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DATABASE ANALYSIS

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Identification of Biomarkers Based on Bioinformatics Analysis: The Expression of Ubiquitin-Conjugating Enzyme E2T (UBE2T) in the Carcinogenesis and Progression of Hepatocellular Carcinoma

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Data Collection B
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Data Interpretation D
Manuscript Preparation E
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Background: The purpose of this study was to screen and identify key genes in the occurrence and development of hepatocellular carcinoma (HCC) based on bioinformatics analysis.

Material/Methods: Three Gene Expression Omnibus (GEO) series (GSE) – GSE121248, GSE87630, and GSE84598 – were downloaded from the GEO database. GEO2R was used to screen different genes and a Venn diagram was drawn to screen coexpressed differentially expressed genes (DEGs). Coexpressed DEGs were obtained by Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis, a protein-protein interaction network diagram was produced by Cytoscape, and module genes were calculated by the Molecular Complex Detection Cytoscape plug-in. Finally, overall survival, progression-free survival, and relapse-free survival analysis of the key genes selected were performed using the online Kaplan-Meier plotter. For the target genes, the online network UCSC Cancer Genome Browser was used to analyze the gene expression profiles of the grade and vascular invasion of HCC.

Results: A total of 296 coexpressed DEGs were obtained from the 3 GSEs and 12 key genes were obtained from the modular analysis. Survival analysis showed that the upregulated genes UBE2T and FBLN5 were involved in the poor prognosis of HCC. Furthermore, the expression of UBE2T was significantly related to the grade and vascular invasion of HCC.

Conclusions: The expression of the UBE2T gene was significantly upregulated in HCC tissue compared to in normal liver tissue. UBE2T may be a new marker for the diagnosis and subsequent therapy of HCC.

Keywords: **Carcinoma, Hepatocellular • Gene Expression Profiling • Protein Interaction Mapping**

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Background

Hepatocellular carcinoma (HCC) accounts for 85% to 90% of primary liver cancer and is the third leading cause of cancer death in the world [1]. With clinical characteristics such as insidious onset and rapid progression, most patients with HCC are already in the middle and advanced stages when they are diagnosed, thereby missing the optimum opportunity for surgical resection [2]. Making the situation for patients even worse, resistance to sorafenib and lenvatinib, the first-line drugs for the treatment of advanced HCC, develops within a few months of use [3]. Therefore, there is an urgent need to develop more effective clinical treatments for HCC. The drug resistance to sorafenib and lenvatinib forced researchers to pay more attention to gene therapy. Gene therapy is a treatment method that intervenes in and regulates gene expression at the molecular level to achieve therapeutic goals [4,5]. Brown et al reported that blocking carnitine palmitoyltransferase decreased the apoptosis of intrahepatic CD4+ T cells and inhibited HCC tumor formation [6]. Shi et al reported that the FOXP3 gene can inhibit HCC progression through the TGF-β/Smad2/3 signaling pathway [7]. The above studies revealed encouraging potential new therapies for HCC.

Nevertheless, owing to the complexity of the carcinogenesis and progression of HCC, its genetic development mechanism is still not understood. To explore the gene expression characteristics of HCC and find new diagnostic markers and therapeutic targets, we downloaded gene expression profile data from the Gene Expression Omnibus (GEO) database, and analyzed differentially expressed genes (DEGs) between HCC tissue and normal liver tissue based on biometric analysis. The selection of DEGs was performed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis, a protein-protein interaction (PPI) network was drawn, and key genes were selected out. The survival analysis of key genes was calculated through the Kaplan-Meier online tool, and the most characteristic genes in different conditions were analyzed using the University of California Santa Cruz (UCSC) Cancer Genome Browser. The results showed that the ubiquitin-conjugating enzyme E2T (UBE2T) gene had high clinical value and might contribute to the diagnosis and treatment of HCC.

UBE2T is well known as a conspicuous gene that plays a crucial role in many kinds of malignancies, including renal cell carcinoma, lung cancer, cervical cancer, multiple myeloma, osteosarcoma, and, especially, HCC [8,9]. The present study is one of many to illustrate that UBE2T is an independent biomarker for HCC [10,11].

Material and Methods

Microarray Data

GEO (*http://www.ncbi.nlm.nih.gov/geo*) is a public gene database containing high-throughput functional genes, from which 3 GEO series (GSE) – GSE121248, GSE87630, and GSE84598 – were downloaded. GSE121248 contains 70 HCC tissue samples and 37 normal liver tissue samples adjacent to HCC. GSE87630 contains 64 HCC tissue samples and 30 normal liver tissue samples adjacent to HCC. GSE84598 contains 22 HCC tissue samples and 22 normal liver tissue samples adjacent to HCC.

Identification of DEGs

The online tool GEO2R (*https://www.ncbi.nlm.nih.gov/geo/geo2r/*) was used to screen the DEGs between HCC tissue and normal liver tissue. The probes with no corresponding gene symbol and duplicate genes were removed. Variables with adjusted P values <0.01 and |log FC| ≥1 were considered statistically significant. The Venn diagram displayed the coexpressed DEGs (bioinformatics.psb.ugent.be/webtools/Venn/).

GO and KEGG Pathway Analysis

The Database for Annotation, Visualization and Integrated Discovery (DAVID) database provides a comprehensive set of functional annotation tools for researchers to better understand the biological meaning underlying the innumerable existing genes. GO enrichment analysis is a common method to discriminate the enrichment degree of GO terms of different genes. GO enrichment analysis is divided into 3 aspects: biological process (BP), cell component (CC), and molecular function (MF). KEGG is a genome deciphering database and an enrichment analysis tool for the research of biological regulatory networks. In this study, the enrichment analysis of DEGs was completed using the online tool DAVID (*https://david.ncifcrf.gov/*), and false discovery rate (FDR) <0.01, and the number of enriched genes ≥10 were considered to be significantly different.

PPI Network Construction and Module Analysis

The PPI network information of DEGs was analyzed using the online tool STRING (*http://string-db.org/*) version 11.0. The minimum interaction score >0.04 was considered statistically significant. The PPI network was then visualized by Cytoscape software (*www.cytoscape.org/*). The key modules of PPI were calculated and extracted through Molecular Complex Detection (MCODE). MCODE, as a functional plug-in of Cytoscape, was used to screen closely related modules in the PPI network. The module selection criteria in this study were as follows: degree cut-off=2, node score cut-off=0.2, max depth=100, k-score=2.

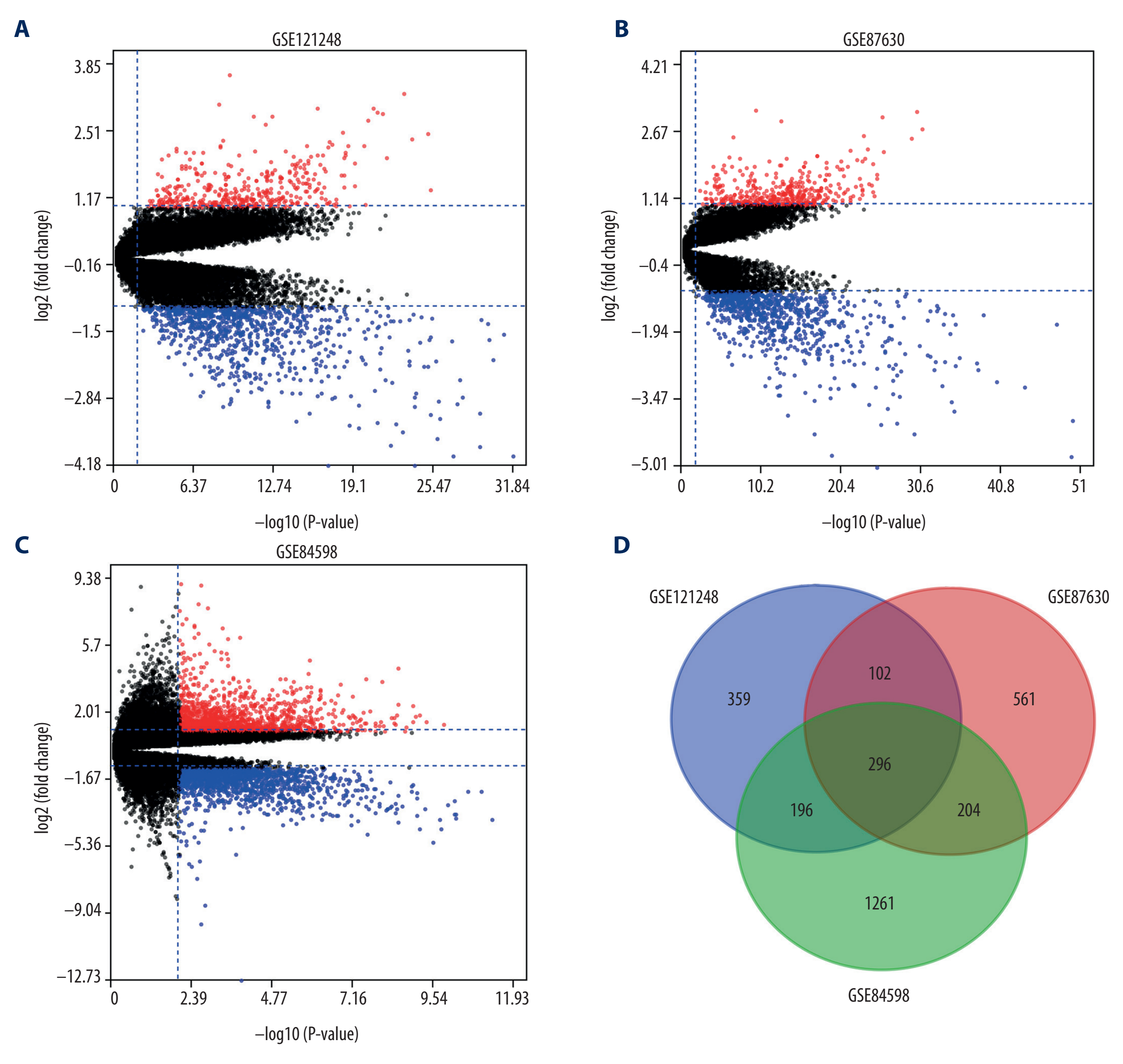

Figure 1. Volcano map and Venn diagram of GSE121248, GSE87630, and GSE84598. (**A–C**) In the volcano map, the adjusted *P* value <0.01 and |log FC| ≥1 was considered statistically significant. Upregulated genes are marked in red and downregulated genes are marked in blue. (**D**) An overlap of 296 differentially expressed genes (DEGs) were finally screened on the Venn diagram.

Functional enrichment analysis on the key modular genes was performed using DAVID.

Hub Genes Analysis

Key genes consisted of seed genes selected from each module. The Biological Networks Gene Oncology tool (BINGO) plug-in in Cytoscape was used to analyze and visualize the BP of key genes. Hierarchical cluster analysis of key genes was done by the UCSC Cancer Genome Browser (*http://generic-cancer.ucsc.edu*), which was used to explore the connection between key gene expression and sample type and the grade of HCC. Overall survival (OS) and relapse-free survival (RFS) survival analysis on key genes were performed by the Kaplan-Meier plotter (*http://kmplot.com/analysis/*) online network. Online gene expression data (SAGE; *http://www.ncbi.nlm.nih.gov/SAGE*) was used to analyze and visualize the expression profiles of UBE2T and FBLN, and the online Oncomine database (*http://www.oncomine.com*) was used to determine the relationship between gene expression and tumor grade, hepatitis virus infection, satellite lesions, and vascular invasion.

Table 1. GO and KEGG pathway enrichment analysis of DEGs in HCC samples.

Category	Term	Description	Count	FDR
Downregulated				
GOTERM_BP_DIRECT	GO: 0019373	Epoxygenase P450 pathway	10	8.46E-10
GOTERM_BP_DIRECT	GO: 0055114	Oxidation-reduction process	30	1.60E-06
GOTERM_BP_DIRECT	GO: 0006956	Complement activation	11	5.79E-05
GOTERM_BP_DIRECT	GO: 0006805	Xenobiotic metabolic process	10	1.74E-04
GOTERM_BP_DIRECT	GO: 0071356	Cellular response to tumor necrosis factor	10	0.002280078
GOTERM_BP_DIRECT	GO: 0006508	Proteolysis	20	0.004661937
GOTERM_CC_DIRECT	GO: 0005576	Extracellular region	63	2.51E-13
GOTERM_CC_DIRECT	GO: 0031090	Organelle membrane	16	2.80E-11
GOTERM_CC_DIRECT	GO: 0070062	Extracellular exosome	79	3.65E-10
GOTERM_CC_DIRECT	GO: 0005615	Extracellular space	48	1.08E-08
GOTERM_CC_DIRECT	GO: 0072562	Blood microparticle	12	1.30E-04
GOTERM_MF_DIRECT	GO: 0020037	Heme binding	19	8.03E-11
GOTERM_MF_DIRECT	GO: 0016705	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	14	8.03E-11
GOTERM_MF_DIRECT	GO: 0004497	Monooxygenase activity	13	1.55E-09
GOTERM_MF_DIRECT	GO: 0005506	Iron ion binding	18	1.94E-09
GOTERM_MF_DIRECT	GO: 0019825	Oxygen binding	11	3.24E-08
GOTERM_MF_DIRECT	GO: 0004252	Serine-type endopeptidase activity	17	1.73E-05
GOTERM_MF_DIRECT	GO: 0003824	Catalytic activity	11	0.008200616
KEGG_PATHWAY	hsa01100	Metabolic pathways	58	5.92E-08
KEGG_PATHWAY	hsa04610	Complement and coagulation cascades	11	7.69E-05
KEGG_PATHWAY	hsa05204	Chemical carcinogenesis	11	2.30E-04
KEGG_PATHWAY	hsa01200	Carbon metabolism	12	7.12E-04
KEGG_PATHWAY	hsa01130	Biosynthesis of antibiotics	14	0.007712682
Upregulated				
GOTERM_BP_DIRECT	GO: 0007067	Mitotic nuclear division	10	9.83E-06
GOTERM_BP_DIRECT	GO: 0051301	Cell division	11	9.83E-06
GOTERM_CC_DIRECT	GO: 0005654	Nucleoplasm	22	1.84E-04
GOTERM_CC_DIRECT	GO: 0005634	Nucleus	30	7.93E-04
GOTERM_CC_DIRECT	GO: 0005829	Cytosol	21	0.005534764

GO – Gene Ontology; KEGG – Kyoto Encyclopedia of Genes and Genomes; DEGs – differentially expressed genes; HCC – hepatocellular carcinoma; FDR – false discovery rate.

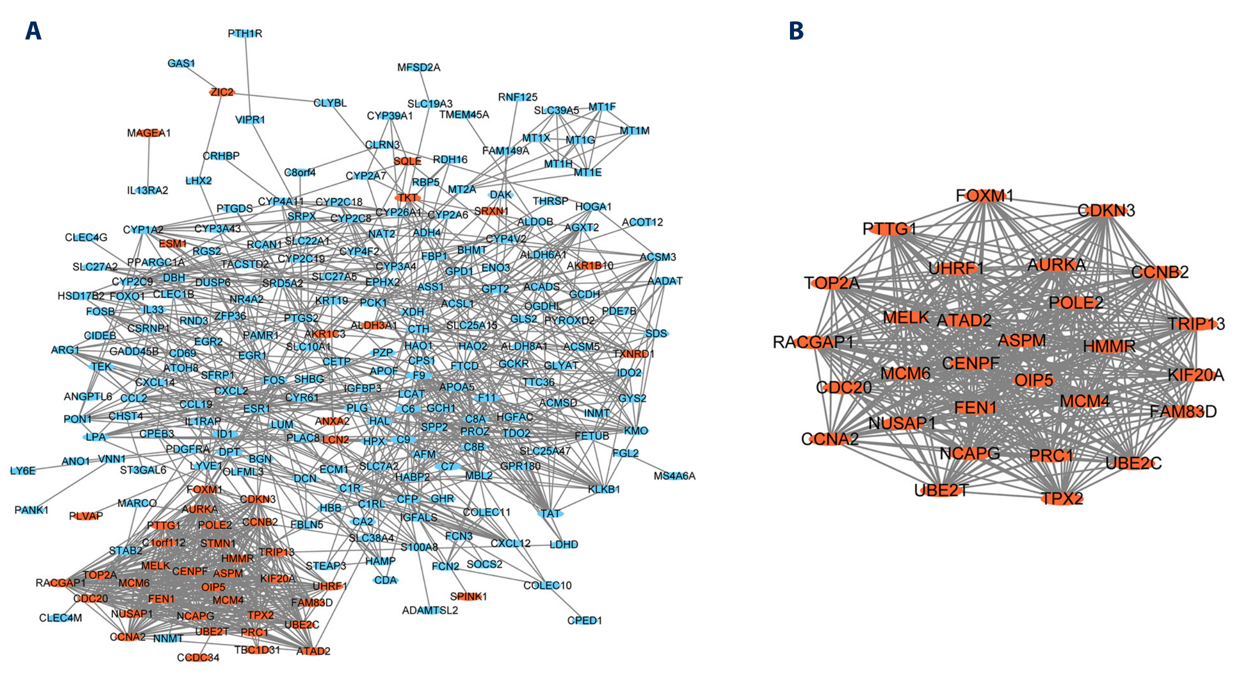

Figure 2. Protein-protein interaction (PPI) network and the most significant modules. (**A**) PPI network was drawn by Cytoscape. Upregulated genes are marked in red, downregulated genes are marked in blue. (**B**) The most significant module, including 29 nodes and 388 edges, was obtained from the PPI network.

Table 2. GO and KEGG pathway enrichment analysis of DEGs in the most significant module.

Category	Term	Description	Count	FDR
GOTERM_BP_DIRECT	GO: 0051301	Cell division	11	1.66E-08
GOTERM_BP_DIRECT	GO: 0007067	Mitotic nuclear division	10	1.66E-08
GOTERM_CC_DIRECT	GO: 0005654	Nucleoplasm	19	3.33E-07
GOTERM_CC_DIRECT	GO: 0005634	Nucleus	24	4.13E-07
GOTERM_MF_DIRECT	GO: 0005515	Protein binding	26	0.001379194
GOTERM_MF_DIRECT	GO: 0005524	ATP binding	11	0.002387081

GO – Gene Ontology; KEGG – Kyoto Encyclopedia of Genes and Genomes; DEGs – differentially expressed genes; FDR – false discovery rate.

Results

Identification of DEGs in HCC

The differential genes in each data series were confirmed after screening, with 953 DEGs in GSE121248, 1163 in GSE87630, and 1957 in GSE84598 (**Figure 1A-1C**). The overlap of the 3 data sets is shown in the Venn diagram (**Figure 1D**), in which 296 DEGs were coexpressed, consisting of 54 upregulated genes and 242 downregulated genes.

KEGG and GO Enrichment Analyses of DEGs

The results of GO enrichment showed the downregulated genes of DEGs were mainly enriched in the epoxygenase P450 pathway, oxidation-reduction process complement activation, xenobiotic metabolic process, cellular response to tumor necrosis factor, and proteolysis on BP; extracellular region, organelle membrane, extracellular exosome, extracellular space, and blood microparticle on CC; heme binding, oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, monooxygenase activity, iron ion binding, oxygen binding, serine-type endopeptidase activity,

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Table 3. Functional roles of 16 hub genes with degree ≥10.

Gene symbol	Full name	Function
UBE2T	Ubiquitin-conjugating enzyme E2 T	Catalyzes the covalent attachment of ubiquitin to protein substrates
HABP2	Hyaluronan binding protein 2	Encodes a member of the peptidase S1 family of serine proteases
MT1M	Metallothionein 1M	Encodes a member of the metallothionein superfamily, type 1 family
CFP	Complement factor properdin	Encodes a plasma glycoprotein that positively regulates the alternative complement pathway of the innate immune system
ENO3	Enolase 3	Encodes 1 of the 3 enolase isoenzymes found in vertebrates
CYP2C18	Cytochrome P450 family 2 subfamily C member 18	Encodes a member of the cytochrome P450 superfamily of enzymes.
CCL2	C-C motif chemokine ligand 2	1 of several cytokine genes clustered on the q-arm of chromosome 17
FBLN5	Fibulin 5	Protein encoded is a secreted, extracellular matrix protein containing an Arg-Gly-Asp motif and calcium-binding EGF-like domains
KMO	Kynurenine 3-monooxygenase	Encodes a mitochondrion outer membrane protein that catalyzes the hydroxylation of L-tryptophan metabolite, L-kynurenine, to form L-3-hydroxykynurenine
ACMSD	Aminocarboxymuconate semialdehyde decarboxylase	Converts alpha-amino-beta-carboxymuconate-epsilon-semialdehyde to alpha-aminomuconate semialdehyde
PTGS2	Prostaglandin-endoperoxide synthase 2	Encodes an enzyme that is a member of the prostaglandin G/H synthase family
CLEC1B	C-type lectin domain family 1, member b	CLEC2 is a C-type lectin-like receptor expressed in myeloid cells and NK cells

and catalytic activity on MF; and metabolic pathways, complement and coagulation cascades, chemical carcinogenesis, carbon metabolism, and biosynthesis of antibiotics on KEGG. The upregulated genes of DEGs were mainly enriched in mitotic nuclear division and cell division on BP, and nucleoplasm, nucleus, and cytosol on CC (**Table 1**).

PPI Network Construction and Module Analysis

The PPI network of DEGs was constructed using Cytoscape (**Figure 2A**), and the most significant module was obtained (**Figure 2B**). Enrichment analysis of key modules using DAVID showed that the key module genes were mainly enriched in cell division, mitotic nuclear division, nucleoplasm, nucleus, protein binding, and ATP binding (**Table 2**).

Hub Gene Selection and Analysis

A total of 12 key genes with degree ≥10 were screened. Their abbreviations, full names, and functions are shown in **Table 3**. The visualized BP process diagram of key genes is shown in **Figure 3A**. Hierarchical cluster analysis demonstrated that the UBE2T gene was upregulated in tumor samples and downregulated in normal tissue, in contrast to other genes (**Figure 3B**). Subsequently, OS survival analysis of these key genes was performed using Kaplan-Meier curve analysis. The results showed that patients with high expression of UBE2T and FBLN5 genes tended to have poorer OS (**Figure 4A**). The upregulation of UBE2T, CFP, and FBLN5 genes was significantly correlated with poor RFS (**Figure 4B**), while the high expression of UBE2T, CFP, and FBLN5 was associated with poor progression-free survival (PFS) (**Figure 4C**). Based on the Kaplan-Meier online database, we found that the high expression of UBE2T and FBLN5 in patients with HCC was involved in poor prognosis in multiple survival analyses, suggesting that they may have an important role in the development of HCC. Oncomine analysis showed that the TOP2A gene was clearly highly expressed in HCC among different data sets, while FBLN5 did not show a significant correlation (**Figure 5**). In the Wurmbach liver data set, a high level of UBE2T was related to tumor grade, sample type, satellite lesions, and vascular invasion (**Figure 6**).

Discussion

For patients with advanced HCC, drug therapy based on sorafenib and lenvatinib is the main palliative treatment, but resistance to the therapy will develop within a few months [12,13]. Therefore, the discovery of new gene therapy sites is crucial. Based on GSE121248, GSE87630, and

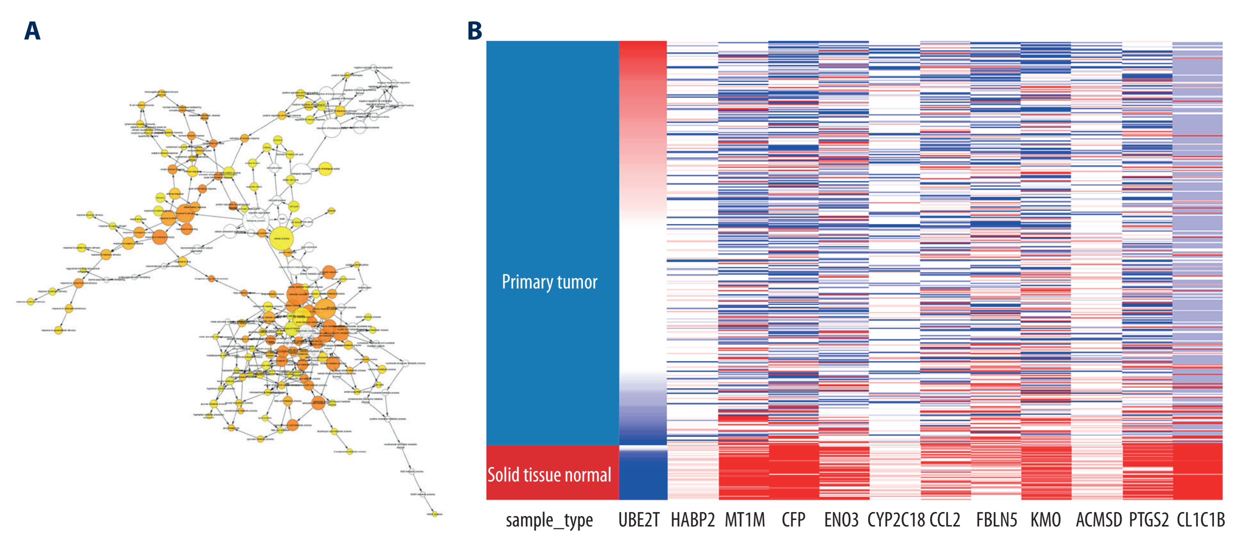


Figure 3. BP analysis and hierarchical cluster analysis of key gene. (**A**) In the BP graph drawn by the BINGO plug-in in Cytoscape, the size of the node was decided by the number of corresponding genes. (**B**) Hierarchical cluster analysis graph shows the expression of 12 hub genes in primary hepatocellular carcinoma (HCC) tissue and normal tissue. Upregulated genes are marked in red, downregulated genes are marked in blue.

GSE84598 from the GEO public database, we screened out 296 DEGs in HCC and normal liver tissues, of which 54 were upregulated genes and 242 were downregulated genes. These genes are mainly enriched in the epoxygenase P450 pathway, oxidation-reduction process, and complement activation by GO enrichment analysis, and in mitotic nuclear division, cell division, nucleoplasm, nucleus, and cytosol by KEGG enrichment analysis. It has been reported that cytochrome CYP450 cyclooxygenase can catalyze the epoxidation of unsaturated fatty acids such as arachidonic acid and that arachidonic acid-derived products can effectively promote angiogenesis of lipids and tumor development [14]. Zhang et al reported that the growth and prognosis of cancer can be regulated by affecting the balance of redox reactions [15]. These findings support our enrichment analysis results. A PPI network diagram of DEGs was drawn to explore the interrelationships among different genes, and the key modules were identified by the MCODE plug-in. Enrichment analysis showed that the genes of the key modules were mainly enriched in cell division, mitotic nuclear division, nucleoplasm, nucleus, protein binding, and ATP binding. Neil et al found that the division error of the formation of chromosome bridges of a single cell could rapidly increase the complexity of genes and promote the continuous evolution and subclonal heterogeneity of many cancers [16]. Fletcher et al found that ATP binding plays a considerable role in tumor progression and metastases [17]. All of these reports further verified the enrichment analysis results of the key genes in our research. In our present study, the key genes were extracted from all modules, and the hierarchical cluster analysis of key genes showed that UBE2T gene was significantly highly expressed in HCC. The results of the OS survival curve revealed that the high expression of UBE2T and FBLN5 genes was markedly involved in the poor prognosis of patients with HCC, and the low expression of the CFP gene was apparently involved in the poor prognosis of patients with HCC. The RFS and PFS of these 3 genes showed that the high expression of UBE2T, FBLN5, and CFP were significantly related to the prognosis of patients, yet only UBE2T and FBLN5 were statistically related to the prognosis of HCC in various survival analyses. Meta-analysis of UBE2T and FBLN5 using the Oncomine database showed that UBE2T was evidently higher in HCC tissue than in normal liver tissue. The results produced by the UCSC Cancer Genomics Browser showed that UBE2T was notably positively correlated with sample type, HCC grade, HCC satellite lesions, and vascular invasion, while FBLN5 showed no obvious correlations. Consequently, the high expression of UBE2T may be a poor prognostic factor that promotes the occurrence and development of HCC.

The protein encoded by the UBE2T (ubiquitin-conjugating enzyme E2T) gene catalyzes the covalent attachment of ubiquitin to protein substrates [18,19]. Many studies have confirmed that UBE2T plays an essential role in tumor cell proliferation, invasion, and metastasis [20,21]. The high expression of UBE2T is associated with poor prognosis of a variety of cancers. Hao et al found that in kidney cancer, UBE2T promotes the proliferation of renal cell carcinoma cells by regulating Pi3K/akt signaling [8]. The authors found that UBE2T was highly expressed in lung cancer tissues and cell lines, indicating that UBE2T is involved in the formation of cancer cells [22]. Alagpulinsa et al found

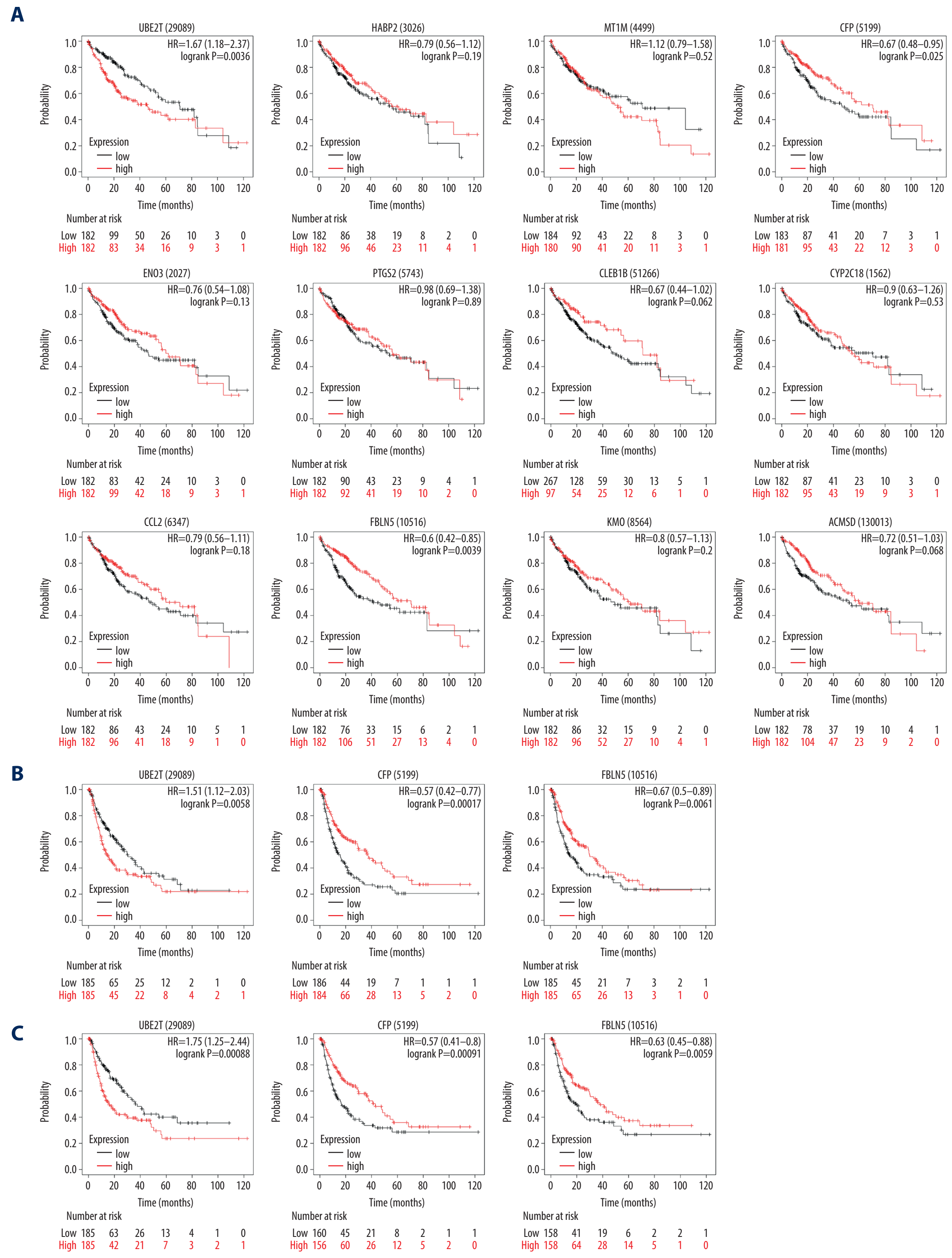


Figure 4. The survival analysis chart was drawn by the Kaplan-Meier plotter online tool; *P*<0.01 was considered statistically significant. (**A**) Overall survival curve analysis of key genes. (**B**) Progression-free survival curve analysis of UBE2T, CFP, and FBLN5. (**C**) Relapse-free survival curve analysis of UBE2T, CFP, and FBLN5.

that the amplification and overexpression of UBE2T promoted homologous recombination in multiple myeloma [21]. Liu et al found that the overexpression of UBE2T was related to tumor proliferation and invasion and was an independent prognostic factor of HCC. The high expression of UBE2T is associated with higher pathological grades of HCC, advanced TMN staging, poor overall survival rate, and disease-free survival rate, confirming that UBE2T is an independent prognostic factor for the overall survival of patients with HCC [10]. Wei et al found that miR-1305 targeted UBE2T to inhibit the Akt signaling pathway, thereby inhibiting the self-renewal and tumorigenicity of HCC stem cells [16]. In the present study, we found that UBE2T interacted with genes including aurora kinase A (AURKA), TPX2, and CDC20 through the PPI network. AURKA is a mitotic serine/threonine kinase that acts as an oncogene and plays a key role in the development of HCC [23]. Overexpression of TPX2

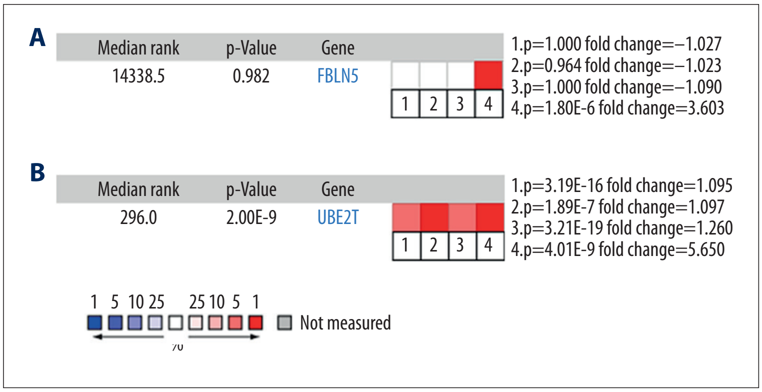
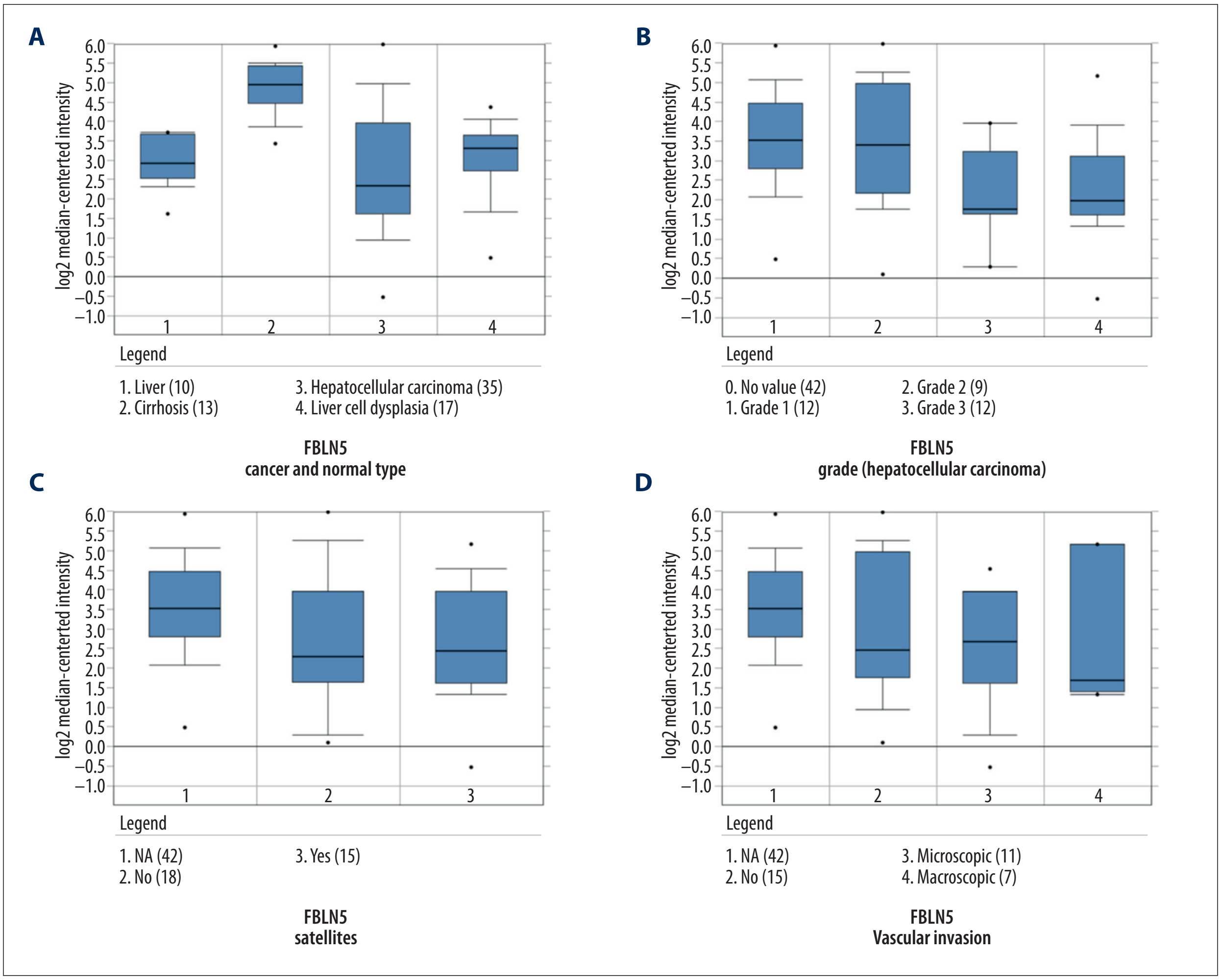


Figure 5. Analysis of (**A**) FBLN5 and (**B**) UBE2T in hepatocellular carcinoma (HCC) and normal liver tissues based on the Oncomine database. (1) Hepatocellular carcinoma vs normal Guichard liver, Nat Genet, 2012. (2) Hepatocellular carcinoma vs normal Guichard liver 2, Nat Genet, 2012. (3) Hepatocellular carcinoma vs normal TCGA liver, no associated paper, 2012. (4) Hepatocellular carcinoma vs normal Wurmbach liver, Hepatology, 2007.



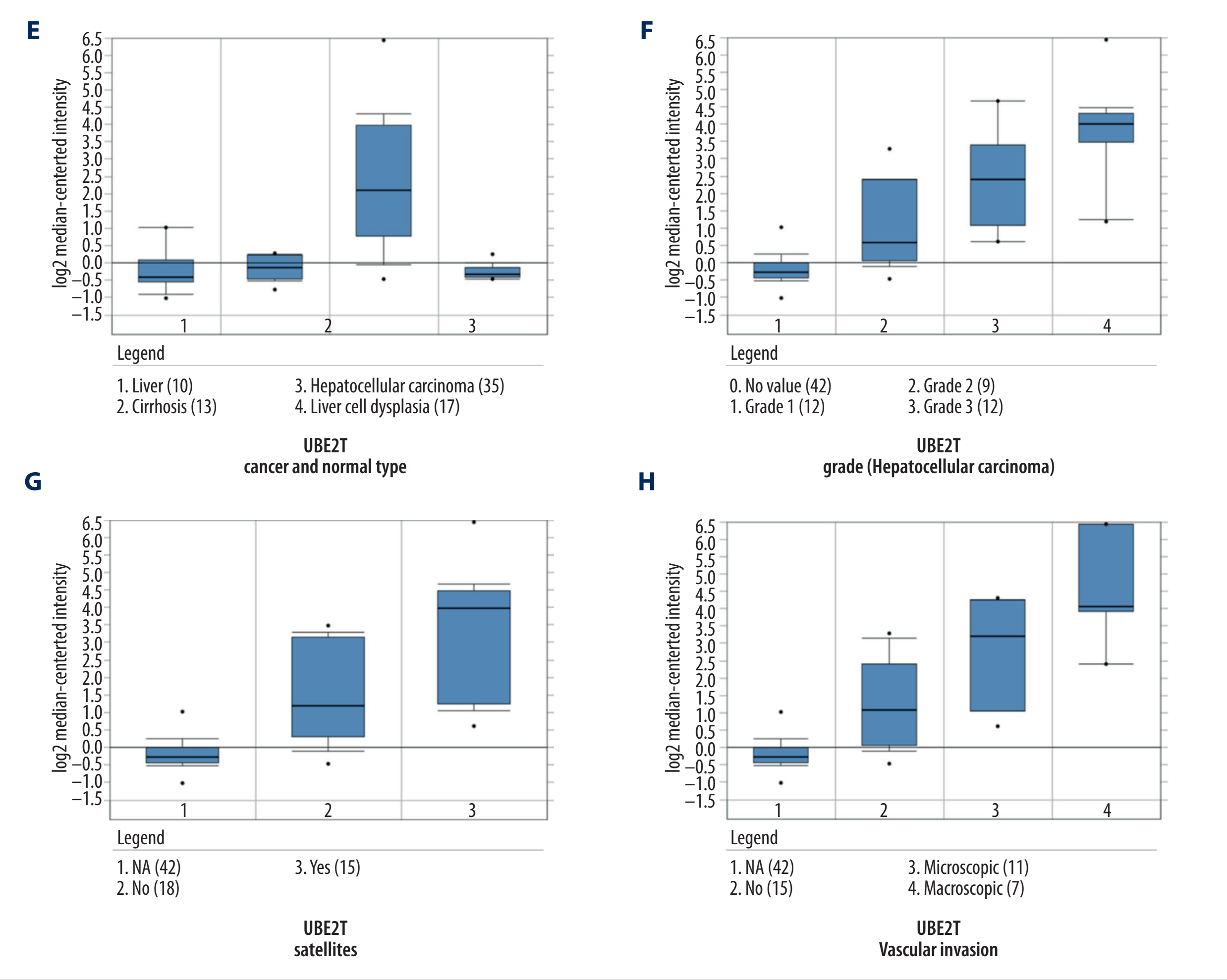


Figure 6. The Box plot of gene expression. The relationships between UBE2T and (**A**) sample type, (**B**) HCC grade, (**C**) satellite lesions, and (**D**) vascular invasion are shown. The relationships between FBLN5 and (**E**) sample type, (**F**) HCC grade, (**G**) satellite lesions, and (**H**) vascular invasion are shown.

regulates the cell cycle and thus promotes the development of HCC, ensuring the principal role of the UBE2T gene in the occurrence and development of HCC [24]. In our study, the expression level of UBE2T in HCC tissue was significantly higher than that in normal liver tissue, and the high expression of UBE2T was involved in the poor prognosis of patients with HCC. Ubiquitin signaling is a fundamental eukaryotic regulatory system, controlling diverse cellular functions, and once there are mutations or impairment of the E2 genes, severe disease states can occur [21]. Various studies reported that UBE2T influences tumors through the Fanconi anemia pathway [25,26].

This study has limitations. We have not conducted further experimental verification of the UBE2T gene at the cellular and molecular level; therefore, further research should be done to identify the entire mechanism of UBE2T's biological effects.

Conclusions

We obtained 296 DEGs in HCC and normal liver tissues through bioinformatic analysis, from which the independent predictor UBE2T was screened out. We determined that UBE2T may be a potential treatment target and prognostic marker for HCC.

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