Mining of single nucleotide polymorphisms in the 3' untranslated region of liver cancer-implicated miR-122 target genes

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Currently there has been a lot of focus on the microRNA (miR)-122 to understand the genetics of hepatocellular carcinoma (HCC), pathology of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, hepatic insulin resistance, and lipid metabolism (1-4). Interestingly, miR-122 expression levels were significantly reduced than the normal levels in HBV-associated liver cancer, but not in HCV related liver cancer (5). Also, there is an overwhelming amount of data suggesting the role of single nucleotide polymorphisms (SNPs) in hepatic genes and its association with the altered risk/development of hepatic cancer and its progression. Polymorphisms in the miRNA-binding sites of the target genes are more frequent than SNPs in miRNA genes and therefore, it is considered that polymorphisms in the cytokines and other genes have correlations with chronic HBV or HCV infections. These SNPs in the miRNA binding sites of the target genes can potentially enhance or weaken the interaction between the miRNAs and the target transcripts. Therefore, it is important to study the SNPs in miR-122 binding sites of the target genes to understand the genetic basis of HCC.

Tumor suppressor miR-122 levels are relatively different in both HBV and HCV infections although both types of infection ultimately can lead to HCC. This is an interesting evidence to look for alternate mechanisms involved in hepatic carcinogenesis. The use of *in silico* prediction and experimental validation will only be the beginning steps in a large scale effort to analyze a variety of clinical liver cancer samples associated with altered miR-122 levels. Therefore, in this report by using bioinformatics tool we catalogued SNPs in the 3' untranslated region (UTR) of hepatic cancer implicated genes that can affect miR-122 regulation (1, 6). The list of genes in the current study was chosen based on the previous study (1). These genes have miR-122 binding sites and also participate in pathogenesis of HCC as reported by Tsai *et al.*, 2009 (1). Analyses of SNPs and INDELs in miR-122 target sites were performed by using PolymiRTS Database 3.0 that can be accessed at http://compbio.uthsc.edu/miRSNP/ (6). The Percentage of SNPs in 3' UTR of all the studied genes were obtained by using dbSNP database that can be accessed at https://www.ncbi.nlm.nih.gov/snp. The results are shown in *Table 1*. The table provides information about SNPs/INDELs in miR-122 target sites of hepatic cancer implicated genes that are predicted by the PolymiRTS database.

We believe that our report provides the first step towards integrating SNP analysis with studies on miRNA-122 and global de-repression of host miR-122 targets in hepatic cancer cells. This will provide a suitable base for future research that can improve our understanding of 3' UTR polymorphisms and the failure of miR122 regulation in varied clinical samples. Therefore, integrating SNP analysis with studies on miR-122 regulation in liver cancer cells by framing suitable hypotheses and experimental designs can result in the development of novel cancer-targeting therapeutics.

Table 1 Summary of SNPs in miR-122 target sites of studied genes

Gene symbol	Transcript ID	SNPs (PolymiRTS Database 3.0) and INDELs in miR-122 target sites	% of SNPs in 3' untranslated region (dbSNP database)	Minor allele frequency (MAF)/minor allele count
NUMBL	NM_004756	Nil	6.20	–
FOXJ3	M_001198851	Nil	1.94	–
XPO6	NM_015171	rs28574753	0.75	MAF/minor allele count (A=0.0164/82)
SLC7A1	NM_003045	rs35196293	5.65	NA
STX6	NM_005819	rs190938353	5.72	MAF/minor allele count (A=0.0078/39)
AP3M2	NM_001134296	rs190451219	10.36	MAF/minor allele count (A=0.0020/10)
G6PC3	NM_138387	Nil	8.89	–
GALNT10	NM_198321	Nil	1.68	–
TPD52L2	NM_001243891	Nil	7.05	–
				–
FUNDC2	NM_023934	Nil	6.19	–
MAPK11	NM_002751	rs200443930	14.49	NA
ATP11A	NM_015205	Nil	3.47	–
SORT1	NM_001205228	Nil	6.23	–
ATP1A2	NM_000702	rs78930771	5.15	MAF/minor allele count (T=0.0240/120)
ADAM17	NM_003183	Nil	1.69	–
DUSP2	NM_004418	Nil	10.90	–
OSMR	NM_001168355	Nil	6.61	–
RABIF	NM_002871	Nil	18.34	–
PALM	NM_002579	Nil	3.37	–
AACS	NM_023928	Nil	1.28	–
TBX19	NM_005149	Nil	4.03	–
UBAP2	NM_018449	Nil	0.83	–
EGLN3	NM_022073	Nil	6.75	–
NCAM1	NM_181351	Nil	1.37	–
MECP2	NM_001110792	Nil	8.03	–
CS	NM_004077	rs193099996	3.35	MAF/minor allele count (C=0.0002/1)
FOXP1	NM_001244808	Nil	0.83	–
RAB11FIP1	NM_001002814	Nil	7.77	–
RAB6B	NM_016577	rs200553268	5.89	NA
TRIB1	NM_025195	Nil	15.01	–
TTYH3	NM_025250	Nil	7.92	–
ALDOA	NM_000034	rs1138624, rs12831	2.86	NA
ANXA11	NM_145869	Nil	6.38	–
ENTPD4	NM_001128930	Nil	11.07	–

Table 1 *(continued)*

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Gene symbol	Transcript ID	SNPs (PolymiRTS Database 3.0) and INDELs in miR-122 target sites	% of SNPs in 3' untranslated region (dbSNP database)	Minor allele frequency (MAF)/minor allele count
NFATC2IP	NM_032815	Nil	11.24	–
ANK2	NM_001148	Nil	0.42	–
MEP1A	NM_005588	Nil	1.95	–
NFATC1	NM_006162	Nil	1.83	–
SLC7A11	NM_014331	Nil	5.01	–

SNP, single nucleotide polymorphism.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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