

# Bioinformatics Analysis and Insights for the Role of COMMD7 in Hepatocellular Carcinoma

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## Research article

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# Abstract

**Background:** The tumorigenesis and development of hepatocellular carcinoma (HCC) is a process involving multiple factors. The COMMDs family proteins were reported to play important roles in various disease and cancers including HCC. We previously found COMMD7 acted as a HCC-promotion factor; however, further understanding on COMMD7 was needed. We conducted these bioinformatics analysis for the purpose of comprehensive understanding of the functional role of COMMD7 in HCC.

**Methods:** The bioinformatics analysis of COMMD7 were launched by online platforms including KEGG, GEPIA, cBioportal, Gene Ontology and The Kaplan-Meier plotter. Data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) were downloaded, and the data analysis and processing were conducted by RStudio (version 1.3.959) software.

**Results:** The expression profile results of COMMD7 in TCGA and GTEx database suggested that COMMD7 expressed highly in liver tumor tissues and positively related with poorer prognosis ( $p < 0.01$ ); COMMD7 also contributed to the early development of HCC as its higher expression resulted in progression from stage I to stage III ( $p < 0.01$ ). Based on our previous studies, COMMD7 may target NF- $\kappa$ B signaling and CXCL10 to enhance the proliferation of hepatoma cells so that promoting the development of HCC.

**Conclusions:** This study updates the current studies about the newly recognized roles of COMMD7 in the progression of HCC, summarizing the research progress and prospects of COMMD7 comprehensively, offering an outlook for the future investigation and targeted therapy of HCC.

## Background

Chronic liver disease and primary liver cancer are a massive global problem, as the most prevalent form of primary liver cancer, hepatocellular carcinoma is a global pandemic with a significant increase in morbidity and mortality worldwide[1]. Recent epidemiology statistical data confirms that HCC represents the fourth leading cause of cancer-related death and ranks sixth in terms of new cases worldwide[2]. With a poor 5-year survival, liver cancer is the second most lethal tumor after pancreatic cancer[3]. The tumorigenesis and development of HCC is a complex process involving multiple genes and factors[4] (Fig. 1). It has been reported that the mutation of p53[5], AKT/ $\beta$ -catenin[6], HFE[7], TSC1/2[8] and MBL[9] genes were frequently occurred in aggressive HCC. Meanwhile, the activation of these genes such as mTOR, PI3K, MAP kinase, STAT3, JAK were proved to be related with the progression of HCC[10–13]. Recently, metabolism reprogramming is also confirmed to behave distinctly in different periods of HCC[14–16].

The Copper Metabolism MURR1 Domain-containing (COMMD) family consists of ten members ranging from COMMD1 to COMMD10, which is characterized by a highly conservative COMM domain at the carboxyl terminal[17]. The COMMDs family members have been frequently reported to involve in human disease and cancers (Table 1). For example, the most researched COMMD1 induces apoptosis in human

lung cancer cells by inhibition of NF- $\kappa$ B signaling[18, 19].COMMD1 disrupts HIF-1 $\alpha$ / $\beta$  dimerization and inhibits human tumor cell invasion[20], and downregulation of COMMD1 promotes tumor development by modulating a positive feedback loop that amplifies inflammatory and stemness-associated properties of cancer cells. COMMD3/8 complex selectively recruited GRK6 and induced GRK6-mediated phosphorylation of the receptor and activation of  $\beta$ -arrestin-mediated signaling thus regulates immune response[21]. COMMD4 was defined as an anti-cancer therapeutic target and prognostic factor in non-small cell lung cancer[22]. COMMD5 acts as an adaptor protein to coordinate endosomal trafficking and plays an important role inEGFR transporting and activity in renal cell carcinoma[23]. COMMD6 may modulate the ubiquitination and degradation of NF- $\kappa$ B subunits and regulate ribonucleoprotein and spliceosome complex biogenesis in tumors[24]. COMMD9 participates in TFDP1/E2F1 activation and plays a critical role in non-small cell lung cancer[25]. COMMD10 may play a tumor suppressive role in renal clear cell carcinoma through the miR-590-3p-COMMD10-Cul2-RBX1-NF- $\kappa$ B/HIF/NRF2 pathway and regulate the chemotherapy resistance of various tumor cells to cisplatin[26, 27].In addition, the COMMDs family proteins also regulates plasma LDL Levels and attenuates atherosclerosis through forming COMMD/CCDC22/CCDC93 to stabilize the CCC complex in endosomal LDLR trafficking[28].

Table 1  
Studies about COMMDs family proteins in different cancers and diseases

COMMD proteins	Study	Cancer and disease type	Regulated factors or pathway	Findings
COMMD1	Masso JR et al., 2013 [18]	Lung cancer	NF- $\kappa$ B pathway	COMMD1 inhibited NF- $\kappa$ B activity and decreased the activation of antiapoptotic genes
	Burstein et al., 2010 [20]	Pancreatic cancer, ovarian cancer, breast cancer	HIF-1 $\alpha$	COMMD1 prevented the dimerization of HIF-1 $\alpha$ and HIF-1 $\beta$ and subsequent DNA binding and transcriptional activation
COMMD3/8	Suzuki et al., 2019 [21]	Humoral immune responses	$\beta$ -arrestin-mediated signaling	COMMD3/8 complex selectively recruited GRK6 and induced GRK6-mediated phosphorylation of the receptor and activation of $\beta$ -arrestin-mediated signaling
COMMD4	Suraweera et al., 2020 [22]	Non-small cell lung cancer (NSCLC)	Not mentioned	COMMD4 expressed higher in NSCLC and promoted cell proliferation
COMMD5	Campion et al., 2018 [23]	Renal clear cell carcinoma (RCC)	EGFR	COMMD5 inhibited the growth of renal carcinoma cells by regulating EGFR trafficking
COMMD6	Yang et al., 2019 [24]	Liver cancer, lung cancer, etc.	NF- $\kappa$ B pathway	High expression of COMMD6 related with poor prognosis of tumors
COMMD7	Zheng et al., 2012 [38]	Hepatocellular carcinoma	NF- $\kappa$ B pathway	COMMD7 promoted the progression of HCC by negatively regulating NF- $\kappa$ B pathway
COMMD9	Zhan et al., 2017 [25]	NSCLC	TFDP1/E2F1	High expression of COMMD9 led to advanced NSCLC
COMMD10	Yang et al., 2017 [26]	RCC, Colorectal cancer	NF- $\kappa$ B pathway	COMMD10 inhibited the invasion and metastasis of colorectal cancer by promoting ubiquitination and degradation of NF- $\kappa$ B

As a key member of COMMDs family, COMMD7 consists of 200 amino acids and located on the 20th chromosome. Yet the bio-function of COMMD7 was rarely reported. Goodall et al, found that the SNP of COMMD7 may associated with platelet function of FC and PC[29]. While Bajuna Rashid Salehe confirmed the association of the SNP rs6141803 of COMMD7 with cardiovascular diseases (CVDs) by interfering platelet function[30]. Our preliminary research revealed that COMMD7 was highly expressed in hepatocellular carcinoma and might play as an oncogenic role in HCC, and it may promote HCC through activating NF- $\kappa$ B signaling by regulating the expression of chemokine CXCL10.

In this study, we firstly launched the expression profile data and bioinformatics analysis of COMMD7 in HCC, combining with recent studies, we summarized the functional role of COMMD7 comprehensively, providing an overview for the latest research advances of it, which may help to direct targeted therapy of HCC.

## Methods

### GEPIA2 (Gene Expression Profiling Interactive Analysis) dataset

GEPIA2 is an updated and enhanced version of GEPIA web server which features 198619 isoforms and 84 cancer subtypes based on tumor and normal samples from the TCGA and the GTEx databases, exhibiting a gene signature quantification by single-cell sequencing studies, and provides tools such as correlation analysis and survival analysis[31, 32].

### The Kaplan-Meier plotter

The prognostic value of COMMD7 mRNA expression was evaluated by an online database, Kaplan-Meier Plotter (<https://kmplot.com/>), which contains gene expression data and survival information of 364 clinical liver cancer patients ([https://kmplot.com/analysis/index.php?p=service&cancer=liver\\_rnaseq](https://kmplot.com/analysis/index.php?p=service&cancer=liver_rnaseq)) [33]. To analyze the overall survival (OS), progression-free survival (PFS), and recurrence-free survival (RFS) of patients with liver cancer. COMMD7 was loaded as the only gene symbol, patient samples were split into two groups (high expression vs. Low expression) and assessed by a Kaplan-Meier survival plot, with the hazard ratio (HR) with 95% confidence intervals (CI) and logrank p value.

### TCGA data and cBioPortal

The Cancer Genome Atlas (TCGA) contains both sequencing and pathological data on 30 different cancers[34]. The hepatocellular carcinoma (TCGA, firehose legacy) dataset including data from 373 cases with pathology reports was selected for further analysis of COMMD7 using cBioPortal (<http://www.cbioportal.org>). The genomic profiles included mutations, mRNA expression z-scores (RNA Seq V2 RSEM) and protein expression Z-scores. Co-expression and correlations among COMMD7 and other COMMDs family members were calculated according to the cBioPortal's online instruction.

### Statistical analysis

RStudio is a powerful data processing tool and is frequently applied in bioinformatics analysis[35]. The data from TCGA were processed and analyzed by RStudio, and heatmap drawing of COMMD7 with other COMMDs family members were conducted in R (version 4.0.0, R Development Core Team) within the RStudio platform (version 1.3.959).

### DAVID and Gene Ontology

We conducted Gene Ontology (GO) of significantly differentially expressed genes (SDEGs) after COMMD7 was knocked down using DAVID v6.8 online server (<https://david.ncifcrf.gov/conversion.jsp>), including molecular functions (MF), cellular components (CC), and biologic process (BP).

## Results

### Expression profile of COMMD7 in patients with HCC

In order to understand the expression profile of COMMD7 in liver cancer, we performed bioinformatics analysis of COMMD7. As shown in Fig. 2, according to the 369 liver cancer tissues and 160 normal tissues included in Gene Expression Profiling Interactive Analysis (GEPIA) dataset (<http://gepia2.cancer-pku.cn/>), the mRNA expression level of COMMD7 in liver cancer tissues is much higher, as the transcripts per million (TPM) in tumor tissues was nearly 1.5 times higher than in normal tissues ( $p < 0.01$ ; Fig. 2a). The protein relative expression level of COMMD7 in tumors and non-tumors was consistent with that of mRNA (Fig. 2b). Further, we detected the expression dynamic changes of COMMD7 during the development of HCC. The results showed that the expression of COMMD7 gradually increased from stage I to stage III ( $p < 0.01$ ), indicating that COMMD7 was closely related with the early progression of HCC (Fig. 2c).

Our team also clarified that COMMD7 was highly expressed in liver cancer tissue specimens. We verified the correlation of COMMD7 with early stage of HCC by detecting the mRNA expression level of COMMD7 in 68 pairs of liver cancer and adjacent tissues[36]. Subsequently, a self-prepared monoclonal antibody to COMMD7 was used to detect the protein level of COMMD7 in 7 liver cancer cell lines including HepG2, Huh7, Hep3B, HLE, HLF, SK-Hep-1 and PLC/PRF5. The results revealed that COMMD7 protein expressed totally higher in these hepatoma cells than in normal hepatocytes, especially in HepG2 and SK-Hep-1[36, 37]. For further study, we constructed a pGenesil-COMMD7-shRNA plasmid both in HepG2 and SK-Hep-1 cells by means of short-hairpin RNA targeted technology. As a result, silence of COMMD7 significantly reduced cell proliferation and colony formation, while increased apoptosis and led to cell cycle arrest at S-phase in both two cell lines[38].

### Association of increased mRNA of COMMD7 with poor prognosis of patients with HCC

We further explored the critical efficiency of COMMD7 in the survival of patients with HCC. Kaplan–Meier Plotter tools were used to analyze the correlation between the mRNA level of COMMD7 and the survival of 364 HCC patients in the database (<http://kmplot.com/analysis/index.php?p=service&cancer=liver>). The Kaplan–Meier curve and log-rank test analysis revealed that the increased mRNA level of COMMD7 was significantly associated with lower overall survival (OS) and recurrence-free survival (RFS) ( $p < 0.01$ ) (Fig. 3) in patients with HCC.

### Gene mutation and co-expression analysis of COMMD7 in HCC

We analyzed COMMD7 gene alterations, expression correlation of COMMDs family members, and co-expression genes of COMMD7 by using the cBioPortal online tool for hepatocellular carcinoma (TCGA, Firehose Legacy, <http://www.cbioportal.org/> ). AS a result, COMMD7 was altered in 41 samples out of 373 patients with HCC (11%) (Fig. 4a), and the altered group obtained better overall survival (median month overall survival 81.67 Vs 53.35, Fig. 4b and 4c). We also calculated the mRNA expression correlations of COMMD7 and other COMMDs family members with each other by Pearson's correction. The results indicated that most of the COMMDs family members were expressed positively with COMMD7, however the expression of COMMD2 and COMMD10 were negatively correlated with COMMD7 (Fig. 4d).

Co-expression gene analysis results signified that the top 10 genes such as DYNLRB1, PDRG1, MANBAL, PFDN4, RALY were positively related with COMMD7 in HCC patients ( $p < 0.01$ ), most of these genes were located on chromosome 20, which may be due to COMMD7 was also located on that chromosome (Table 2). The top 10 negatively related genes were ABHD18, ERN1, DDI2, USP12, METTL14, TOR1AIP2, PPTC7, MAP3K2, RSC1A1, ZNF281( $p < 0.01$ ). However, those negatively related genes distributed randomly in chromosome1, 2, 4, 12, 13, and 17 (Table 3).

Table 2  
Top ten positively correlated genes of COMMD7 in HCC

<b>Positively correlated Gene</b>	<b>Cytoband</b>	<b>Spearman's correlation</b>	<b>p-Value</b>
DYNLRB1	20q11.22	0.699	4.58e-56
PDRG1	20q11.21	0.674	1.00e-50
MANBAL	20q11.23	0.646	2.18e-45
PFDN4	20q13.2	0.643	5.86e-45
RALY	20q11.22	0.630	1.12e-42
CHMP4B	20q11.22	0.628	2.68e-42
MRGBP	20q13.33	0.628	2.92e-42
PIGU	20q11.22	0.627	3.45e-42
ARPC4	3p25.3	0.627	4.52e-42
ROMO1	20q11.22	0.620	4.57e-41

Table 3  
Top ten negatively correlated genes of COMMD7 in HCC

Negatively correlated Gene	Cytoband	Spearman's correlation	p-Value
ABHD18	4q28.2	-0.657	1.73e-47
ERN1	17q23.3	-0.653	1.22e-46
DDI2	1p36.21	-0.627	3.89e-42
USP12	13q12.13	-0.625	7.01e-42
METTL14	4q26	-0.613	7.37e-40
TOR1AIP2	1q25.2	-0.605	1.18e-38
PPTC7	12q24.11	-0.602	3.59e-38
MAP3K2	2q14.3	-0.601	6.08e-38
RSC1A1	1p36.21	-0.601	6.17e-38
ZNF281	1q32.1	-0.594	5.43e-37

## Functional analysis of COMMD7 in liver cancer stem cells

We have previously knocked down COMMD7 gene in liver cancer stem cells (LCSCs) to observe the effect of COMMD7 in LCSCs. After gene-sequencing, we analyzed the function of COMMD7 by Gene Ontology (GO) in the Database for Annotation, Visualization, and Integrated Discovery (DAVID, <https://david.ncifcrf.gov/summary.jsp>), the go enrichment including biological processes (BP), cellular components (CC), and molecular functions (MF) were launched. We found that GO:0055114 (oxidation-reduction process), GO:0098590 (plasma membrane region), GO:0070742 (C2H2 zinc finger domain binding) were most enriched for up-regulated genes after COMMD7 knock-down, while GO:0007399 (nervous system development), GO:0031012 (extracellular matrix), GO:0005509 (calcium ion binding) were significantly enriched for down-regulated genes (Fig. 5), indicating that COMMD7 may mainly combined with targeted domain or ions to exert its functional effect.

## Discussion

The bioinformatics analysis results suggested that COMMD7 expressed highly in liver tumor tissues, which donating poor prognosis and early progression of HCC. Since current studies on COMMD7 and HCC was primarily carried out in our center, herein we discussed the potential molecular mechanism by reviewing our previous work and research advances about COMMD7.

## COMMD7 enhanced hepatoma cell proliferation through activating NF- $\kappa$ B signaling

The nuclear factor of  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) transcription factor is well-known for its pivotal role in the maintenance of cellular homeostasis including cell death and apoptosis, inflammation and immunity[39]. Dysregulation of NF- $\kappa$ B pathway is frequently found in common human disease, and it is usually in a state of continuous activation in most cancers including Leukemia[40], lung cancer, HCC[41, 42]. The classical activation of NF- $\kappa$ B needs the 26 S proteasome induced ubiquitination and degradation of I $\kappa$ B $\alpha$ , NF- $\kappa$ B is then released from the cytoplasmic NF- $\kappa$ B/I $\kappa$ B $\alpha$  complex, and exposing the nuclear localization domain, forming a p50/RelA dimer, activating the transcription of tumor-related factors downstream. Additionally, NF- $\kappa$ B also can be activated in other ways such as nucleolar stress, tumor necrosis factor receptor (TNFR) family ligands CD40L[43], ROS[44], and angiotensin[45]. Thus the inhibition of NF- $\kappa$ B activity is considered to be one promising strategy to manipulate the tumorigenesis and development of cancers.

The COMMDs family member COMMD1 has been widely reported to facilitate the ubiquitination of NF- $\kappa$ B subunit RelA and its subsequent proteasomal degradation, therefore down-regulates NF- $\kappa$ B activity as well as the transcription of its targeted cancer-related genes downstream[19], hence COMMD1 negatively regulates the inflammatory responses and acts as an anti-inflammatory effector to repress colitis-associated cancers[46] and even as a tumor suppressor[47] in certain cancers such as prostate cancer[48] and lung cancer[18]. While in our previous studies, we found that COMMD7 is positively related to the expression and activation of NF- $\kappa$ B in HCC. An analysis of the expression relationship between COMMD1 and COMMD7 also showed their negative correlation ( $R=-0.6237$ ,  $p < 0.001$ ).

Furthermore, COMMD7 may be correlated with NF- $\kappa$ B through a positive feedback loop. Scilicet on one hand NF- $\kappa$ B directly binds to the promoter 1, 4, 5 and 6 sites of COMMD7, suggesting that NF- $\kappa$ B could target to COMMD7 and directly regulate its transcription in hepatocellular carcinoma cells[49]; on the other hand, COMMD7 silence in HepG2 cells resulted in 75% inhibition rate of NF- $\kappa$ B, indicating that COMMD7 conversely regulates the nuclear translocation of NF- $\kappa$ B as well as the transcriptions of consequent genes involved in HCC[38]. While how COMMD7 regulates the activity of NF- $\kappa$ B need further study. You et al, demonstrated that oxidative stress was required for COMMD7-mediated NF- $\kappa$ B activation since they found that overexpression of COMMD7 augmented intracellular ROS level and p65 phosphorylation in Huh7 cells[50]. Meanwhile, recent study manifested that COMMD7 activates NF- $\kappa$ B by upregulating protein inhibitor for activated stat4 (PIAS4) in Nanog<sup>+</sup> hepatocellular carcinoma stem cells to maintain its proliferation and metastasis[51].

## **COMMD7 promoted HCC progress and metastasis by modulating the production of CXCL10**

The role of immune system in tumor has been in the spotlight, cancer immunotherapy turns into hot issue. Chemokines are a class of small cytokines or signaling proteins secreted by cells which induce directional chemotaxis of vicinity response cells, these low-molecular-weight cytokines range from 8 kDa to 10 kDa are of critical importance in tumor immune response. C-X-C motif chemokine ligand 10 (CXCL10) belongs to interferon- $\gamma$  (INF- $\gamma$ ) inducible chemokine family which orchestrates leukocyte

trafficking and modulate innate and adaptive immune responses and exerts its biological function by binding with CXCR3 receptor[52]. The role of CXCL10 in cancers and disease remains controversial, although it has been reported to suppress tumor by interferon- $\gamma$ -mediated anti-tumor effect[53], more and more researches revealed it was beneficial for tumor growth, metastasis and recurrence. High serum level of CXCL10 could be a potential biomarker for many kinds of disease such as rheumatoid arthritis[54], psoriasis[55], cGVHD[56] and the CXCL10/CXCR3 axis mediates lung cancer cell migration[57]. Besides, expression of CXCL10 positively correlates with obesity and type 2 diabetes and linked to poor outcomes after islet transplantation[58]. In hepatocytes and liver cancer, CXCL10 was proved to enhance HCV and male HBV infection[59], the CXCL10/CXCR3 signaling promotes liver tumor growth via recruiting more endothelial progenitor cell (EPC) and inducing their mobilization, differentiation and neovessel formation[60]. Likewise, CXCL10 upregulated at liver graft injury directly induced the mobilization and intra-graft recruitment of Tregs, which further promoted HCC recurrence after transplantation [61]. Moreover, immune checkpoint inhibitor (ICI) therapy targeting anti-programmed cell death-1 (anti-PD-1) or its ligand (anti-PD-L1) is the backbone of numerous combination regimens aimed at improving the objective response and survival of patients with HCC[62], and Chow's recent study illustrated that CXCL10 is required for PD-1 blocked therapy responders[63]. Taken together, targeting CXCL10 may attenuate early HCC progression and recurrence.

Interestingly, our present study discovered that CXCL10 dramatically upregulated in COMMD7 overexpressed Huh7 cell line, and the expression levels of CXCL10 in other HCC cell lines including HepG2, Hep3B and HLE have been detected to be consistent with the expression level of COMMD7. In addition, inhibition of CXCL10 impaired COMMD7 mediated HCC cell proliferation and metastasis, indicating that COMMD7 positively regulates CXCL10 production in HCC[64]. Further, it has been reported that NF- $\kappa$ B directly binds to the promoter site of CXCL10 and regulates its expression [65]. For example, the activation NF- $\kappa$ B is required for the induction of CXCL10 during the progress and metastasis of Melanoma[66] and breast cancer[67]. Given that our previous evidence demonstrated that COMMD7 participated in NF- $\kappa$ B activation, therefore it probably promoted CXCL10 production by activating NF- $\kappa$ B, and the subsequent research also proved it[50]. Overall, these researches expounded that COMMD7 could strengthen HCC progress and metastasis by modulating the production of CXCL10 via NF- $\kappa$ B activation.

## Conclusions

In summary, we illuminated the expression profile of COMMD7 in hepatoma cell lines and human liver tumor tissues, shedding light on the promoting effect of COMMD7 on HCC. The results further highlight that high expression of COMMD7 is related with the early progression of HCC and poor prognosis. More importantly, it plays a pivotal role in hepatoma cell proliferation and metastasis through activating NF- $\kappa$ B signaling and CXCL10 via PIAS4 and ROS. In conclusion, since these bioinformatics analysis results and researches direct the positive correlation of COMMD7 high expression with HCC, it is possible to be regarded as a potential biomarker for the prevention and treatment of HCC. However how COMMD7 interacts with these effectors and more detailed mechanism warrants further investigation.

## Abbreviations

HCC: Hepatocellular carcinoma; COMMD7: copper metabolism MURR1 domain-containing protein 7; HCC: hepatocellular carcinoma; TCGA: The Cancer Genome Atlas; GTEx: Genotype-Tissue Expression; NF- $\kappa$ B: nuclear factor of  $\kappa$ -light-chain-enhancer of activated B cells; CXCL10: C-X-C motif chemokine ligand 10; INF- $\gamma$ : interferon- $\gamma$ ; ROS: reactive oxygen species; PIAS4: protein inhibitor for activated stat4. PD-1: programmed cell death-1.

## Declarations

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Army Medical University, PLA. All the data were retrieved from online databases and published literatures, therefore it could be confirmed that all written informed consent had already been obtained.

## Consent for publication

Not applicable.

## Availability of data and materials

The supporting materials and data of this review has been included within the article.

## Competing interests

The authors declare that they have no conflicts of interests.

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## Authors' contributions

Lu Zheng and Jing Li: Study design and guidance; Xuehui Peng and Yonggang He: Analyzing the data and drafting the manuscript; Xiaobing Huang, Nan You and Huiying Gu have participated in the previous

research work of COMMD7; Rui Dong and Xiaomin Yang contributed to data acquisition. All authors read and approved the final version of the manuscript.

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## Figures

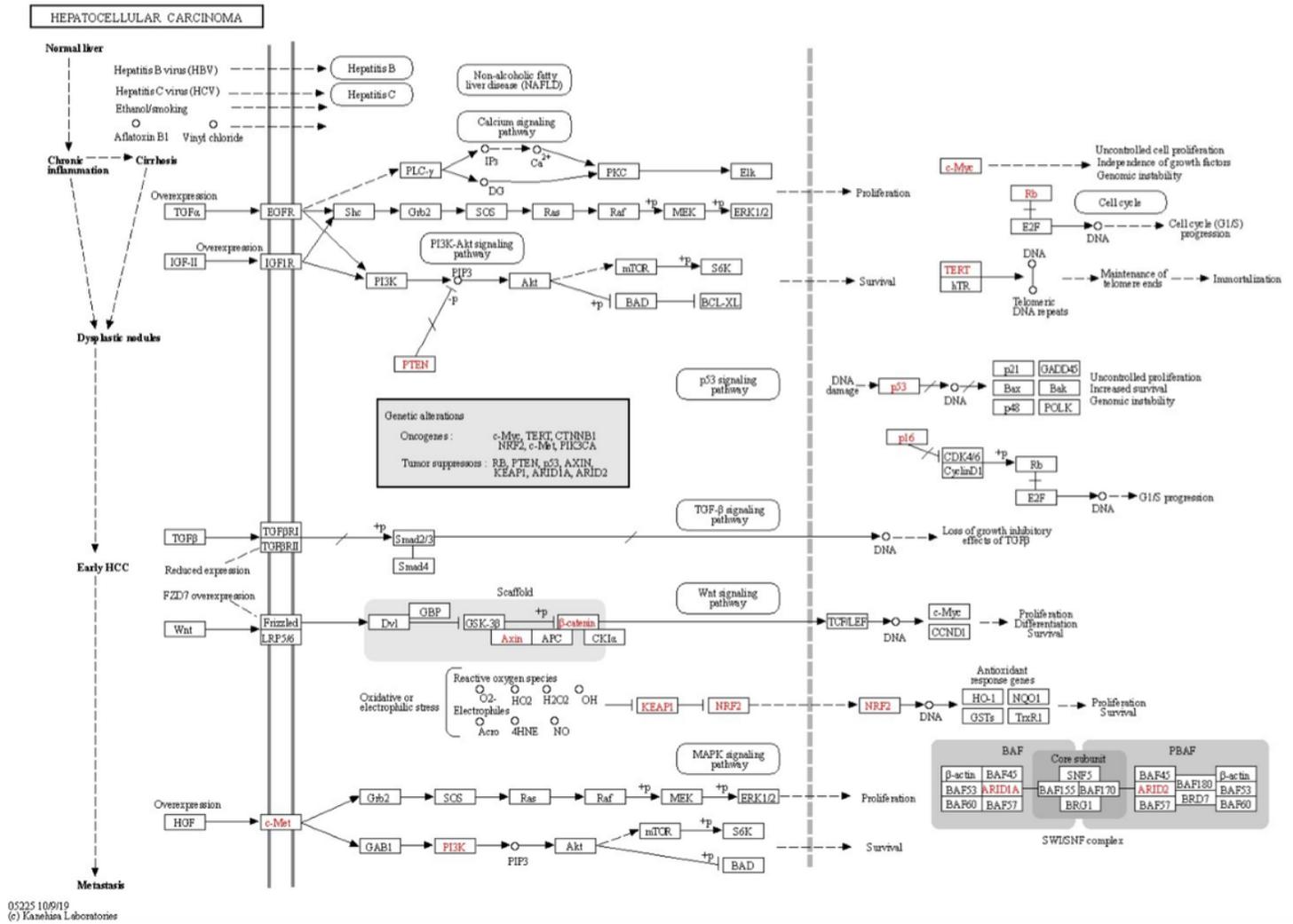


Figure 1

The map of signaling pathways and key factors involved in hepatocellular carcinoma (<https://www.genome.jp/kegg/>, copyright permission has been granted by KEGG rights holder).

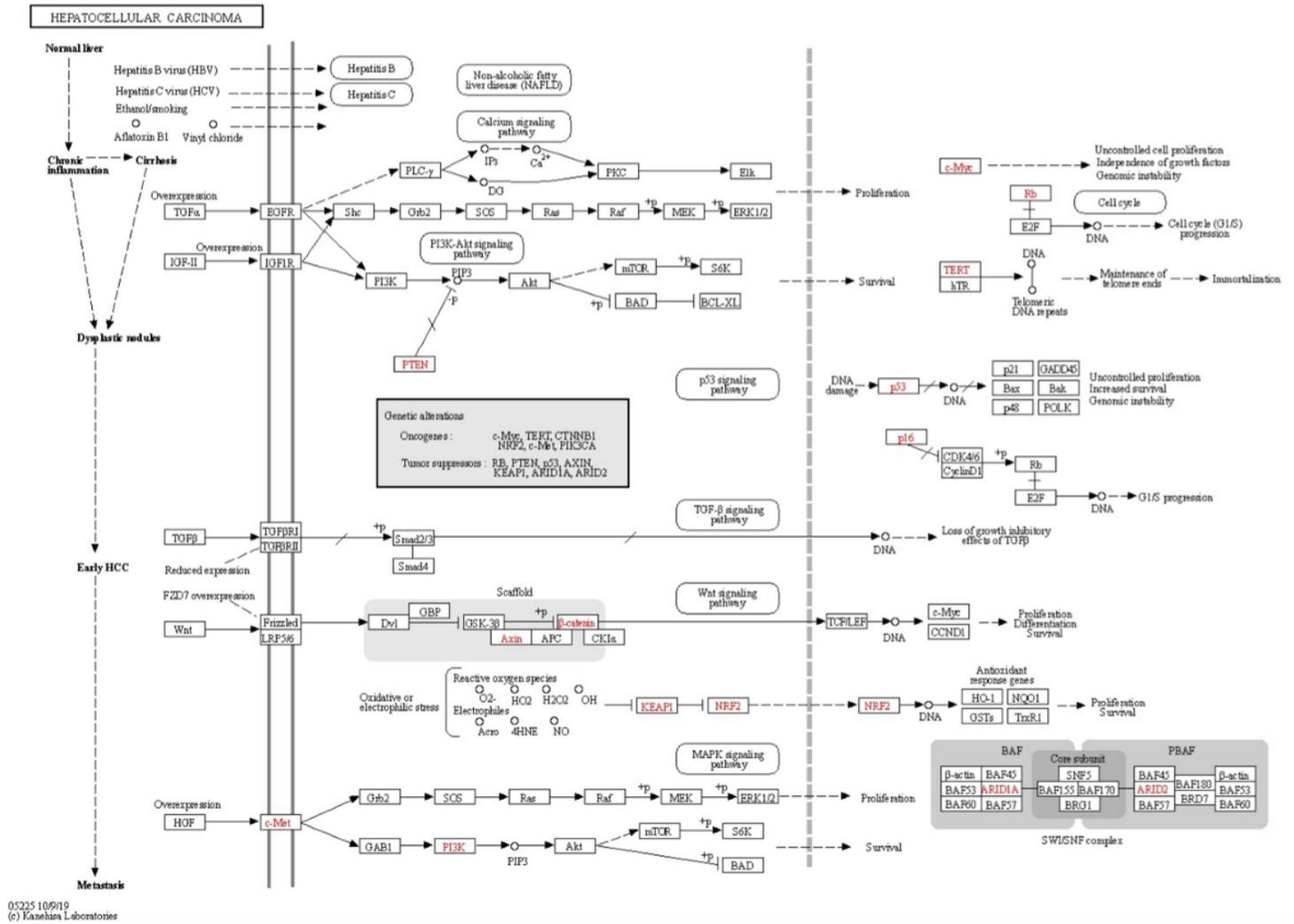


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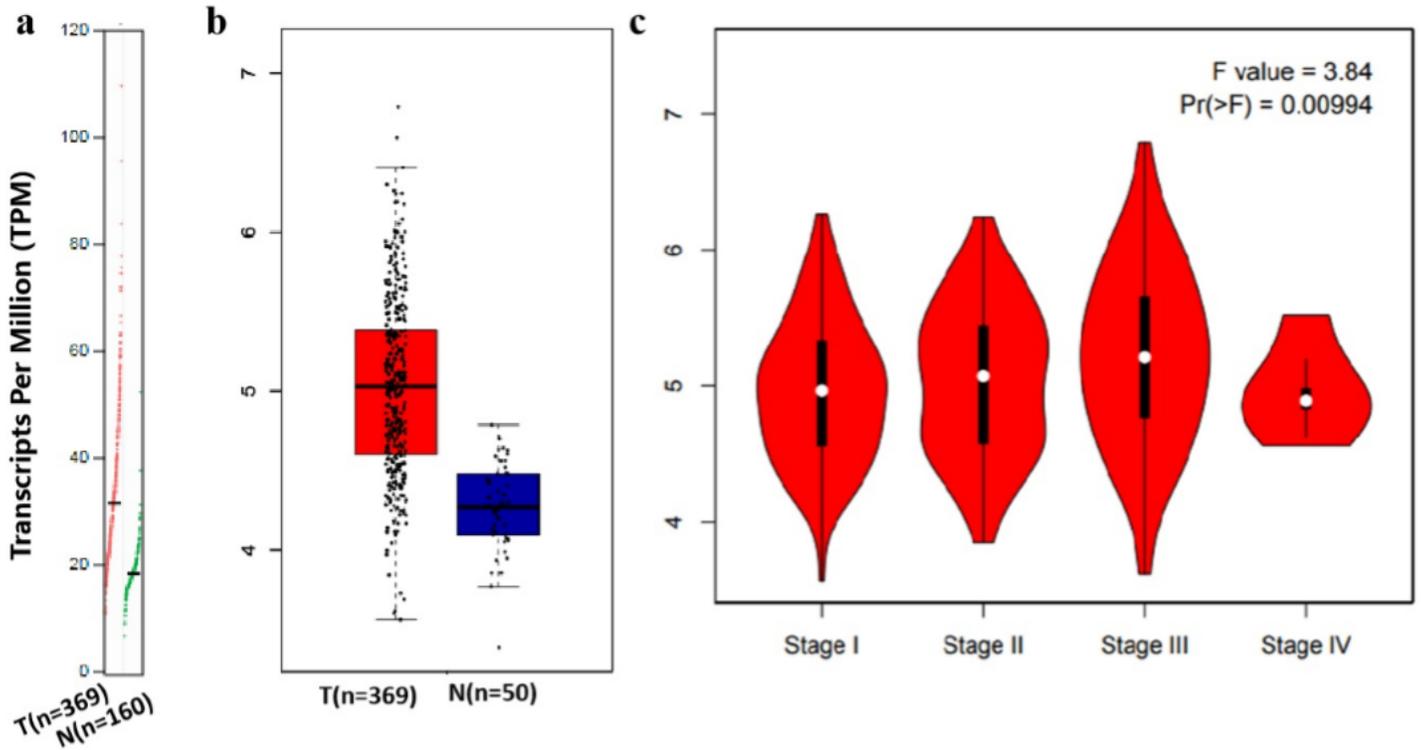


Figure 2

The expression profile of COMMD7 in HCC (GEPIA). (a) Transcription level of COMMD7 in tumor(T) and non-tumor(N) samples. (b) Relative protein level of COMMD7 in tumor(T) and non-tumor(N) samples; (c) Correlation between COMMD7 expression and tumor stage in HCC patients.

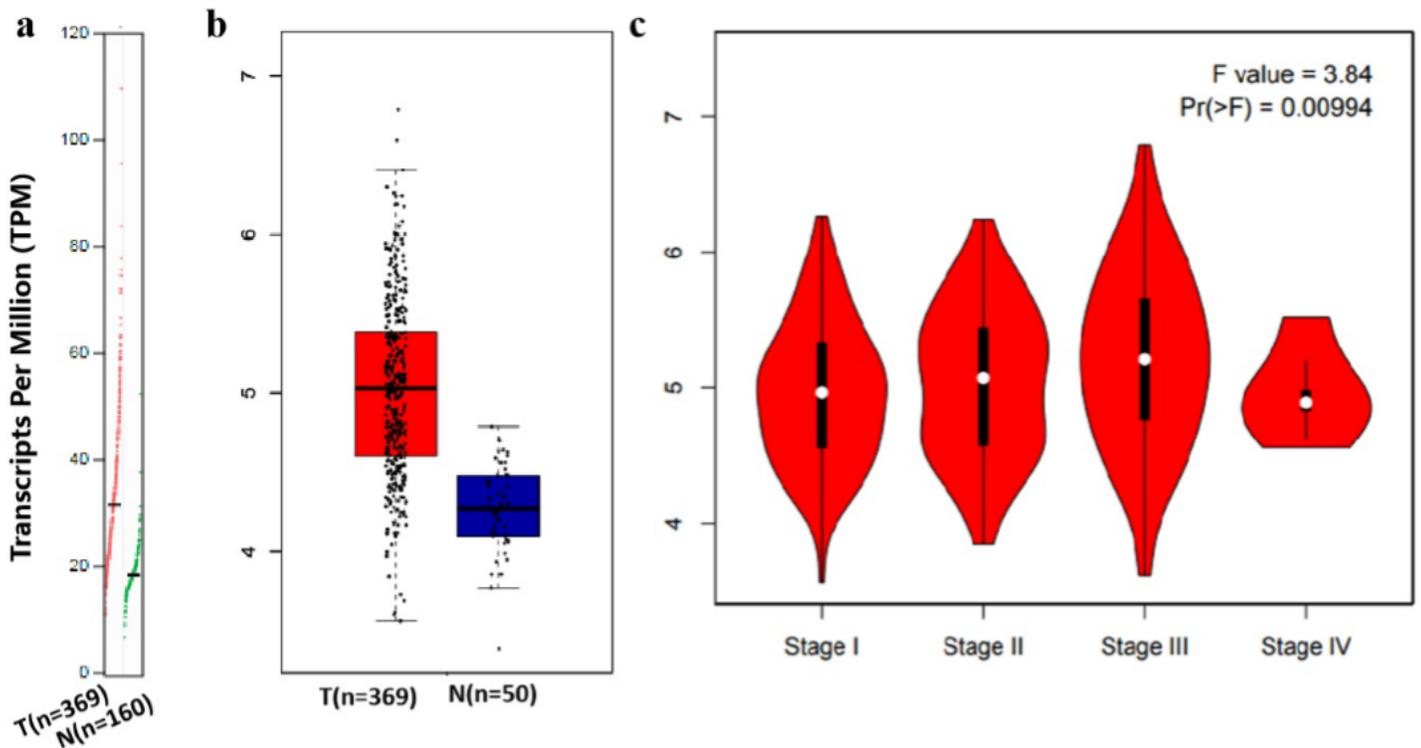
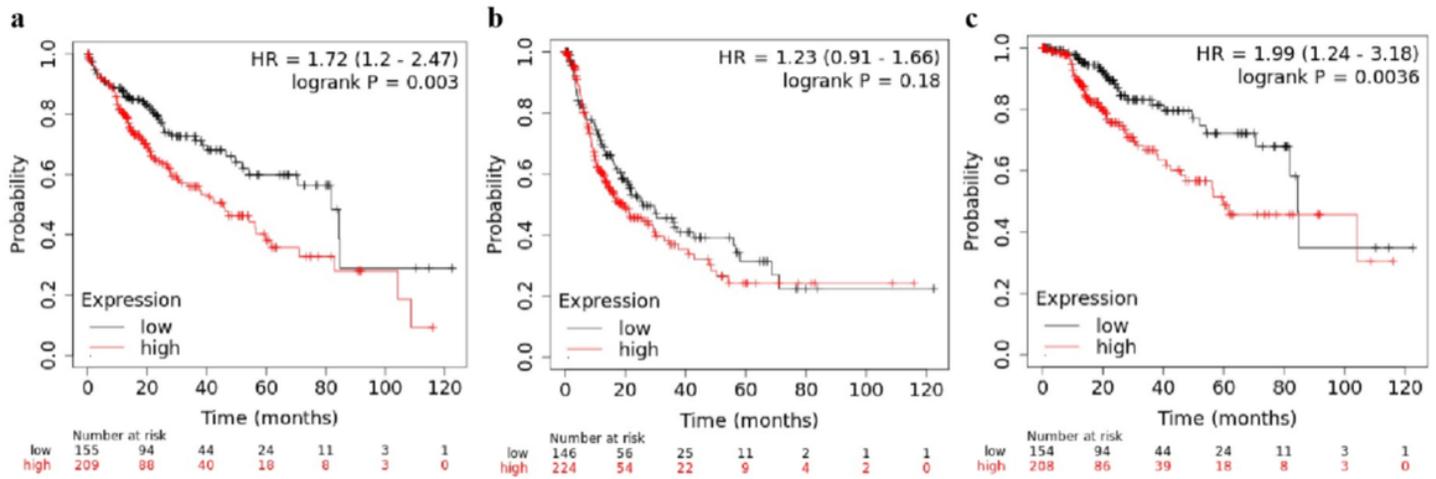


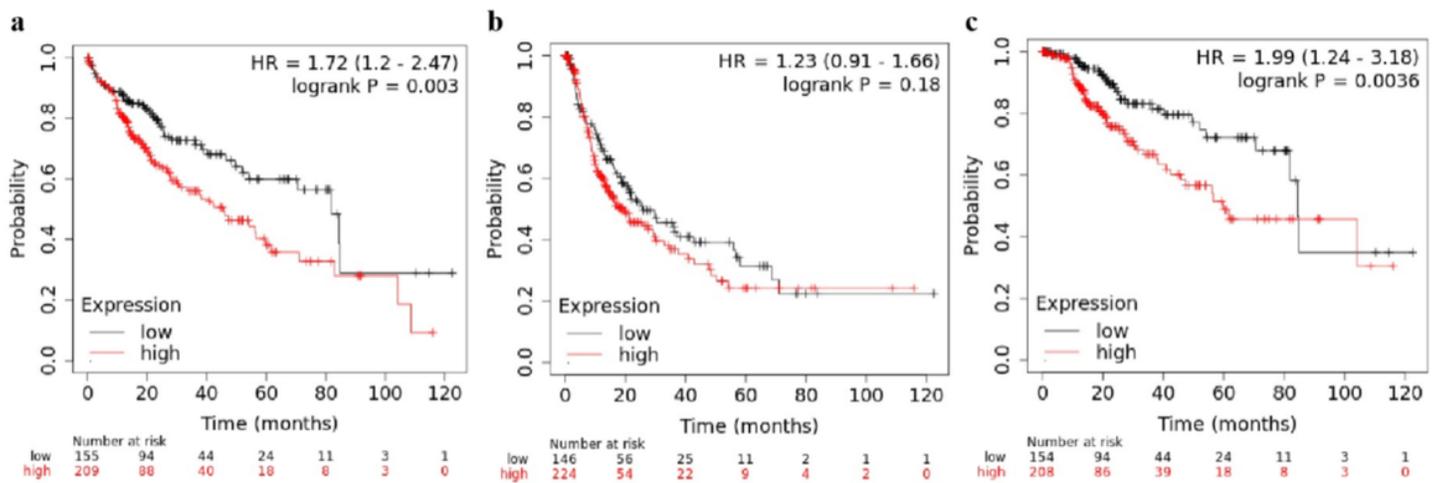
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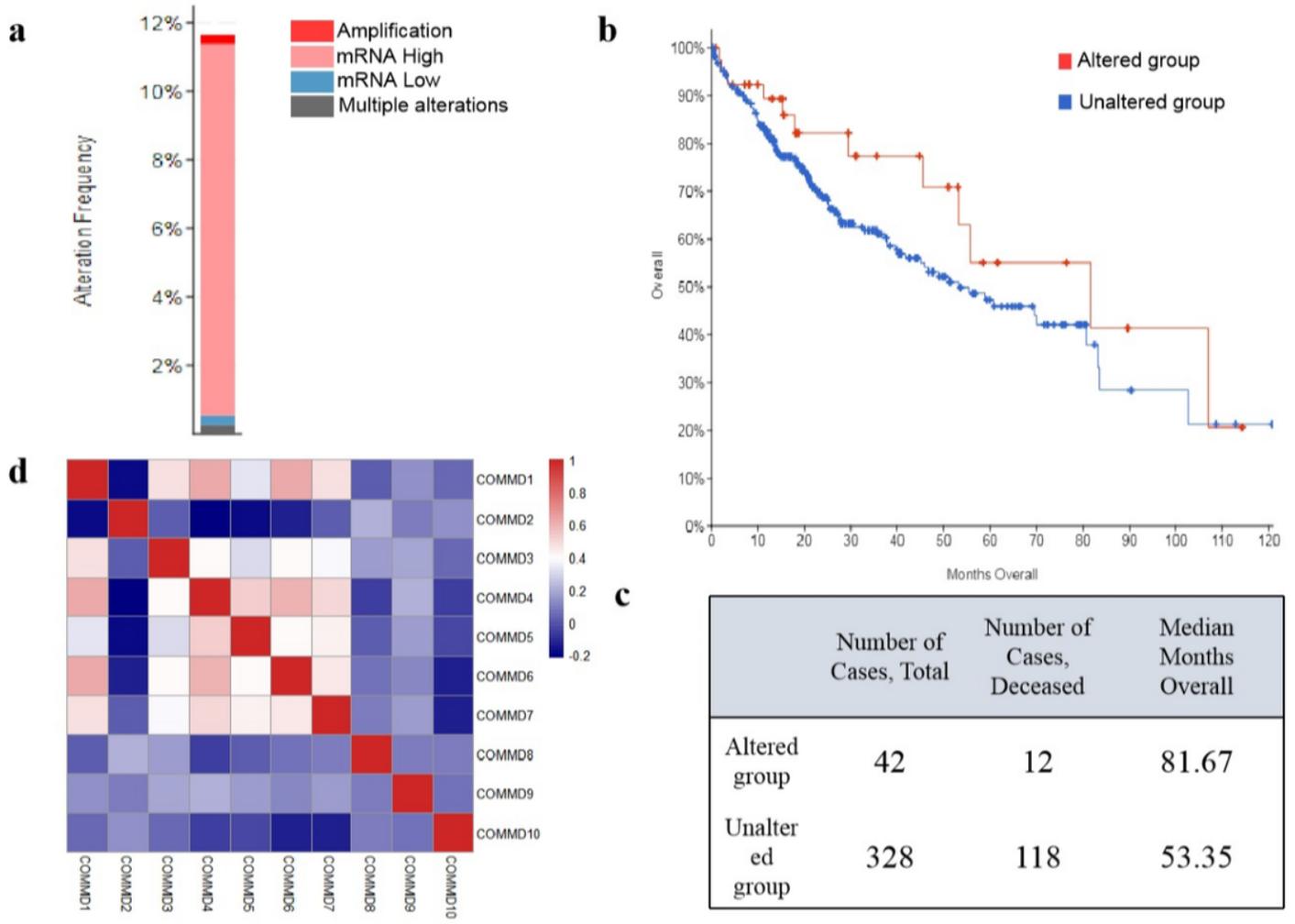
**Figure 3**

The prognostic value of mRNA level of COMMD7 in HCC patients (Kaplan-Meier plotter). The correlation between COMMD7 mRNA expression level and overall survival (OS)(a), progress-free survival(PFS)(b), and recurrence-free survival(RFS)(c).



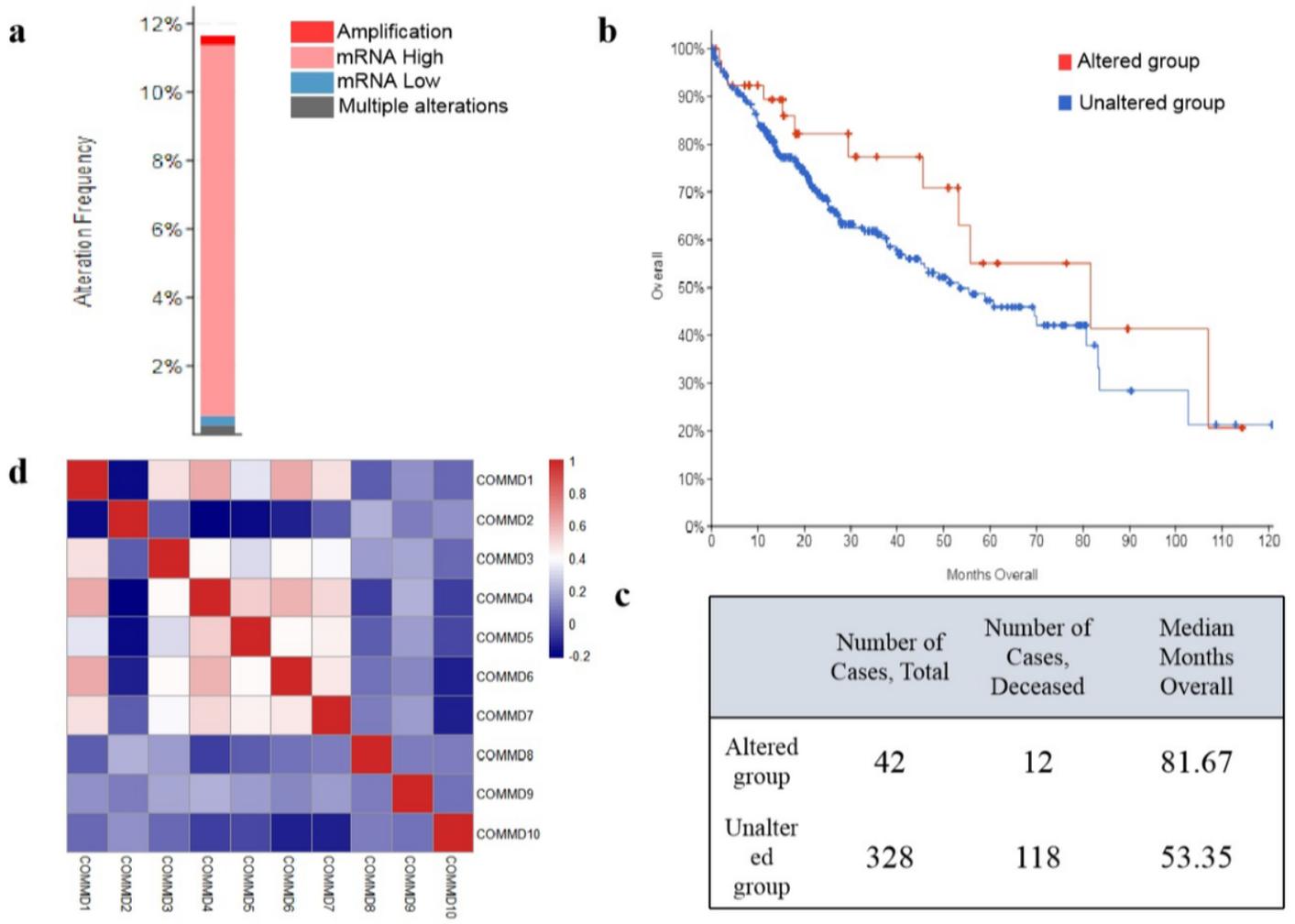
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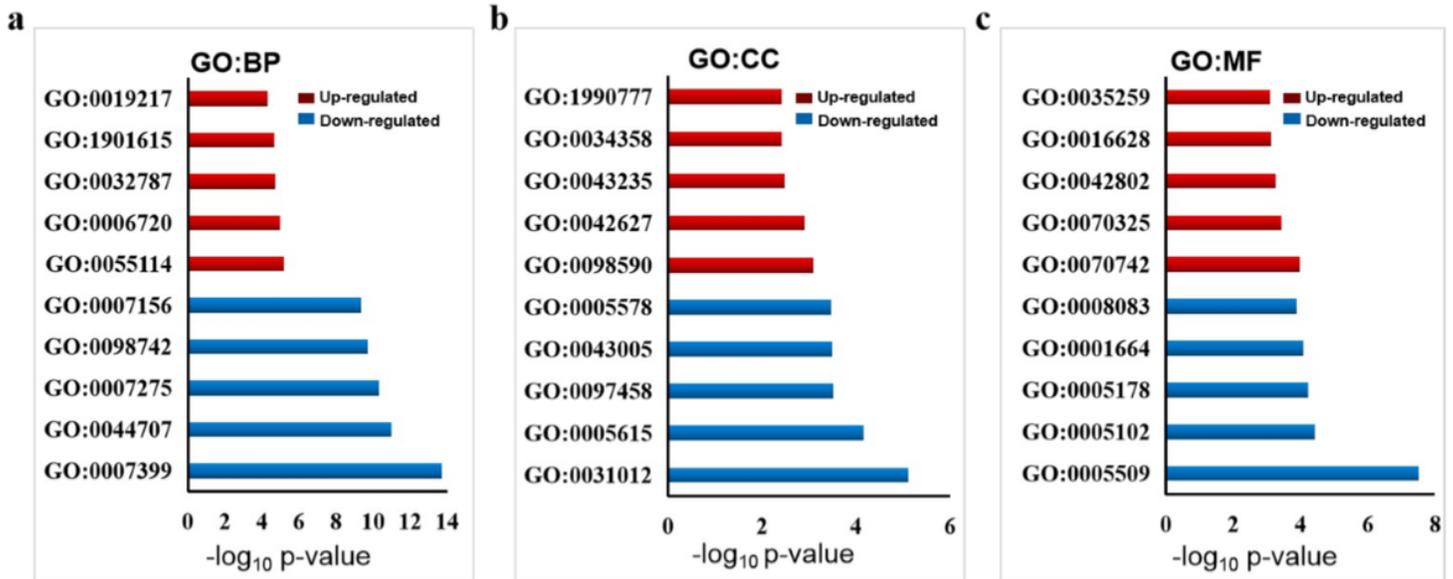
**Figure 4**

COMMD7 gene expression and mutation analysis in hepatocellular carcinoma (cBioPortal). (a) Gene mutation types in HCC; (b) Correlation between COMMD7 alteration and patients survival; (c) COMMD7-altered cases and survival time of HCC patients; (d) Pearson's correlation among the 10 COMMDs family members.



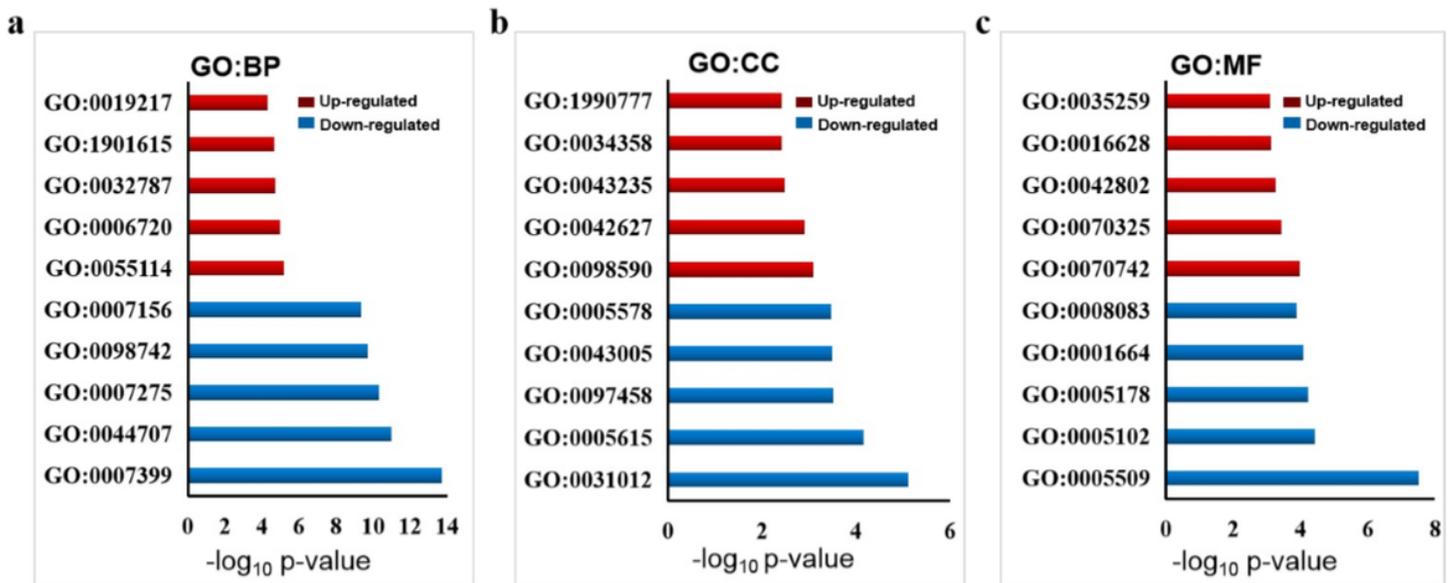
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**Figure 5**

The functions of COMMD7 genes in liver cancer stem cells. (<https://david.ncifcrf.gov/summary.jsp>). GO enrichment analysis predicted the functional roles of COMMD7 based on three aspects including biological processes (a), cellular components (b), and molecular functions (c).



**Figure 5**

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