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ORIGINAL ARTICLE

Long Non-Coding RNA *SNHG6* as a Potential Biomarker for Hepatocellular Carcinoma

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Abstract Long Non-coding RNAs (lncRNAs) refer to all non-protein coding transcripts longer than 200 nucleotides. Their critical roles in different biological pathways have been already well established. Altered expression of lncRNAs can be involved in the cancer initiation and/or progression. Since patients with hepatocellular carcinoma (HCC) are usually diagnosed in late stages, developing diagnostic methods seems to be essential. In this study, the expression levels of different lncRNAs were systematically analysed in different genomic and transcriptome datasets. The analyses showed that *SNHG6* is among the lncRNAs with distinctive dysregulation of expression and copy number variation in HCC tumors compared with normal tissues. The results also suggest that the dysregulation of *SNHG6* is highly cancer type specific. Through co-occurrence analyses, we found that *SNHG6* and its related co-expressed genes on 8q are involved in the structural integrity of ribosome and translation. This comprehensive in silico analysis, provides a resource for investigating *SNHG6* in hepatocellular carcinoma and lays the groundwork for design of next researches.

Keywords Hepatocellular carcinoma · Biomarker · Long noncoding RNA · *SNHG6* · Systematic analysis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide [1]. The viral infection(HBV and HCV), alcoholism, non-alcoholic fatty liver, and some hereditary metabolic diseases are the main recognized risk factors for HCC [2–5]. Since most of the HCC patients are diagnosed at late stages, when medication is no longer effective, the discovery of sensitive and specific biomarkers for early diagnosis and treatment is of great attention [6].

Long non-coding RNAs (lncRNAs) refer to all lengthy functional transcripts which are actively involved in numerous biological processes such as regulation of transcription, translation, protein localization, and function, as well as orchestration of cellular scaffold. Furthermore, lncRNAs can control the cell cycle, differentiation, apoptosis, and DNA repair through the modulation of epigenome [7, 8]. Owing to these functions, it is not surprising if the aberrant expressions of lncRNAs contribute to disease pathogenesis. The altered expression of lncRNAs in different malignancies along with their tissue-specific expression suggests that these long transcripts may be considered as great biomarkers in cancer diagnosis [9–12]. The potential role of

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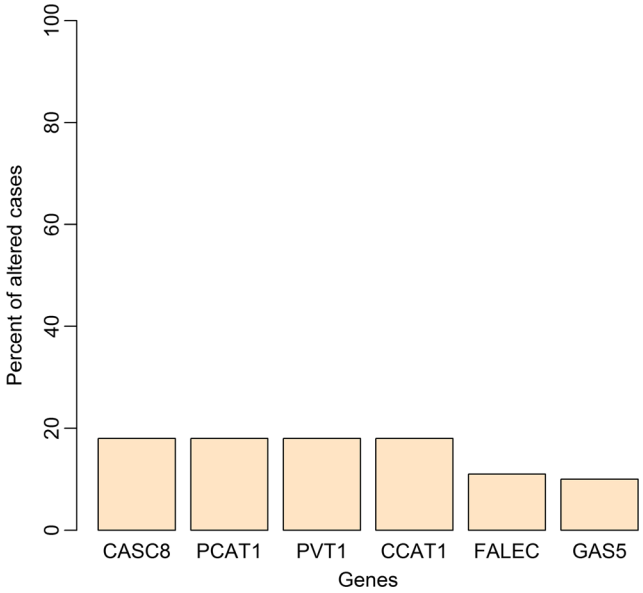


Fig. 1 Genomic alterations (Copy number Variations) of lncRNAs among 373 patients with hepatocellular carcinoma. The chart was drawn for the genes which were altered in more than 10% of the patients with hepatocellular carcinoma. The data obtained from cBioPortal (http://www.cbioportal.org)

lncRNAs in liver malignancies has been recently led into promising novel insights in HCC therapeutic strategies [13, 14]. Therefore, more studies are needed to elucidate the role of lncRNAs in HCC.

In recent decades, systematic analyses of the genomic, transcriptomic, and proteomic datasets have become powerful tools in the discovery and the validation of tumor markers [15]. Due to the lack of enough supporting evidence to associate the lncRNAs with HCC, the present study was aimed to perform a systematic genotranscriptomic meta-analysis of the issue. We tried to screen different genomic and transcriptomic datasets in order to find the potential of lncRNAs as prognostic and diagnostic tools for HCC. The systematic results can help the researchers with further studies on specific lncRNAs in order to develop predictive biomarkers or therapeutic targets. In the current study, we found that *SNHG6, PVT1*, and *GAS5* are potential lncRNAs with a significant role in HCC initiation and progression.

Materials and Methods

The Selection of lncRNAs with High Alteration Frequency in HCC Samples

To investigate the significance of lncRNAs in liver malignancy, we retrieved 189 approved lncRNAs from HGNC (www.genenames.org). All of the genes were interrogated into the cBioPortal database (http://www.cbioportal.org) [16, 17] for geno/transcriptomic analyses. We queried all the samples from TCGA liver hepatocellular carcinoma (TCGA, provisional) with RNA-seq v2 data (n = 373) in our study and considered RNA dysregulation with Z-score threshold: ±2. TCGA data, as one of the major national and international efforts, include the valid comprehensive data derived from large cohorts. Among different HCC data indexed in TCGA, TCGA liver hepatocellular carcinoma constitutes more number of tissues.

The lncRNAs which were altered in more than 10% of the patients were considered as "significant lncRNAs" for further analyses. It should not be forgotten that it was important for us to consider the lncRNAs which were altered at both genomic and transcriptomic levels even if the percent of alteration in patients was near to the threshold of 10%. Regarding to these criteria, these lncRNAs included *SNHG6*, *PVT1,* and *GAS5* due to high levels of alteration in both genomic and transcriptomic levels. By means of the R package, the frequency of each genetic alteration was calculated among the cases carrying at least one alteration for the desired genes. Additionally, the co-occurrence between genetic alterations was considered for all of the three genes.

The Differential Expression of Significant lncRNAs between Tumor and Normal Tissues

TCGA RNA-Seq raw data was extracted in R using the cgdsr extension package (cran.rproject.org/web/packages/cgdsr/) with a threshold of ±2. The data was then presented as Heatmap plot. The selected lncRNAs were examined in several transcriptomic datasets to explore if any significant difference of expression may exist between normal and tumor tissues. The included datasets were Oncomine (http://www.oncomine.org), Gene Expression Atlas [18–20], Gene Expression Omnibus: GEO (http://www.ncbi.nlm.nih.gov/geo), Array express (https://www.ebi.ac.uk/arrayexpress), and UCSC cancer genome browser (https://genome-cancer.ucsc.edu) [21–26] databases. The results with Fold change > 1.5 and P-value < 0.01 between tumor and normal tissues were considered as significant. In the next step, we also considered any correlation for any pair of genes of interest using Pearson's method. In strong positive correlation, the linear correlation coefficient (r) is close to +1; while in strong negative, the correlation is close to −1.

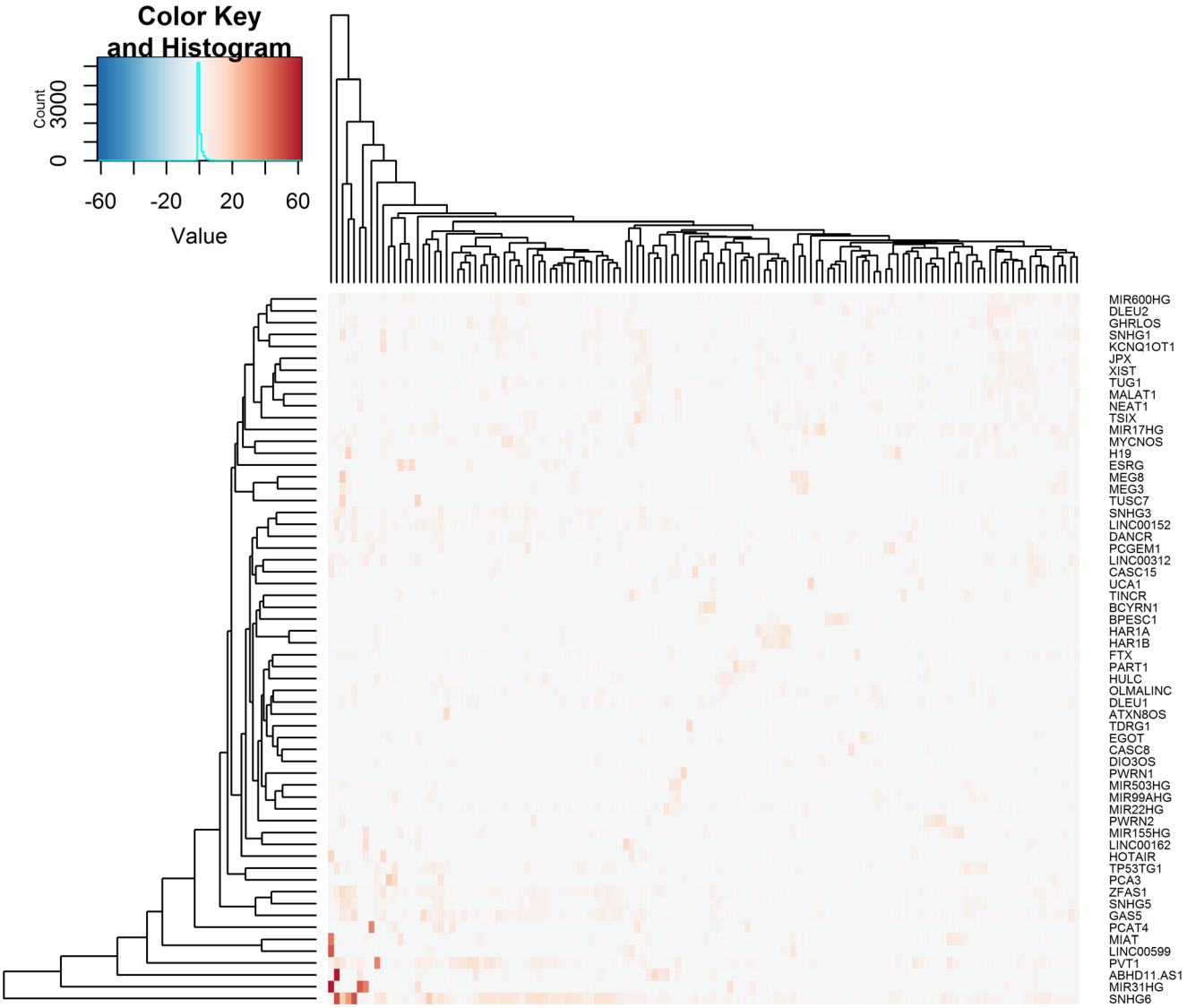


Fig. 2 Altered expression of different lncRNAs in hepatocellular carcinoma with Z score > ±2. Sixty out of 189 genes were altered among 373 patients with HCC. The analysis is done by the R statistical software. The raw data was extracted from cBioPortal (http://www.cbioportal.org)

The Association between lncRNAs and the Clinicopathologic Parameters of Hepatocellular Carcinoma

Using the UCSC Cancer Genome Browser, the association of different lncRNAs with clinicopathologic parameters (the histological type, pathologically *TNM* staging, and grade) was evaluated using Student's *t*-test. Besides, the effect of gene expression dysregulation on the patient's survival was evaluated using the Kaplan-Meier analysis in cBioPortal. The Log-Rank Test *P*-Value <0.05 was considered as statistically significant.

The Comparison of the HCC Profile of lncRNAs with the Profiles of Other Cancers

In order to evaluate whether significant lncRNAs follow an HCC-specific manner, we examined the geno/transcriptomic alteration of these genes in all of the tumor collections of cBioPortal. Thirty cancers with available RNA-seq data were included at this stage, and the expression data corresponding to genes were extracted. The raw data was filtered based on the z-score > +2 and <−2. The mean of the expression levels was calculated using R and the data was presented as heatmaps.

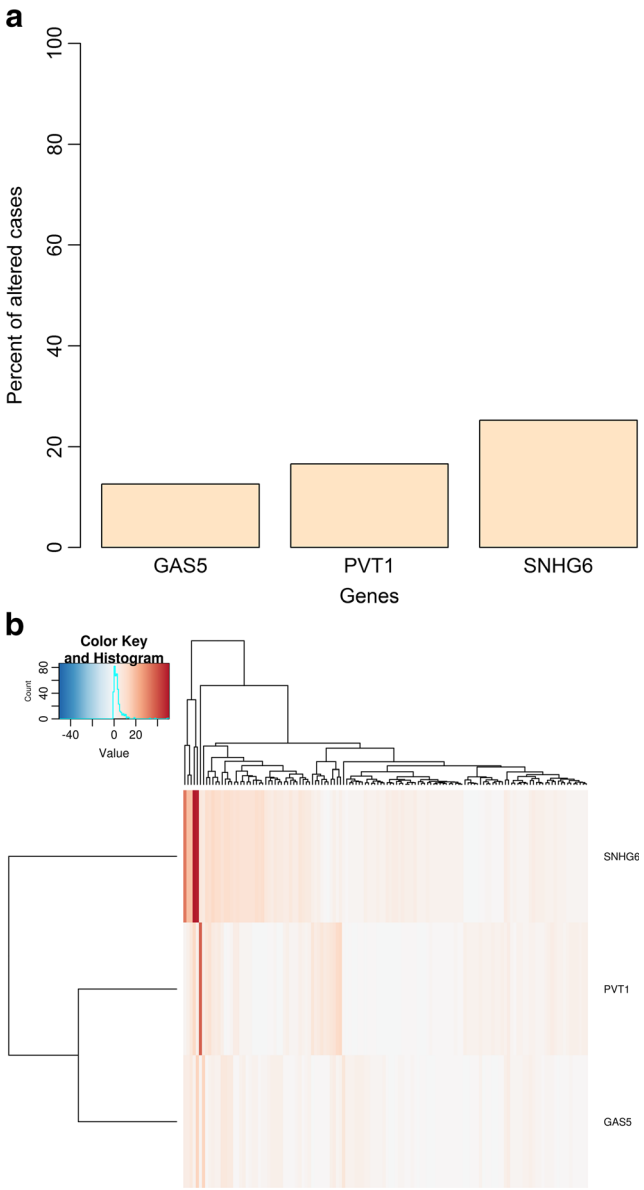


Fig. 3 The expression levels of *SNHG6, PVT1,* and *GAS5* among 373 patients the patients with hepatocellular carcinoma. **a.** The chart shows the genes which were altered in more than 10% of the patients with hepatocellular carcinoma. **b.** The expression levels of *SNHG6*, *PVT1,* and *GAS5* among 130 patients with Z score > ±2 was presented as heatmap. These patients have at least on alteration in *SNHG6*, *PVT1,* and *GAS5* lncRNAs. The analysis is done by the R statistical software. The raw data was extracted from cBioPortal (http://www.cbioportal.org)

The Functional Analysis of Selected lncRNAs

Among 373 patients with hepatocellular carcinoma, 130 cases showed alterations for *SNHG6*, *PVT1,* and *GAS5*. Among these 130 cases, we evaluated the genes which were co-expressed with significant lncRNAs using Pearson's correlation analysis. Then, the genes with correlation value > 0.70 were uploaded into the GSEA dataset (http://www.broadinstitute.org) to compute the gene set overlaps matrix based on the GO molecular function. Using the cBioPortal database, we also drew a network to find any potential contribution of the genes which were co-expressed with significant lncRNAs.

Statistical Analysis

All of the analyses including the t-test, heatmap, and correlation analysis were done by the R statistical software and SPSS. In our analysis, the *P*-values less than 0.05 were considered significant.

Results

Significant lncRNAs with a Potential Role in Liver Malignancies

Although we could not find any mutations in lncRNAs of interest, 67 out of the 189 lncRNAs were found to be altered in their copy numbers at least in one patient. LncRNAs, including *CASC8, PCAT1, PVT1, CCAT1, FALEC,* and *GAS5*, were the genes whose copy numbers were altered in more than 10% of the patients (Fig. 1). We also found 60 lncRNAs with altered expression patterns at least in 1% of patients (Fig. 2). However, *SNHG6*, *PVT1,* and *GAS5* were the lncRNAs with the highest RNA dysregulation among the 373 samples of HCC (Fig. 3). For further analysis, we focused on *SNHG6*, *PVT1,* and *GAS5* in which both CNVs (Copy number variations) and RNA dysregulation were higher than other lncRNAs. It is necessary to mentioned that we granted an exception for selection of SNHG6 due to some reasons; 1) among 189 lncRNAs, *SNHG6* allocated the highest score in total alteration regardless of whether alterations occur at ge-

Table 1 The frequency of genetic alterations (CNV) of *SNHG6*, *PVT1* and *GAS5* among 373 cases of hepatocellular carcinoma using R analysis

GAS5		SNHG6		PVT1		
Not altered	Duplication	Not altered	Duplication	Not altered	Duplication	Homodeletion
337	36	340	33	307	65	1

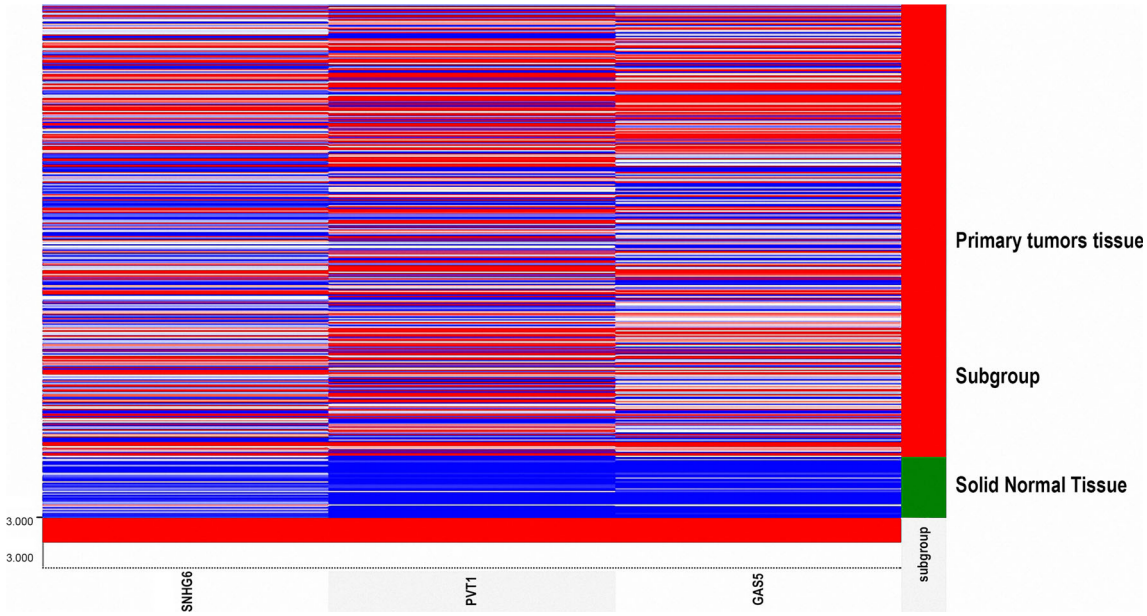


Fig. 4 TCGA hepatocellular carcinoma (LIHC) gene expression by RNA seq (IlluminaHiseq $N = 423$) and the differential expression of *SNHG6*, *PVT1,* and *GAS5*betweenthe primary tumor and the solid normal tissue. The statistical track displayed under the genomic heatmap shows the logarithmic plot of *p*-values for each genomic position, where the center line indicates a *p*-value of 1. The primary tumor tissue and the solid normal tissue subgroups were illustrated in red and green respectively. The student *t*-Test was performed to analyze the differentially expressed genes between the tumor cells and the normal ones, and $P < 0.05$ was considered statistically significant. The red bar indicates that the expression levels of genes are significantly higher in cancerous cells than normal ones. The data was extracted from Cancer Genome Browser

nomic or transcriptomic level. 2) among 189 lncRNAs, *SNHG6* allocated the highest score at transcriptomic level so although *SNHG6* apportioned the 9% alteration among the patients at genomic level but due to the two previous reasons, we decided to continue our analysis on it as well as *PVT1* and *GAS5*. On the other hand, when we compared the data at both level of genomic and transcriptomic, *SNHG6, PVT1* and *GAS5* were common in data of two groups.

Regarding to your true comments, we explain clearly the reason of SNHG6 selection (in spite of 9% alteration) in the manuscript.

In our results, around 35% of the cases ($n = 130$) had an RNA dysregulation in at least one gene, and *SNHG6* was altered in more cases than *PVT1* and *GAS5*. We called these patients "target samples" in the next steps. The co-occurrence of different genetic alterations for each paired loci was calculated among this group (Table 1).

SNHG6, *PVT1,* and *GAS5* are Differentially Expressed between Tumor and Normal Tissues

According to the Cancer Genome Browser, *SNHG6*, *PVT1,* and *GAS5* are significantly upregulated in hepatocellular carcinoma in comparison with the normal counterparts (*P*-value = 0.001) (Fig. 4). Furthermore, the oncomine datasets confirmed the differential expression of these lncRNAs between cancerous and normal tissues (Table 2).

The Overexpression of *SNHG6* is a Novel Indicator of Reduced Survival in Patients with Hepatocellular Carcinoma

We found that the over-expression of *SNHG6* in hepatocellular carcinoma was nearly associated with reduced survival to a median of 19.74 months in *SNHG6* over-

Table 2 The differential expression of lncRNAs*SNHG6, PVT1* and *GAS5* between normal and tumour samples (Oncomine, the gene expression atlas, and GEO)

lncRNA	Fold change	*P* value	Down-regulated	Up-regulated	Experiment type	Ref
SNHG6	1.983	3.43E-5	Non-Tumour Tissue ($n = 10$)	HCC ($n = 35$)	Human Genome U133 Plus 2.0 Array	[27]
PVT1	4.258	1.88E-11	Non-Tumour Tissue ($n = 10$)	HCC ($n = 35$)	Human Genome U133 Plus 2.0 Array	[27]
GAS5	2.69	2.3E-8	Non-Tumour Tissue ($n = 10$)	HCC ($n = 35$)	Human Genome U133 Plus 2.0 Array	[27]

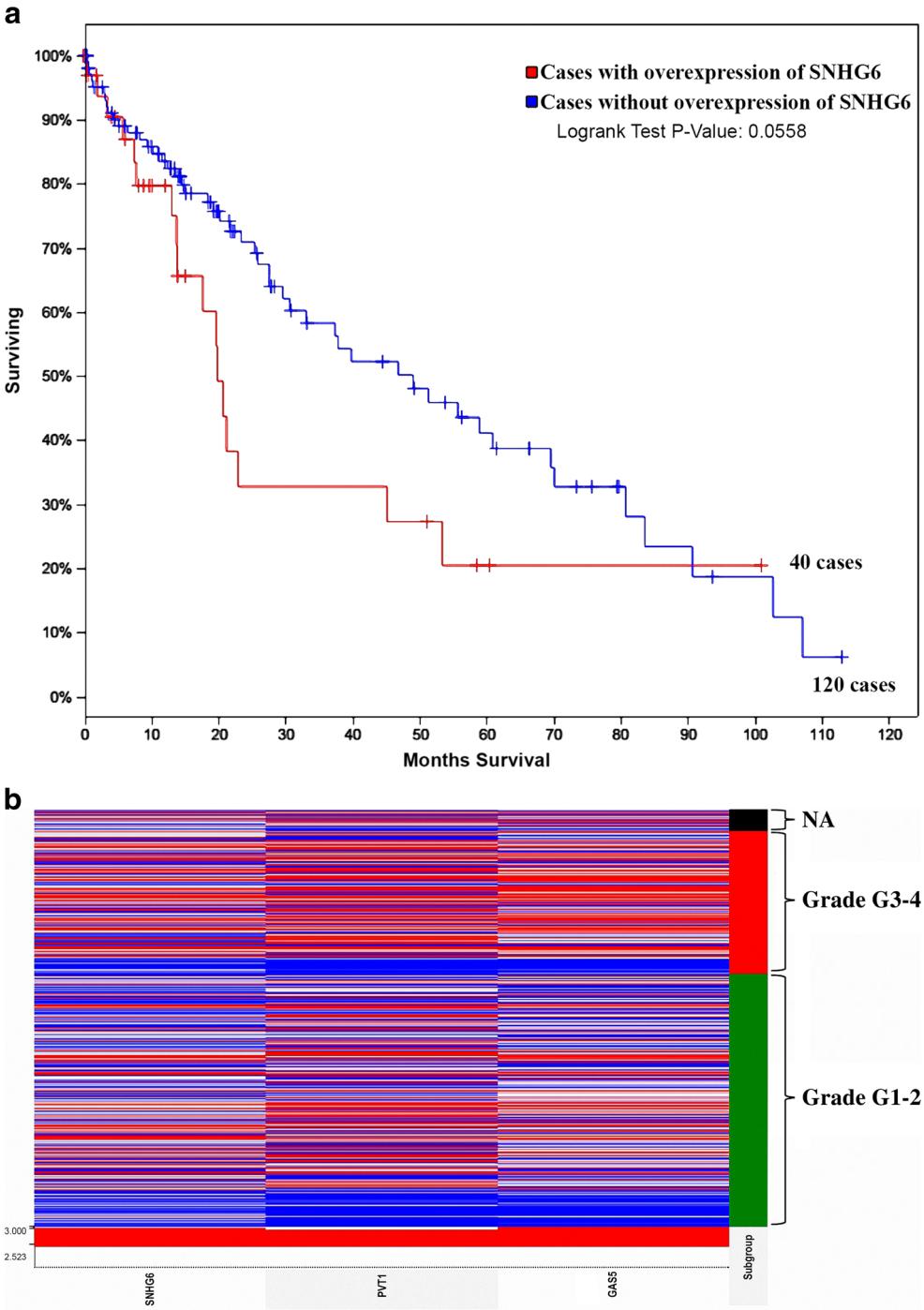
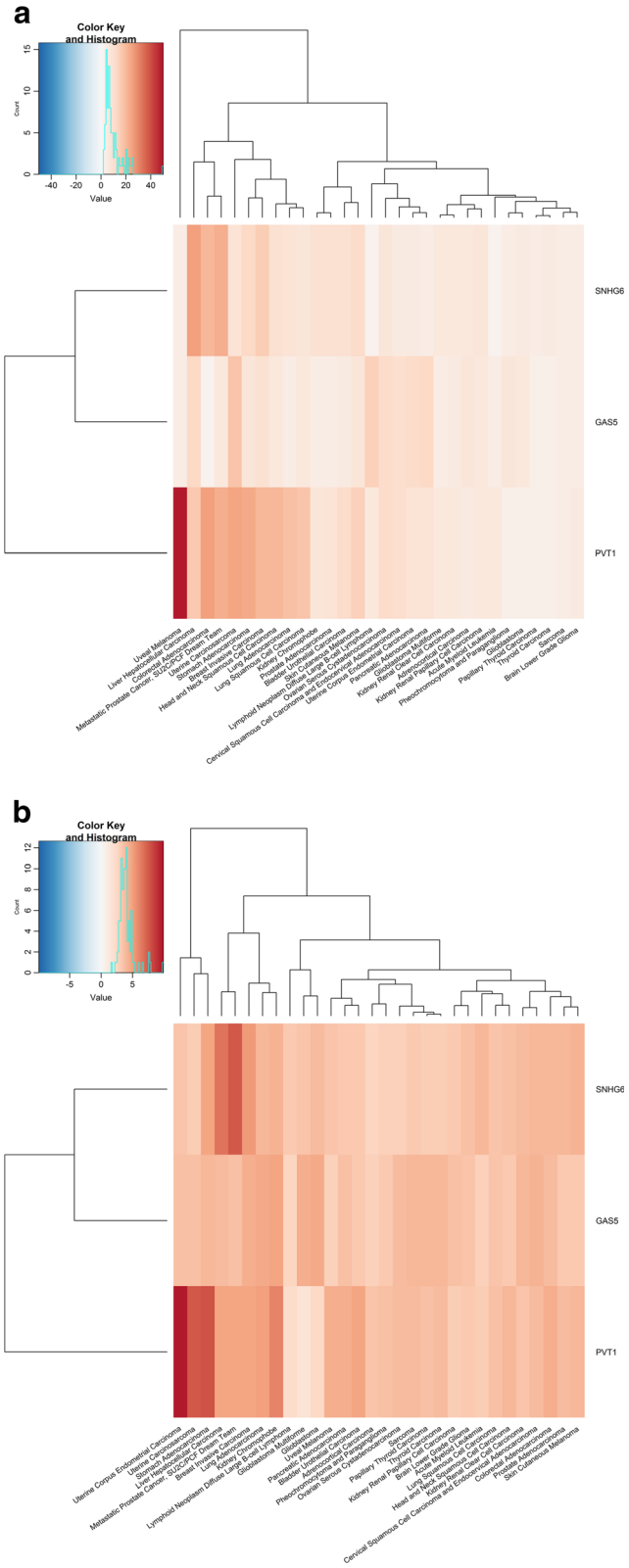


Fig. 5 Study of the clinical association of *SNHG6*, *PVT1,* and *GAS5* with the clinicopathologic parameters of hepatocellular carcinoma. **a** Kaplan-Meier plots comparing the overall survival in cases with or without *SNHG6* over-expression. The data was recruited from cBioPortal. **b** The association of expression of lncRNAs with the histological grade of HCC; we divided tissues based on their grade (G1–2 and G3–4 as green and red bars respectively), which shown in right column. The statistical track which is displayed under the genomic heatmap shows the logarithmic plot of *p*-values for each lncRNA, where the centreline indicates a *p*-value of 1. The bar above the line indicates that the red subgroup (G3–4) is greater than the green subgroup (*P*-value < 0.05). The patients with no pathological data (NA) were omitted from the analysis. The data was extracted from Cancer Genome Browser, TCGA LIHC gene expression by RNA seq (IlluminaHiseq *n* = 423)

expressing cases, compared with the period of over 48.95 months for the remaining cases (Logrank Test *P*-Value: 0.0558) (Fig. 5a). Although the value was not significant for *PVT1* and *GAS5*, studying the clinical associations of these lncRNAs with clinicopathologic parameters of HCC represented that all the three genes (*SNHG6*, *PVT1* and *GAS5)* were significantly expressed in high-grade HCC samples compared with low-grade tissues (*P*-value = 0.001) (Fig. 5b).

The Association of *SNHG6*, *PVT1,* and *GAS5* with the Progression of Other Human Cancers

We evaluated the transcriptomic alterations of these genes among different human tumors. We considered the genes at two levels; first, their frequency among the patients and second, their related expression among them. In comparison with *PVT1* and *GAS5*, *SNHG6* allocated a good value to itself at both levels. Therefore, *SNHG6* seems to be a stronger



◀ **Fig. 6** The genetic alterations of *SNHG6*, *PVT1,* and *GAS5* among different human cancers. **a** The frequency of*SNHG6*, *PVT1* and *GAS5* genetic alterations among the patients of 30 cancers with available RNA-seq on the portal. **b** The heatmap of the mean expression levels of *SNHG6*, *PVT1* and *GAS5* among 30 cancers with RNA-seq. The heatmaps were drawn using the R software and the raw data of cBioPortal. The grey column represents cancer with no data in case of the gene of interest in the portal

potential biomarker for liver hepatocellular carcinoma in comparison with *PVT1* and *GAS5*. However, *PVT1* and *GAS5* can be useful for other cancers such as Uterine Carcinosarcoma (Fig. 6).

SNHG6 is Possibly Involved in the Structural Integrity of Ribosome and Translation

Through co-occurrence analyses, we found that *SNHG6* and *GAS5* have a tendency toward co-occurrence among target samples (n = 130), although it was not significant (Table 3). We considered all the genes which had been co-expressed with *SNHG6* and *GAS5*. Pearson value >0.7 was taken as the threshold. Computing the gene set overlaps matrix based on the GO molecular function showed that 13 of these genes act as molecules contributing to the structural integrity of the ribosome (Table 4). Interestingly, drawn from cBioPortal data, we found that 35% (n = 130) of the patients among the target samples had the alteration at least for one of these genes. Among the genes, *RPL8*, *TOP1MT,* and *RPL30* were the top ones which were altered among the patients. We then visualized *SNHG6*, its co-expressed genes, and the most frequently altered neighbour genes network to investigate any probable mode of interaction. Although we did not observe any interaction between *SNHG6* and these genes, most of the high frequently altered genes were located on 8q, near the *SNHG6* locus (data not shown).

Discussion

Although the dysregulation of lncRNAs has been reported in some studies, their functional mechanism remains to be challenging. Here is a report considering the

Table 3 The mutual exclusivity analysis of *SNHG6, PVT1* and *GAS5* among 130 tumor samples with alterations at least in one gene. The data was recruited from cBioPortal

Gene Pair		*p*-Value	Log Odds Ratio	Association
SNHG6	*PVT1*	<0.001	−1.821	Tendency towards mutual exclusivity (significant)
SNHG6	*GAS5*	<0.001	0.344	Tendency towards co-occurrence
PVT1	*GAS5*	<0.001	−0.189	Tendency towards mutual exclusivity

Table 4 TheGeneSet analysis of the genes that are commonly co-expressed with *SNHG6* and *GAS5*, based on the GO molecular function. The data was extracted from GSEA

Gene Set Name	Genes in Gene Set (K)	Description	Genes in Overlap (k)	k/K	*p*-value	FDR q-value
Structural constituent of ribosome	80	Genes annotated by the GO term GO: 0003735 The action of a molecule that contributes to the structural integrity of the ribosome	13	0.1625	3.37E-26	1.33E-2
Structural molecule activity	244	Genes annotated by the GO term GO: 0005198 The action of a molecule that contributes to the structural integrity of a complex or assembly within or outside a cell	13	0.0533	1.21E-19	2.40E-17
RNA Binding	259	Genes annotated by the GO term GO: 0003723 Interacting selectively with an RNA molecule or a portion thereof	6	0.0309	1.64E-10	2.17E-08

contribution of lncRNAs to hepatocellular carcinoma using available bioportals. We queried 189 approved lncRNAs in cancer gene expression datasets. It was observed that the expression levels of 68 lncRNAs were altered at least in one case. We chose *SNHG6*, *PVT1,* and *GAS5* as lncRNAs with high levels of alteration. We also observed that *SNHG6*, *PVT1,* and *GAS5* were differentially expressed between the HCC tumors tissues and normal tissues. It was also found that *SNHG6* allocated the most RNA dysregulation in cancerous tissues. Although all the three genes were associated with high grades of HCC, the *SNHG6* up-regulation was more correlated with the shorter survival of patients. However, this value was on the borderline of the statistical significance. In a report by Liu et al., the potential involvement of of *SNHG6* in portal vein tumor thrombus, tumor stage, metastasis, and the shorter overall survival of HCC patients was experimentally confirmed [28]. The expression and mutation analyses of desired lncRNAs in other human tumours showed the *SNHG6* as a potential biomarker. To study the possible function of *SNHG6*, we recruited all the genes that were co-expressed with it. We classified the co-expressed genes based on the GO molecular function. Interestingly, we found that some of these genes were involved in ribosome structure/translation and altered in around 35% of our analysed HCC samples. Additionally, we found that most of the high frequently altered genes were located on 8q21–24, near the*SNHG6* locus. This data showed that 8q may be associated with HCC.

There are merely a few studies showing the role of some ribosomal genes including *RP36A*, *RP44* in HCC progression [29]. It seems that ribosomal proteins are capable to control the gene expression by preparing a selectivity for translating ribosomes [30]. The role of the chromosomal alteration, especially 8q24 in HCC samples, has been the subject of several studies [31]. It has been confirmed that this region encodes several lncRNAs involved in tumorogenesis [32]. Altogether, this data introduced *SNHG6* as a good candidate for experimental works in HCC researches. However, clinical experiments are urgent to evaluate the molecular role of *SNHG6* in HCC progression as well as its specificity and sensitivity as a biomarker of HCC.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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