chr2:716808	protein_coding	0.42264	
	52-71913778		97	
	chr2:716938	protein_coding	0.04173	
	32-71913778		04	
	chr2:716938	protein_coding	0.26152	
	32-71913778		3	
	chr2:716808	protein_coding	0.42264	
	52-71913778		97	
	chr2:716808	protein_coding	0.42264	
	52-71913778		97	
	chr2:718040	processed_trans	0.00236	
	29-71913893	cript	87	
	chr4:110970			Fatty Acyl-CoA
	543-	protein_coding	0.02468	
	111119832		44	Biosynthesis;Metabolism;alpha-
ELOVL6	chr4:110967			linolenic (omega3) and linoleic
	002-	protein_coding	0.05650	(omega6) acid metabolism;
	111119809		42	Regulation of cholesterol
	chr4:111119	processed_trans	0.70845	biosynthesis by SREBP
	047-	cript	27	(SREBF);Regulation of lipid
	111119522			metabolism by Peroxisome
	chr7:139326	protein_coding	0.00223	proliferator-activated receptor
	55-14029301		37	alpha (PPARAlpha)
	chr7:139340	protein_coding	0.12480	
	06-14029572		61	Transcriptional misregulation in
ETV1	chr7:139308	protein_coding	0.73473	cancer; MAPK Erk
	53-14029571		11	Pathway;P38 MAPK Signaling
	chr7:140277	protein_coding	0.21277	Pathway (sino); Akt
	84-14029291		08	Signaling;Development_TGF-
	chr7:140144	processed_trans	0.03533	beta receptor signaling
	89-14029264	cript	55	
	chr1:251823	protein_coding	0.01508	
	7-2522902		95	
	chr1:251821	protein_coding	0.55011	
FAM213	4-2522907		58	Metabolism; Arachidonic acid
B	chr1:251827	protein_coding	0.22331	metabolism;Linoleic acid
	2-2520416		06	metabolism
	chr1:251848	processed_trans	0.39287	
	1-2520952	cript	2	

	chr1:240255				
	180-	protein_coding	0.30059		
	240638489		04		
	chr1:240408				
FMN2	560-	protein_coding	0.93234	Cellular response to DNA	
	240492692		89	damage stimulus;Wnt-	
	chr1:240492			Associated β-Catenin pathway	
	444-	protein_coding	0.00494		
	240638483		31		
	chr17:73717				
	516-	protein_coding	0.64850		
	73753899		75		
	chr17:73720				
	776-	protein_coding	0.02246	Apoptotic Pathways in Synovial	
	73753899		85	Fibroblasts;ERK	
	chr17:73717			Signaling;Integrin	
ITGB4	408-	protein_coding	0.77899	Pathway;Focal Adhesion;Actin	
	73753685		32	Nucleation by ARP-WASP	
	chr17:73720			Complex	
	784-	processed_transcript	0.00244		
	73738738		8		
	chr17:73750				
	699-	protein_coding	0.19058		
	73753083		88		
	chr2:261494				
	65-26205366	protein_coding	0.00814	Golgi-to-ER retrograde	
	chr2:261516		29	transport;Organelle biogenesis	
	22-26205618	protein_coding	0.62480	and maintenance;Vesicle-	
KIF3C			69	mediated transport;Class I MHC	
				mediated antigen processing and	
	chr2:261522	processed_transcript	0.84653	presentation;Factors involved in	
	88-26174788		47	megakaryocyte development and	
				platelet production	
				Defective B4GALT1 causes	
	chr12:91496			B4GALT1-CDG (CDG-	
LUM	406-	protein_coding	0.00469	2d);Keratan sulfate/keratin	
	91505608		83	metabolism;3	
				Glycosaminoglycan metabolism;	
				Proteoglycans in cancer;HIV	
				Life Cycle	
MAGED	chrX:516366				
	98-51645453	protein_coding	0.37550	p75 NTR receptor-mediated	
1	chrX:516367		72	signalling;Development HGF	
	35-51645450	protein_coding	0.02533	signaling pathway;Apoptotic	
			06		

	chrX:516366	protein_coding	0.06080	execution phase;CASP8 activity
	29-51645450		61	is inhibited;Signaling by GPCR
	chrX:515461	protein_coding	0.00509	
	03-51645450		74	
	chrX:516367	processed_trans	0.41509	
	42-51638848	cript	08	
	chrX:516376	processed_trans	0.74103	
	65-51638798	cript	87	
	chrX:516387	processed_trans	0.04201	
	52-51639570	cript	94	
	chrX:516367	processed_trans	0.98552	
	54-51645448	cript	95	
	chrX:516367	processed_trans	0.02028	
	45-51645450	cript	18	
	chr15:89441			
	945-	protein_coding	0.27023	
	89456642		48	
	chr15:89441			
	944-	protein_coding	0.62703	
	89456612		74	
	chr15:89442			
	546-	protein_coding	0.22527	
	89456610			
MFGE8	chr15:89444			
	782-	protein_coding	0.28661	Activated PKN1 stimulates
	89456593		73	transcription of AR (androgen
	chr15:89448			receptor) regulated genes KLK2
	630-	processed_trans	0.21549	and KLK3; Metabolism of
	89456610	cript	45	proteins; Extracellular vesicle-
	chr15:89447			mediated signaling in recipient
	021-	processed_trans	0.04067	cells;Integrins in angiogenesis
	89448159	cript	88	
	chr15:89441			
	946-	protein_coding	0.00780	
	89456612		43	
	chr15:89445			
	414-	processed_trans	0.26111	Innate Immune
	89447877	cript	09	System;Phagosome;PPAR
	chr12:10310			signaling pathway;Cell surface
	900-	protein_coding	0.01202	interactions at the vascular
	10324737		61	wall;Response to elevated
OLR1	chr12:10313			platelet cytosolic Ca2+
	477-	protein_coding	0.26043	
	10322986		33	

	chr22:35936 915- 35950048	protein_coding	0.03155 4	cAMP/PKA-dependent signaling pathway;Mtor1 pathway
	chr2:220299 568- 220358354	protein_coding	0.00650 73	
	chr2:220306 767- 220331582	protein_coding	0.02972 17	
	chr2:220306 745- 220313237	protein_coding	0.49543 99	Muscle organ development;Negative
SPEG	chr2:220310 349- 220358315	processed_trans cript	0.00119 73	regulation of cell proliferation
	chr2:220310 302- 220313177	processed_trans cript	0.48433 69	
	chr2:220301 997- 220331583	processed_trans cript	0.01559 58	
	chr3:186648 274- 186796341	protein_coding	0.04778 2	Synthesis of substrates in N- glycan biosynthesis;Transport to the Golgi and subsequent modification;Metabolism of proteins;N-glycan antennae elongation in the medial/trans-
ST6GAL 1	chr3:186648 315- 186796341	protein_coding	0.19230 71	Golgi;O-linked glycosylation