Co-amplification of Genes in Chromosome 8q24: a Robust Prognostic Marker in Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the major cause of cancer related deaths worldwide, due to high 5 year postoperative recurrence rate and individual heterogeneity. Thus, prognostic model has dramatically urgently needed on HCC in recent years. Several research have reported that copy number amplification of the 8q24 chromosomal region is associated with low survival in many cancers. The objective of this study was to construct a multi-gene model to predict the prognosis of HCC.

Methods: RNAseq and copy number variant (CNV) data of tumor tissue samples of HCC from TCGA (N = 328) was used to identify differentially expressed mRNAs of genes located on chromosomal 8q24 regions by Wilcoxon test. Univariate Cox and Lasso Cox regression were performed to screen and construct prognostic multi-gene signature in TCGA cohort (N = 119). The multi-gene signature was validated in ICGC cohort (N = 240). A nomogram for prognosis prediction was built and Gene Set Enrichment Analysis (GSEA) was used to further study the underlying molecular mechanisms.

Results: A 7-gene prognosis signature model was established for predicting HCC prognosis. Using the model, we divided individuals into high-risk and low-risk sets with significantly different overall survival in training dataset (HR = 0.17, 95% CI 0.1–0.28; $P < 0.001$) and in testing dataset (HR = 0.42, 95% CI 0.23–0.74; $P = 0.002$). Multivariate Cox regression analysis indicated that this signature was an independent prognostic factor of HCC survival. Nomogram including the prognostic signature was constructed and showed better predictive performance in short term (1 and 3 year) than long term (5 year) survival. Furthermore, GSEA revealed several significantly pathways, which may help explain the underlying molecular mechanism.

Conclusions: The 7-gene signature was a reliable prognostic marker in HCC, which may provide meaningful information to therapeutic customization and treatment decision making.

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Figures

Figure 1

Flow chart of multi gene signature identification and validation

Figure 2

Time dependent ROC analysis of the 7 gene signature for prediction overall survival at 1 -, 3 -, and 5- years in the training set (a), the testing set (b), the TCGA discovery cohort (and the ICGC validation cohort (d)

Figure 3

Kaplan Meier analysis to compare patients between high risk and low risk groups based on 7 gene signature in the training set (a), the testing set (b), the TCGA discovery cohort (c) and (D) the ICGC validation cohort.

Figure 4

The mRNA expression level of seven genes between high risk and low risk groups of HCC in TCGA cohort and ICGC cohort.

Figure 5

The nomogram to predict probability of overall survival (OS) for H CC in TCGA cohort. The nomogram for predicting the proportion of patients with OS a The calibration plot of the nomogram for the probability of OS at 1 -, 3- and 5- years (b). The DCA curve of the nomograms compared for 1 -, 3-, and 5- year OS, respectively (c)

Figure 6

The significantly enriched KEGG pathways in TCGA by GSEA. Ten representative KEGG pathways in high risk patients (a). Seven representative KEGG pathways in low risk patients (b).

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