Comprehensive Analysis of the Expression and Prognostic Value for Snrp Members in Hepatocellular Carcinoma

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Primary research

Keywords: hepatocellular carcinoma, SNRP members, mRNA expression, prognosis, TCGA

Posted Date: June 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-633291/v1

Abstract

Background Heterogeneity and epigenetic modifications result in a difference in management and prognosis of hepatocellular carcinomas (HCC). The family of small nuclear ribonucleoprotein polypeptides (SNRPs) plays a vital role in tumorigenesis and development. However, the expression and prognosis of these members have been poorly clear. Here, we discussed the expression levels and prognosis of SNRPs.

Methods ONCOMINE, UALCAN, GEPIA, Kaplan-Meier Plotter, cBioPortal, GeneMANIA, STRING, and Metascape databases were used in this study.

Results These results showed that the mRNA level of each member (B, D1, D2, D3, E, F, G) was significantly upregulated compared to normal tissues and was a higher expression in clinical stages of advanced cancer patients, relatively. Survival analysis were considered statistically significant, that is, high mRNA expression of SNRPD1 was associated with worse overall survival (OS), disease-free survival (DFS), progress-free survival (PFS) . And high levels of SNRPB or SNRPE predicted worse DFS or OS, respectively.

Conclusion Collectively, our data revealed that SNRP members' function as an oncogene served as a potential indicator of HCC.

Background

Hepatocellular carcinoma (HCC), the most common of primary liver cancer, remains the high cancer mortality rate globally [1]. HCC, as the highest incidence in China compared to the world, is now the third leading cause of cancer-related death and the forth commonly diagnosed cancers in China in 2018 [2, 3]. Different from other malignancies, obvious heterogeneity greatly affect the treatment and prognosis of HCC. More potential indicators have been identified in the overall management of tumors in clinical practice.

Splicing process is accurate by the spliceosome to ensure stability and normalization [4]. Smith (Sm) protein plays a decisive role to maintain the small nuclear ribonucleic acid (snRNA) integrity to avoid nucleases and the downstream RNA processing steps [5]. It is one of crucial mechanism of Sm protein that the formation of heterodimeric (SmD1-SmD2 and SmB-SmD3) or heterotrimeric (SmE-SmF-SmG) subcomplexes [6]. Small nuclear ribonucleoprotein polypeptides (SNRP) B, D1, D2, D3, E, F, G genes are the core components of spliceosomal small nuclear ribonucleoproteins (snRNPs) and form a 7-member ring/Sm-core-complex which is precursors of both the major and minor spliceosome [6] to ensure RNA stability [5]. SNRP members have attracted value attention on these complementary roles in tumor initiation and metastasis [7].

The increasing evidence showed the indispensable role of the splicing components in the initiation, angiogenesis, apoptosis, and invasion in cancers [7–10]. Relevant researches [11–15] had reported the difference of expression and clinical value of a single SNRP member in different types of cancers. The function of SNRPB as an oncogene served as a potential prognostic factor in HCC [11]. Another research [12] displayed the mRNA expression of SNRPB might be a potent therapeutic target in cervical cancer by interfering with the alternaration of the p53 pathway. Besides, the high level of SNRPD1 was identifed as a predictive biomarker for tumorigenesis and poor prognosis of lung adenocarcinoma and ovarian cancer [13, 14]. Even, siRNA depletion of SNRPE or SNRPD1, which contributed to cell death by autophagy, led to a marked reduction of cell viability in breast, lung, and melanoma cancer cell lines [15]. In short, current studies [11–15] presented the differential expression of a single SNRP in a tumor, however, few studies concentrate on the expression and prognostic values of the family of Sm core complex (B, D1, D2, D3, E, F and G) in HCC patients.

In our study, we performed comprehensively the expression and prognosis of SNRP family in HCC patients. In addition, we also analyzed the interaction network, genetic alteration, and functional enrichment based on the several databsets.

Methods

The study has been permitted by the Institutional Review Board of Peking University International Hospital. All the data was derived from the online databases, so it could be confirmed that all written informed consent had already been obtained.

ONCOMINE Database

Oncomine (https://www.Oncomine.org) is a publicly accessible online cancer analysis database to compute gene expression signatures, clusters and gene-set modules, automatically extracting biological insights from datasets [16]. We analyzed the transcriptional levels of each SNRP member in HCC and their corresponding normal tissues.

UALCAN

UALCAN (http://ualcan.path.uab.edu/) is an user-friendly, and interactive web resource for analyzing cancer based on TCGA from 31 cancer types [17]. In our study, it was utilized to analyze the expression levels of tumor and normal tissues to further verify differences. Student's *t*-test was used to generate a *p*-value and the *p*-value cutoff was 0.05.

GEPIA

Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/), is a newly web server to offer customizable functions such as tumor/normal differential expression analysis, profiling according to cancer types or pathological stages, patient survival analysis, similar gene detection, correlation analysis, and dimensionality reduction analysis based on TCGA and Genotype-tissue Expression (GTE) data [18]. The expression of SNRP members and the tumor stages of HCC were analyzed.

Kaplan–Meier Plotter

The Kaplan-Meier (KM) Plotter (http://kmplot.com/analysis/) includes the data of patients on survival in 21 cancer types [19]. The prognostic value of the SNRP members mRNA expression based on median values in HCC was evaluated using the KM plotter with the hazard ratio (HR) with 95% confidence intervals (CI), logrank *p*-value and median overall survival (OS), disease-free survival (DFS), progress-free survival (PFS) in low and high expression groups. It was considered to be statically different when a *p*-value was <0.05.

cBioPortal

cBioPortal for Cancer Genomics (http://www.cbioportal.org/) is an open web tool for interactive exploration of multiple cancer genomic datasets [20]. SNRPs genetic alteration frequency, and the association between alterations and survival outcome in HCC were assessed.

GeneMANIA and STRING

GeneMANIA (http://genemania.org) is an online tool for predicting genes and gene sets [21]. It covered 2277 association networks containing 597 million interactions mapped to 163 k genes from 9 organisms [21]. In this study, GeneMANIA was used to describe the genes network of SNRP members and neighbouring genes into network diagram. STRING (https://string-dborg/) is a database that predicted for interactions networks between proteins and proteins (PPI) [22]. It was applied to perform reciprocities among the PPI network of SNRP members co-expressed genes, and the species were set to Homo sapiens. The relations of expression level for SNRPs at the gene and protein were identified.

Metascape

Metascape (http://metascape.org), is a online website focusing on gene function and enrichment pathway analysis [23]. In this study, the pathway and enrichment of SNRPs and the neighboring genes were analyzed in Metascape.

Results

Differential expression of SNRP members in patients with HCC

Firstly, The genes of SNRP members were determined to be located on definite genomic sites [24, 25] (Table 1). We used Oncomine database [16] to analyze the transcriptional levels of SNRP members in various cancer types and corresponding normal tissues (Fig. 1). The result showed that there were a total of 26, 32, 22, 12, 39, 15 and 23 significant unique analyses for SNRPB, SNRPD1, SNRPD2, SNRPD3, SNRPE, SNRPF and SNRPG, respectively. In tumor tissues, SNRPB was significantly increased in tumor tissues,

especially in breast, bladder, cervical, colorectal, gastric, head and neck, kidney, and liver cancers. Additionally, a dataset of SNRPB illustrated downregulation in breast cancer. Compared to normal tissues, SNRPD1, D2, E showed high mRNA levels in most tumor tissues but were downregulated in brain and CNS cancer, breast cancer and esophageal cancer, respectively. On the contrary, there were few cancer types in high levels of SNRPD3. For SNRPF, G datasets also showed increased expression in varying cancers.

Table 1
The chromosomal locations of SNRP members

SNRP familys	SNRPB	SNRPD1	SNRPD2	SNRPD3	SNRPE	SNRPF	SNRPG
Chromosomal location	20p13	18q11.2	19q13.2	22q11.23	1q32	12q32.1	2p13.3

The results from Oncomine[16] described that the transcription levels of SNRPB, D1, D2 were significantly higher in HCC tissues in two datasets, respectively [24, 26]. Conversely, SNRPD3, F, G was no datasets to analysis the expression. For SNRPE mRNA levels, there was upregulated in three data analysis of TCGA database [24–26]. All *p*-values with the results for statistically significance were summarized in Fig. 1 and Table 2.

Table 2
Differential expression analyses of SNRP family in transcription level in hepatocellular carcinoma (ONCOMINE).

	Types of cancer *vs.* normal	Fold change	*p*-value	t-test	References
SNRPB	Hepatocellular carcinoma vs. normal	2.315	4.23E-75	22.843	Roessler et al., 2010
	Hepatocellular carcinoma vs. normal	2.338	1.12E-6	5.744	Roessler et al., 2010
SNRPD1	Hepatocellular carcinoma vs. normal	3.270	2.55E-97	27.765	Roessler et al., 2010
	Hepatocellular carcinoma vs. normal	2.880	7.91E-9	7.287	Roessler et al., 2010
SNRPD2	Hepatocellular carcinoma vs. normal	2.160	4.05E-82	24.017	Roessler et al., 2010
	Hepatocellular carcinoma vs. normal	2.052	5.00E-9	7.882	Roessler et al., 2010
SNRPE	Hepatocellular carcinoma vs. normal	2.971	1.81E-103	28.959	Roessler et al., 2010
	Hepatocellular carcinoma vs. normal	2.046	1.10E-25	12.246	Chen et al., 2002
	Hepatocellular carcinoma vs. normal	2.344	2.12E-7	6.554	Roessler et al., 2010

We also compared the transcription levels of SNRPs between HCC and normal tissues by using UALCAN [17] (Fig. 2a-2g). We found that SNRPB, D1, D2, D3, E, F, G were all upregulated in tumor tissues. Besides, we analysed the correlative expression of SNRP members in HCC tissues and determined that SNRPD2 was the highest expression (Fig. 2h). Taken together, our results showed that transcriptional expressions of SNRPB, D1, D2, D3, E, F, G were overexpressed in patients with HCC.

Correlation between mRNA expression and tumor stages of SNRP members in HCC patients

We characterized the correlation between the mRNA expression of SNRP members and cancer stages of patients undergoing HCC using GEPIA [18]. SNRPB, D1, D2, D3, F, and G groups were obviously different in stage I, II, III, and IV, while no difference between SNRPE groups and tumor stages (Fig. 3). That is, the results above illustrated that mRNA expressions of SNRPB, D1, D2, D3, F, G were appreciably related to patients' cancer stages in HCC, and patients in advanced cancer stages tended to express higher mRNA expression of SNRPB, D1, D2, D3, F, G.

Prognostic value of SNRP members in patients undergoing HCC

By online database analysis of the KM plotter [19], prognostic value of mRNA including OS, DFS, and PFS came under observation in HCC patients. It could be found that, patients were grouped into low (black) and high (red) risk based on respective cutoff value (Fig. 4 and Table 3). High mRNA levels of SNRPD1, E could get worse OS; however, there was no significant relations between OS and SNRPB, D2, D3, F, G in HCC patients. And high mRNA levels of SNRPB, D1 led to shorter DFS, and not statistical difference in

groups of SNRPD2, D3, E, F, G. Furthermore, only increased SNRPD1 mRNA expression was related to PFS. In short, it was seen that, only mRNA expression of SNRPD1 in high risk was associated with prognosis with OS, DFS and PFS.

Table 3
The prognostic values of SNRP family members in liver and gastric cancer patients (Kaplan–Meier plotter) .

SNRP family	OS				RFS				PFS			
	Cases	HR	95%CI	p	Cases	HR	95%CI	p	Cases	HR	95%CI	p
SNRPB	364	1.38	0.97–1.95	0.07	**316**	**1.52**	**1.09–2.12**	**0.013**	370	1.32	0.98–1.77	0.065
SNRPD1	**364**	**1.45**	**1.02–2.05**	**0.036**	**316**	**1.59**	**1.14–2.21**	**0.0057**	**370**	**1.47**	**1.1–1.97**	**0.0096**
SNRPD2	364	1.16	0.82–1.64	0.4	316	1.38	0.99–1.92	0.053	370	1.3	0.97–1.74	0.082
SNRPD3	364	1.04	0.74–1.47	0.81	316	1.2	0.87–1.67	0.27	370	1.13	0.84–1.51	0.41
SNRPE	**364**	**1.5**	**1.06–2.12**	**0.022**	316	1	0.72–1.39	0.98	370	0.97	0.73–1.31	0.86
SNRPF	364	1.14	0.81–1.61	0.46	316	1.14	0.82–1.58	0.45	370	1.08	0.8–1.44	0.63
SNRPG	364	1.2	0.85–1.69	0.31	316	1.35	0.97–1.88	0.073	370	1.33	0.99–1.79	0.055

Bold values mean p < 0.05

Genetic alterations and correlations of SNRP members in HCC patients

We analyzed gene mutations and interactions of SNRP members by cBioPortal online tool [20] for HCC patients (INSERM Cancer Cell 2014 dataset, MSK Clin Cancer Res 2018 dataset, INSERM Nat Genet 2015 dataset, MSK PLOS One 2018, AMC Hepatology 2014 dataset, RIKEN Nat Genet 2012 dataset, TCGA Firehose Legacy dataset, TCGA PanCancer Atlas dataset). The results in liver hepatocellular carcinoma databases (TCGA PanCancer Atlas dataset) illustrated that the percentages of genetic alterations were 0.27% gene mutation (1/372), 0.53% deep deletion (2/372), 7.53% amplification (28/372) in SNRP members, respectively (Fig. 5a). The alteration frequency of SNRPs by using the AMC Hepatology 2014 dataset, TCGA Firehose Legacy dataset, TCGA PanCancer Atlas dataset were analyzed (SNRPB, 0.5%; SNRPD1, 0.3%; SNRPD2, 0.8%; SNRPD3, 0.3%; SNRPE, 5%; SNRPF, 0.2%; SNRPG, 0.2%) (Fig. 5b). Then, we presented the correlations between SNRPs genetic alterations and survival outcome for patients. Unfortunately, we found no correlations between patients with SNRPs genetic alterations and OS, DFS or PFS outcomes, respectively (p = 0.792, 0.0977, 0.662, Fig. 5c-5e). The reason why the SNRPs genetic alterations and prognosis seemed to be no significance might be a result of small sample size in varying researchs' backgrounds and materials.

Interaction of correlated genes and proteins of SNRP members in HCC patients

We stated breifly the correlations among SNRP members at the gene level by GeneMANIA online tool [21] (Fig. 6a). The results demonstrated SNRP members were very close sharing of genetic thresholds. Markedly, relations were noticed in co-localization among SNRPD1, D3, E, F. Additionally, the relations were found among SNRP members in protein-protein interactions. We identified the correlations of SNRP members at the protein expression level using STRING [22] (Fig. 6b).

Functional enrichment analysis of SNRP members in HCC

To see the functions of SNRP members and their neighboring proteins, we used GO and KEGG pathways by Metascape [23]. The result indicated top 8 expand enrichment (Fig. 7a&7b), structutral complexes: Sm core complex; CORUM: SMN1-SIP1-SNRP complex, SMN comlex, U7 snRNA specific; cellular components: plCln-Sm protein complex, telomerase holoenzyme complex; biological progresses: spliceosomal complex assembly; chemical and genetic perturbations: CHIAS RB1 TARGETS LOW SERUM;

immunologic signatures. The top 5 GO enrichment (Fig. 7c&7d) were cellular components: methylosome, plCln-Sm protein complex, U5 snRNP, U7 snRNP; molecular functions: U1 snRNP binding. The top 2 KEGG enrichment (Fig. 7e&7f) were structural complexes: Sm core complex; pathway: systemic lupus erythematosus. Subsequently, we analysed protein-protein interaction enrichment (Fig. 7g), and found that the protein-complex functions mostly involved in intron transcription splicing process.

Discussion

A growing number of researches have illustrated that SNRP members were upregulated in various cancer types and affected the initiation and progression in cancers [7], and particularly SNRPB functioned as an oncogene and served as a potential prognostic factor in HCC [11]. Recent studies [13, 14] showed that SNRPD1 was a predictive biomarker for tumorigenesis and poor prognosis of lung adenocarcinomas and ovarian cancer. In addition, siRNA depletion of SNRPE, D1 led to a reduction of cell viability in breast, lung, and melanoma cancer cell lines [15]. However, SNRPs as a Sm core complex are precursors of both the major and minor spliceosome [6]. We need to study the complex as an intergration to explore different function in SNRP members of HCC tissues. We hypothesized that SNRP members might act as oncopromoters to affect prognosis in HCC, in the members that outstanding units are more suitable for potential studies. Therefore, our study performed a systematic analysis of the transcriptional level and prognostic significance of SNRP members in HCC.

We discussed that the mRNA levels of SNRPB, D1, D2, E were up-regulated in HCC tissues compared to normal tissues and no positive results in high levels of SNRPD3, F, G by ONCOMINE [16], whereas, high expression of SNRPB, D1, D2, D3, E, F, G was found in primary tumors using UALCAN [17]. The two inconsistent results may be mainly due to the diversity of the background and materials of such abundant researches. The protein encoded by SNRPB was, one of nuclear proteins, found among U1, U2, U4, U6, and U5 snRNPs which affected pre-mRNA splicing and might play a important role in snRNP combination [24]. Peng NF and his colleagues [11] showed that the expression of SNRPB was increased in HCC tissues. Also, higher expression was significantly associated with higher pathological grade, vascular invasion, serum alpha-fetoprotein level, tumor metastasis, and worse DFS and OS. In our study, we found high expression was significantly correlated with patients' advanced cancer stages. What was more, higher mRNA expression of SNRPB got better DFS yet OS and PFS irrelevantly. These were similar to the findings of Peng et al.'s studies. The gene of SNRPD1 encoded snRNP [24]. The studies [13, 14] reported that a free-scale gene coexpression network to assess the relations between multiple-gene datasets and patients' clinical characteristics, then comfirmed predictive factors by weighted gene coexpression network analysis (WGCNA). The mentioned studies indicated that the mRNA expression and the protein of SNRPD1, as one of predictive biomarkers for tumorigenesis and poor prognosis, had strong specifcity and sensitivity to identify tumor lesions from normal tissues. In our report, we found mRNA expression of SNRPD1 was high expression in HCC tissues and led to reduced OS, DFS and PFS. These results were similar to previous studies. Furthermore, SNRPD1 was firstly reported in HCC patients systematacially by several online databases. The protein encoded by SNRPD2, D3 also belonged to the snRNP core proteins [26]. It was proved to involve in pre-mRNA splicing and snRNP biogenesis. There were few studies on SNRPD2, D3 association, because SNRPD1-SNRPD2 or SNRPB-SNRPD3 preferently form heterodimeric subcomplexes before the formation of Sm complex [6]. We revealed that the mRNA expression of SNRPD2, D3 was up-regulated in liver cancer and was related to cancer stages. However, there was no correlation between abnormal levels of SNRPD2, D3 and prognosis of HCC. This suggested that SNRPD2, D3 were high expression in tumor tissues, but were not suitable to be studied as potential prognostic indicators. Likewise SNRPD2, D3 heterodimeric subcomplexes, SNRPE, F, G could form heterotrimeric subcomplex for cooperating with other SNRP members to form a 7-member ring structure/complex and to involve in the splicing process [6]. Current study [15] assumed that knockdown for SNRPE obviously led to reduced expression in mTOR pathway and protein levels, which partly explained the SNRPE-based autophagy. According to Blijlevens and co-workers [27], high levels of SNRPG protein in variaty of cancer types presented such positive interaction with cancer initiation, progression and metastasis. The expression of SNRPG in different cancers can be explained by the high levels of the protein, the bug localization of unassembled or misassembled protein [28]. Thus, SNRPG might lead to the initiation and progression of varying cancers [29–33]. We found that SNRPE was high expressed in tumor tissues but not similar results in groups of SNRPF, G from this study by using ONCOMINE [16]. In addition, the mRNA of SNRPE had no correlation with cancers stages and prognostic value in DFS and PFS. The different results compared to previous studies might be the small sample sizes or different cancer types.

In the study, we found positive interactions among SNRPB, D1, D2, D3, E, G and HCC tissues, negative correlation between SNRPDF and HCC tissues. And that, GeneMANIA [21] and STRING [22] analysis showed that the co-expression were closely noticed among SNRPB, D1, D2, D3, E, F, G at the gene level, while correlations were compactly noticed in co-expression at protein level of each SNRP member.

To study the correlations of the genetic alteration, we revealed SNRPs genetic alteration frequency in HCC by using cBioPortal [20]. Also, we studied the protein functional enrichment of the SNRPs by Metascape [23]. Our results indicated that the functions involved in SNRP members might include methylosome, U1, U5, U7 snRNP binding, Sm core complex, etc., and these functions are researched to be involved in cell cycle, signal transduction, angiogenesis, apoptosis, and invasion [8–10,34–39]. The spliceosomal complex is formed from snRNP [40, 41]. Each snRNP (U1, U2, U4, U6, and U5) includes a snRNA intergrated with a set of Sm core complex. The Sm core complex (B, D1, D2, D3, E, F and G) form a 7 ring core structure/complex to encompass RNA. All SNRP proteins have a conserved Sm domain to help to form the Sm core of the snRNPs [5, 42] and thereby determinned pre-mRNA processing [43]. However, further works need to be performed to comfirm these results. These results will help to understand the role and function of SNRP members in HCC development and metastasis.

There were some limitations in our research. Firstly, all the data were analyzed in our study from various online database tools, which could originate from a variety of research backgrounds, foundations and samples, thus accumulated studies in larger samples need to prove our results. Then, no biological experiments, clinical specimens and cases were conducted to verify this study. Next, studies *in vitro* and *in vivo* will be performed to confirm our findings, and may provide some respectable conclusions.

Conclusion

In this study, we systematically analyzed the mRNA expression of SNRP members and prognostic significance in HCC. Besides, we presented the correlations of co-expression and interaction network, genetic alteration and function enrichment of SNRP members. The results update the the conclusion that the high levels of SNRPB, D1, D2, D3, E, F, G were upregulated compared to normal tissues and characterized the worse OS, DFS and PFS in SNRPD1. In conclusion, SNRPD1 could be as a gene promoter and a new prognostic biomarker for HCC. Our findings will provide valuable researches in the near future.

Declarations

Ethics approval and consent to participate: The study has been permitted by the Institutional Review Board of Peking University International Hospital. All the data was derived from the online databases, so it could be confirmed that all written informed consent had already been obtained.

Consent for publication: All authors agreed to publish this manuscript.

Availability of data and materials: The publical databases includes: Oncomine (https://www.Oncomine.org); UALCAN (http://ualcan.path.uab.edu/); Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/

); The Kaplan-Meier (KM) Plotter (http://kmplot.com/analysis/

); cBioPortal for Cancer Genomics (http://www.cbioportal.org/); GeneMANIA (http://genemania.org/

); STRING (https://string-dborg/); Metascape (http://metascape.org/

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Competing interests: No interests.

Funding: Peking University International Hospital Research Funds (No. YN2018QN09)

Authors' contributions: Ziwei G and Jun L developed the idea, designed the research, and performed the data analysis work. Ziwei G drafted the manuscript. Ziwei G and Jun L reviewed the manuscript, read and approved the final manuscript.

Acknowledgements: Not applicable.

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Figures

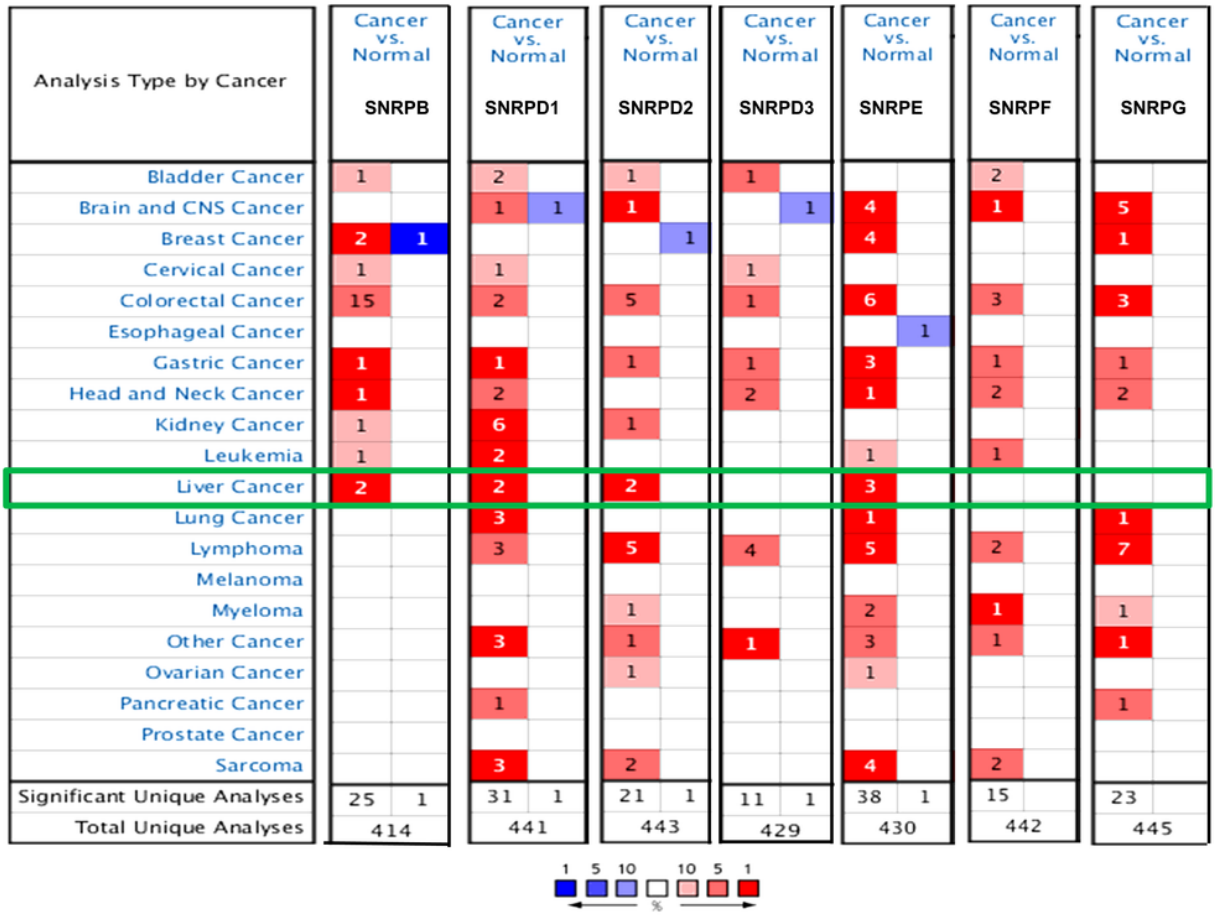

Figure 1

Oncomine analysis of statistically significant mRNA expression levels of SNRPs in different cancers. The differences in expression levels of (up-regulation: red or down-regulated expression: blue) the genes between tumor and normal tissues are summarized. Gene rank is described by the color depth in the cells. It was as following: p-value: 0.01, fold change: 2, gene rank: 10%, data type: mRNA.

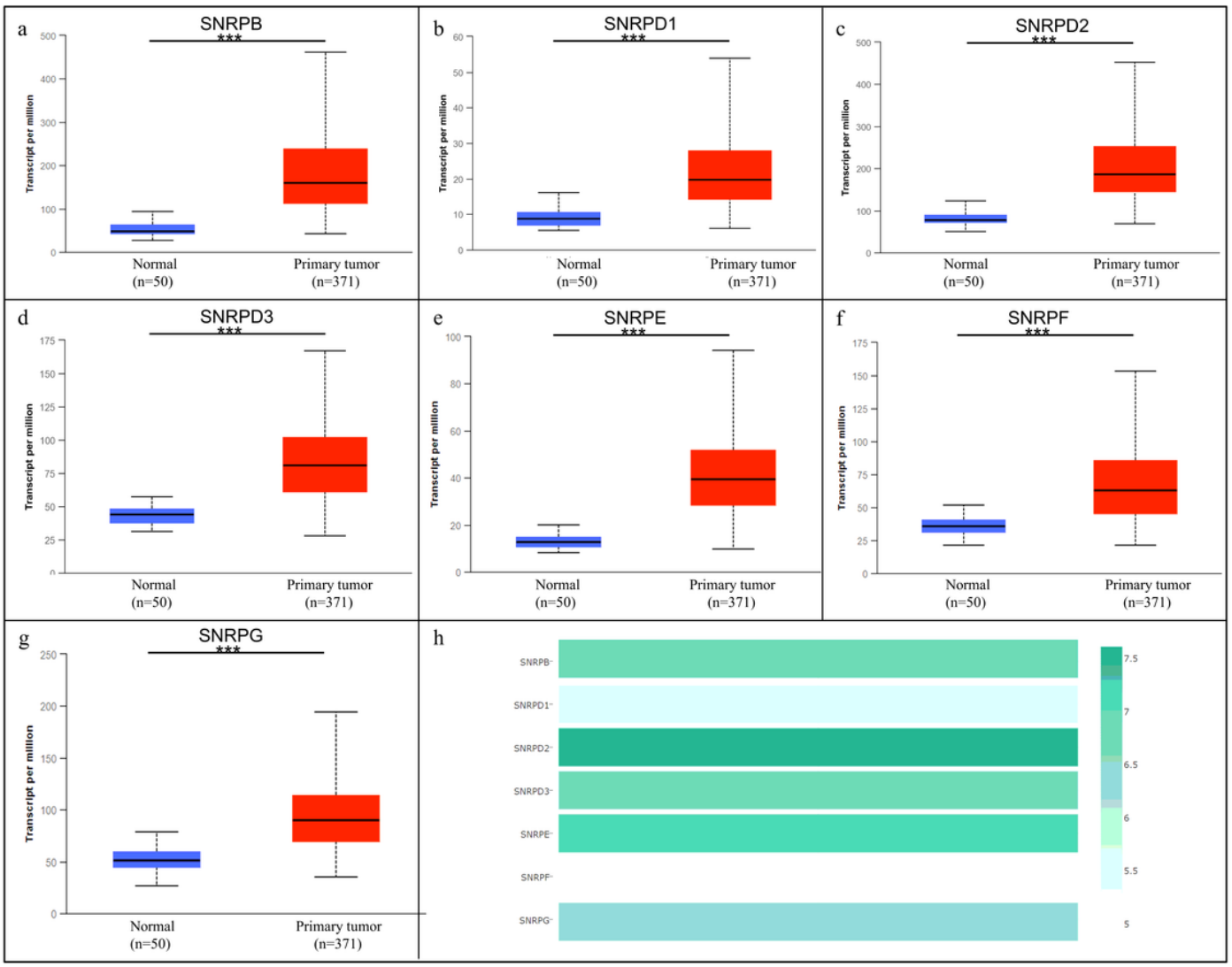

Figure 2

The mRNA expression of various SNRPs in HCC tissues and adjacent liver tissues (UALCAN) and and the relative level of SRNPs in HCC (GEPIA). (a-g) mRNA expressions of SNRPs were found to be over-expressed in HCC tissues compared to normal samples (B/D1/D2/D3/E/F/G). (h) different levels of SNRPs in HCC. ***p < 0.001.

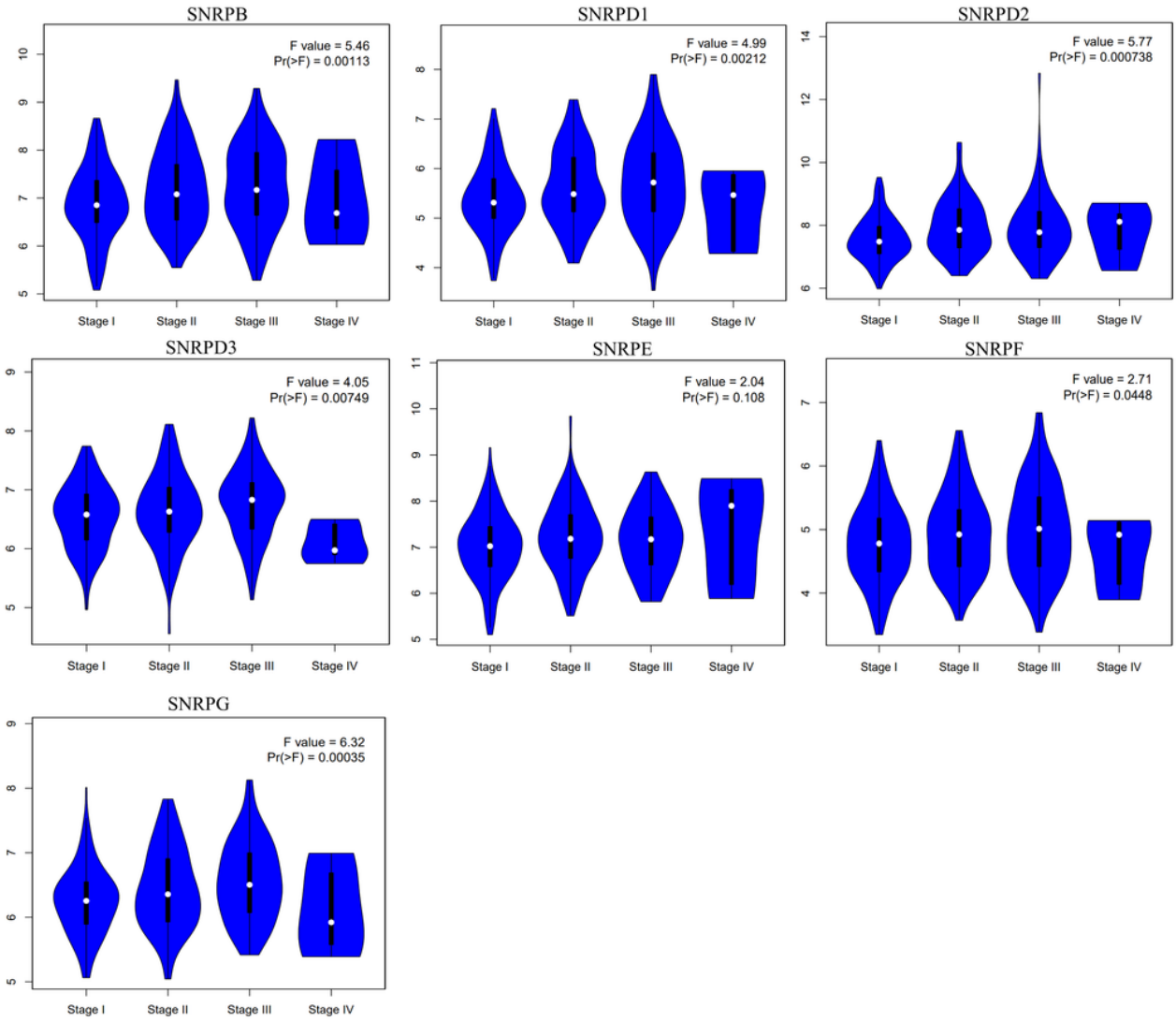

Figure 3

Correlation between mRNA expression and tumor stage of SNRPs in HCC patients (GEPIA). The mRNA expressions of SNRPB/D1/D2/D3/F/G were significantly in connection with patients' cancer stages (B,D1,D2,D3,F,G), while mRNA expressions of SNRPE had not relations with patients' cancer stages (E).

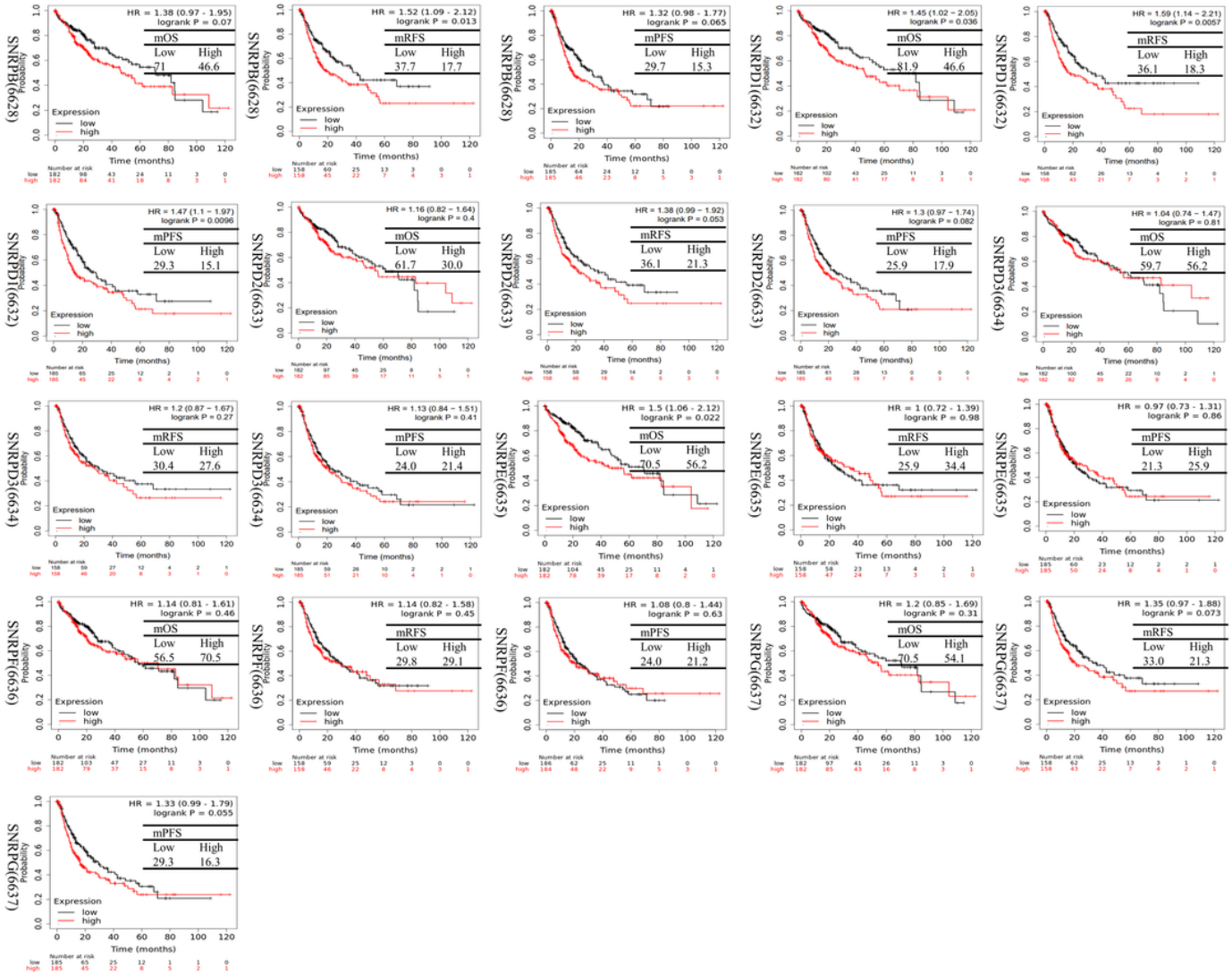

Figure 4

Prognostic value of mRNA expression of relative SNRPs in HCC patients (Kaplan–Meier plotter). The OS, RFS, and PFS survival curves were plotted using the Kaplan–Meier plotter database at p-value of <0.05, comparing patients with high (red) and low (black) SNRPs expression in HCC and distinct median survival in OS, RFS, and PFS. The correlation between prognostic significance and SNRPB, SNRPD1, SNRPD2, SNRPD3, SNRPE, SNRPF, SNRPG protein expression.

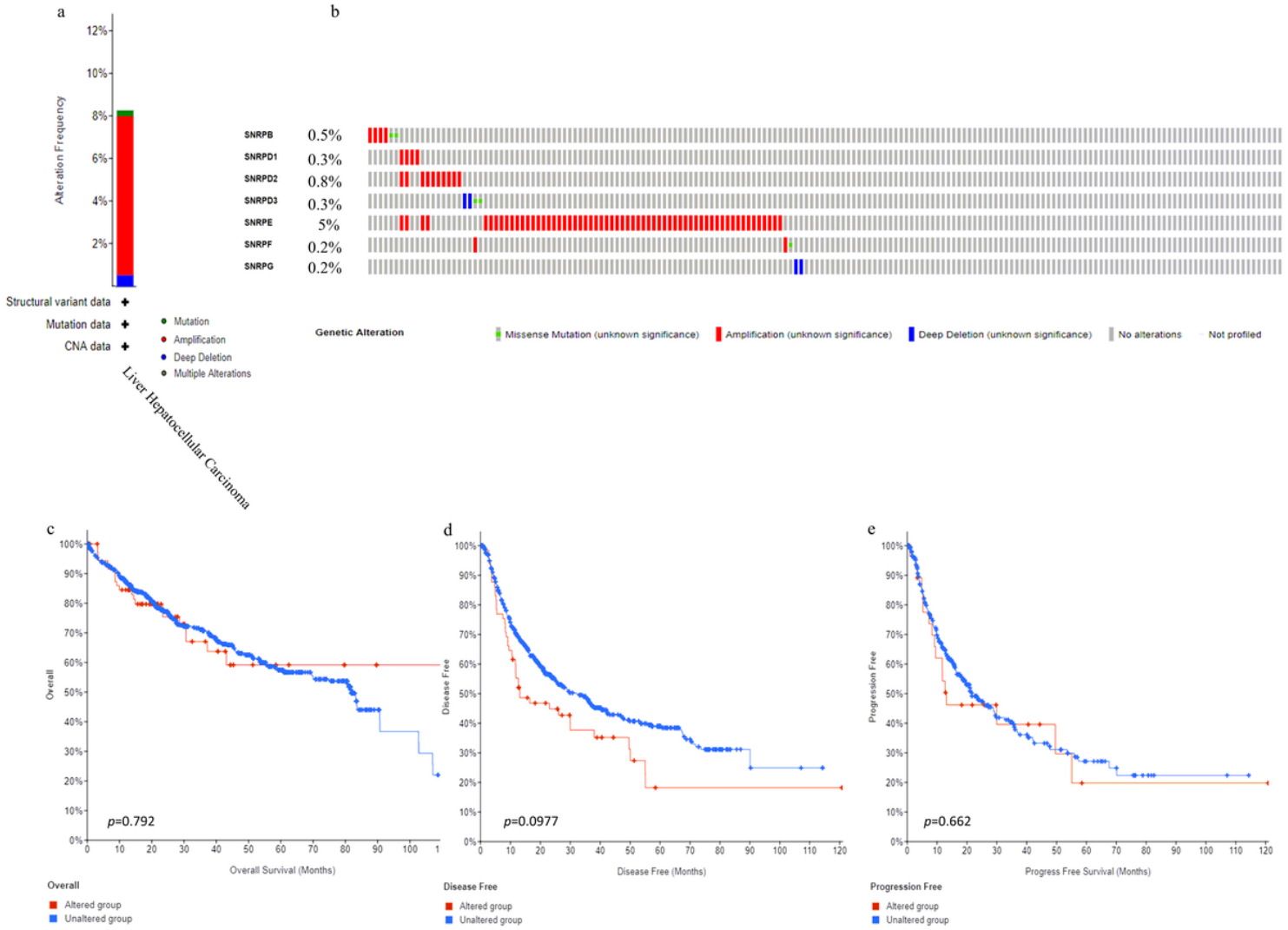

Figure 5

Alteration frequency of SNRPs and neighbor gene network in HCC (cBioPortal). (a) SNRPs genetic alteration in INSERM Cancer Cell 2014 dataset, MSK Clin Cancer Res 2018 dataset, INSERM Nat Genet 2015 dataset, MSK PLOS One 2018, AMC Hepatology 2014 dataset, RIKEN Nat Genet 2012 dataset, TCGA Firehose Legacy dataset, TCGA PanCancer Atlas dataset. (b) Alteration frequency of SNRPs based on the TCGA PanCancer Atlas dataset. (c) Kaplan–Meier plots in OS with/without SNRPs genetic alterations. (d) Kaplan–Meier plots in DFS with/without SNRPs alterations. (e) Kaplan–Meier plots in PFS with/without SNRPs alterations.

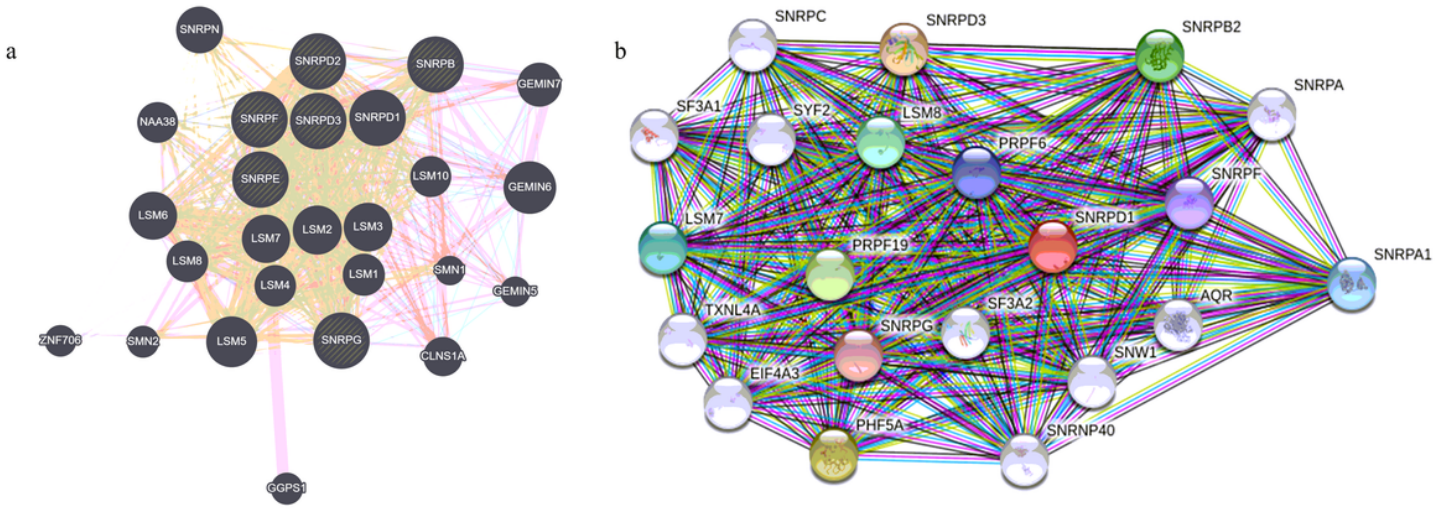

Figure 6

Interaction network of SNRPs at the gene and protein levels in HCC patients. (a) Gene–gene interaction network among SRNPs in the GeneMANIA dataset. (b) Protein–protein interaction network among SNRPs in the STRING dataset.

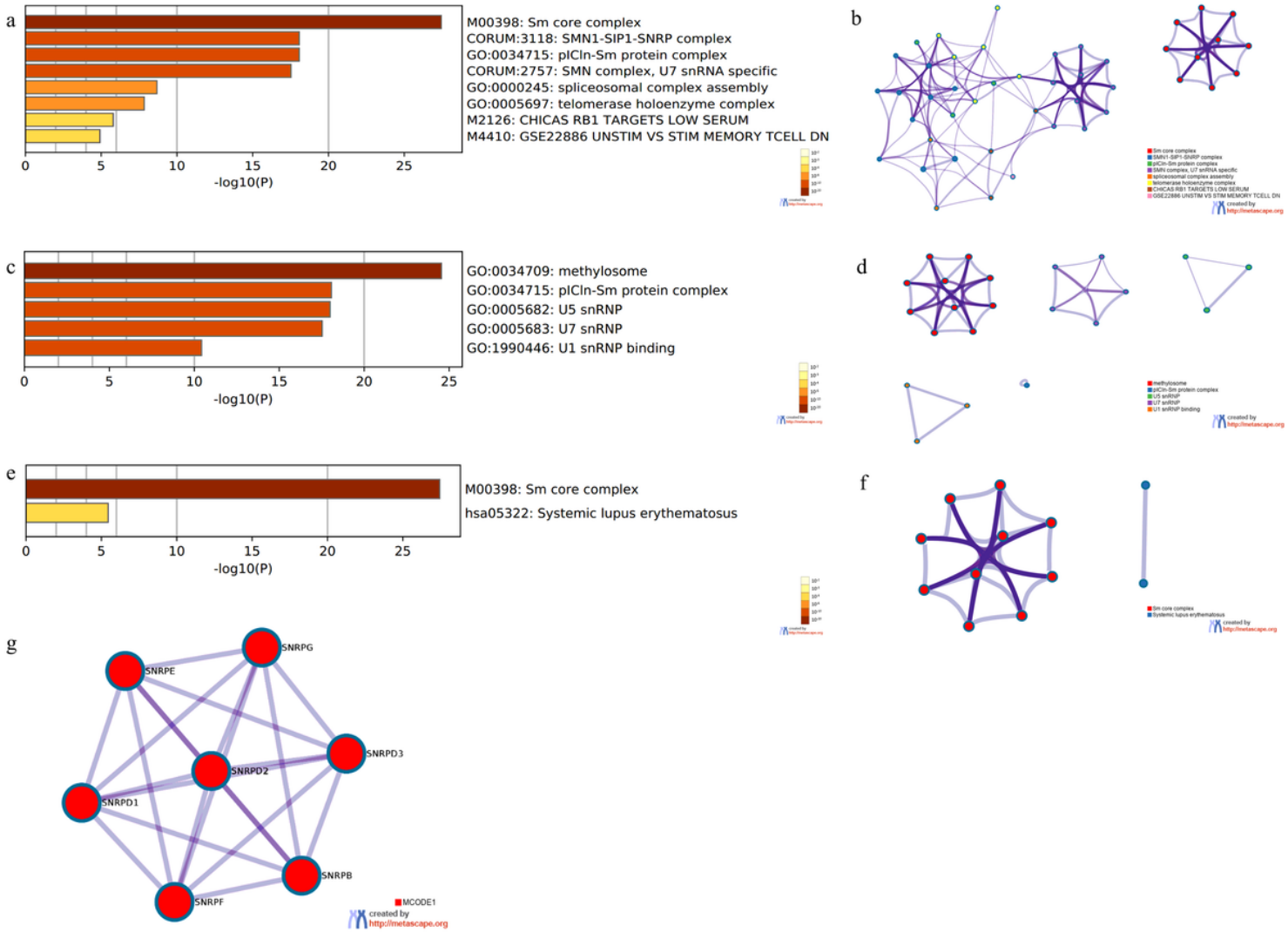

Figure 7

The functions enrichment analysis of SNRPs and neighboring genes in HCC patients. (a) Top 8 expand enrichment. (b) Network of expand enriched terms. (c) Top 5 of Gene Ontology (GO) enrichment. (d) Network of GO enriched terms. (e) Top 2 of Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment. (f) Network of KEGG enriched terms.. (g) Protein–protein interaction (PPI) network.