MALAT1 Gene Polymorphism (rs 4102217) as a Risk Factor for HCC: A Case Control Study among patients in South Egypt

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Abstract:

Background and aim: Hepatocellular Carcinoma is one of the most common malignancies world-wide. Polymorphisms in MALAT1 have been demonstrated to play critical roles in cancer. However, the roles of MALAT1 polymorphisms in the etiology of Hepatocellular Carcinoma have not been well documented. So we aimed to evaluate the MALAT1 (rs4102217G>C) gene polymorphism in Egyptian HCC patients.

Patients and Methods: Our study was conducted on one hundred HCC patients. Age ranged from 40 year to 80 years old with median age 65 years and fifty healthy age and sex matched controls. We genotyped MALAT1 Polymorphism using quantitative polymerase chain reaction with TaqMan probes. To evaluate the association between MALAT1 polymorphism (rs4102217G>C) and the risk of HCC, Comparison of quantitative variables between the study groups was done using student t test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Odds ratio (OR) with 95% Confidence Interval (CI) and Logistic Regression was calculated to measure the different risk factors for HCC. P-value is always 2 tailed set significant at 0.05 level.

Results: We found that the MALAT1 (rs4102217 G>C) polymorphism was significantly associated with HCC risk. further analysis demonstrated that the MALAT1 rs4102217 G>C polymorphism may increase the severity of HCC as CG genotype and the recessive model of rs4102217 polymorphism showed stronger relations with advanced HCC cases with multiple hepatic focal lesions regarding data from imaging studies (P =0.019) .

Conclusion: Our data suggest that MALAT1 rs4102217 G>C polymorphism was significantly associated with HCC risk and Progression in Egyptian patients

Keywords: HCC, MALAT1, risk, single nucleotide polymorphism

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Background:

Hepatocellular carcinoma (HCC) is the commonest primary tumor of the liver, the fifth most common cause of cancer worldwide and the second leading cause of cancer death after lung cancer in men [1].

The most important risk factors for developing of HCC include viral hepatitis (hepatitis B and hepatitis C), alcoholic liver disease, and non-alcoholic liver steatohepatitis /non-alcoholic fatty liver disease. HCC occurs in 80 - 90 % of patients with cirrhosis [2].

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs longer than 200 nucleotides and are involved in several biological processes [3]. Increasing evidence suggests that lncRNAs are involved in tumor genesis, cancer progress and response to treatment [4].

Metastasis associated with lung adenocarcinoma transcript-1 (MALAT1) is a long intergenic non-coding RNA (lincRNA), consisting of more than 8000 nucleotides and located on chromosome 11q13 [5].

MALAT1 plays an important role in several cancers, and increasing efforts have been devoted to developing MALAT1-based cancer diagnosis and treatment. The dysregulation of MALAT1 in certain types of tumor and association with tumor cell proliferation, migration

and invasion make it potential diagnostic biomarkers [6].

However, few studies have focused on the association between the genetic variants of MALAT1 and the risks of HCC. In this study, we evaluated the association of MALAT1 (rs4102217G>C) gene polymorphism with the risk of HCC susceptibility in Egyptian population.

Patients and Methods:

This case control study; included one hundred HCC patients and fifty age and sex matched controls. Patients were presented to Assiut University Alraghi Liver Hospital, Tropical Medicine and Gastroenterology Department, Faculty of Medicine Assiut University and South Egypt cancer institute (SECI), Assiut University, the study was held between January 2021 and July 2021.

Inclusion criteria

(1) Age range from 40 to 80 years old.

(2) Confirmed cases of HCC following careful history taking, clinical examination, Laboratory Investigations and Imaging Studies.

Exclusion criteria

(1) Age less than 18 years.

(2) Patients on chemotherapy given before enrolment in the study.

(3) Primary Hepatic Adenoma or liver metastatic disease.

Methods

Study population

All patients were subjected to history taking and clinical examination, with careful assessment of clinical signs relevant to liver cirrhosis as liver size, splenomegaly, jaundice, Ascites, Pedal edema, Periumbilical collateral veins or Enlarged hemorrhoidal veins. Laboratory investigations including: CBC, Coagulation Profile, testing for anti HCV antibodies and HBsAg, liver function tests, kidney function tests and AFP, imaging studies include triphasic computed tomography or dynamic MRI showing the typical criteria of HCC (Arterial hyperenhancement and washout in porto-venous and delayed phase) were performed in Assiut University Alraghi Liver Hospital. Age and sex matched controls were selected during the same period.

SNP selection

We selected MALAT1 (rs4102217 G > C) for analysis as it is a functional SNP located in promotor region of MALAT1 with minor allele frequencies (MAF) > 0.10 in global population from the 1000 Genome Projects and has been identified in published literature.

Genotyping

3-5 ml whole blood samples were taken into ethylene diamine tetraacetic acid tubes from each subject followed by DNA Extraction from Whole Blood using Qiagen (QIAamp DNA Blood Mini Kits for genomic DNA purification- Cat. no. 51104), supplied by Qiagen, Germany. Single Nucleotide Polymorphism (SNP) Genotyping Assay for MALAT1 using a single, ready-to-use tube containing taqman genotyping assay for MALAT1 gene (supplied by Thermo Fischer, USA, Catalog number: 4351379) and its rs4102217 supplied by Thermo Fisher Scientific, Waltham, MA USA. Genotyping was performed on Applied Biosystems™ 7500 Real-Time PCR System. All steps of DNA extraction and genotyping assay were performed as per manufacturer instructions.

Statistical Analysis:

Data was collected and entered into Microsoft Excel Database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 22). Quantitative data was statistically described in terms of mean ± standard deviation (±SD), median and range; qualitative data was statistically described in terms of frequencies (number of cases) and relative frequencies (percentages). Comparison of quantitative variables between the study groups was done using student t test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Odds ratio (OR) with 95% Confidence Interval (CI) and Logistic Regression was calculated to measure the different risk factors for HCC. P-value is always 2 tailed set significant at 0.05 level.

Results:

In the present study we enrolled 100 HCC patients with a median age of 65 years and 50 cancer-free controls with a median age of 62.5 years. The frequency distributions of selected demographic characteristics of the cases and controls are shown in Table 1. There was no significant difference between cases and controls in age (P = 0.312), sex (P = 0.757), smoking (P = 0.908), Diabetes (P = 0.402), and Hypertension (P = 0.416) but there was a significant difference between cases and controls in viral hepatitis infection The frequency of HCV and HBV infections in HCC patients was obviously high than those in control (P = 0.000) and (P = 0.004) respectively.

The analysis of MALAT (rs4102217) for HCC risk is revealed in Table 2. The genotype distributions in controls conformed to HWE which used to identify genotyping errors in cancer-free controls. Single-locus analysis indicated that MALAT1 (rs4102217 G>C) was significantly associated with HCC risk

The GC+CC genotypes of rs4102217 polymorphism showed stronger relations with higher HCC risk (P=0.000, odds ratio (OR): 5.09, 95% confidence interval (CI) = 2.422 – 10.701)

Multivariate logistic regression analysis showed that the dominant model of rs4102217 remained an independent risk factor for HCC [odds ratio (OR) =5.091, 95% confidence interval (CI): 2.422– 10.701, P=0.000]. Another interpretation (patients with CG+CC

variant are five times more likely to develop HCC than patients with GG variant, 95% confidence interval (CI): 2.422– 10.701, P=0.000).

Multiple logistic regression analysis as shown in Table 3, the rs 4102217 CG+CC affected the HCC risk together with HCV infection. The specific data were as follows: HCV (OR = 119.57; 95%CI, 35.958–397.61), another interpretation, Patients with positive anti HCV are 120 times more likely to develop HCC than patients with negative anti HCC, 95% confidence interval (CI): 35.958 – 397.61, P=0.000).

As shown in table 4, MALTA1 rs4102217 genotyping shows no significant differences in the laboratory data among cases, but there was significant differences in imaging data among cases, as CG+CC genotypes of rs4102217 polymorphism showed stronger relations with advanced HCC cases with multiple hepatic focal lesions (P =0.019) as shown in table 5.

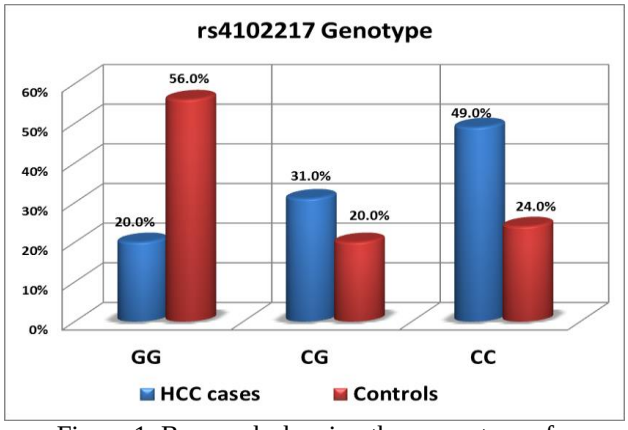

Figure 1: Bar graph showing the percentage of rs4102217 Genotype among the two studies groups.

Table 1: Baseline characteristics and life style related characteristics between HCC cases and controls

Characteristics	**HCC (n=100)**		**Controls (n=50)**		***P-value***
Age (years), Mean ± SD	63.86±7.17		62.54±8.18		0.312
Median (range)	65 (42 – 83)		62.5 (40 – 77)		
Sex, n (%)					0.757
• **Male**	84	(84.0)	41	(82.0)	
• **Female**	16	(16.0)	9	(18.0)	
Smoking, n (%)					0.908
• **No**	51	(51.0)	26	(52.0)	
• **Yes**	49	(49.0)	24	(48.0)	
Diabetes, n (%)					0.402
• **No**	61	(61.0)	34	(68.0)	
• **Yes**	39	(39.0)	16	(32.0)	
Hypertension, n (%)					0.416
• **No**	53	(53.0)	30	(60.0)	
• **Yes**	47	(47.0)	20	(40.0)	
Serology (positive), n (%)					
➢ **HBs Ag**					**0.004***
• **Negative**	85	(85.0)	50	(100.0)	
• **Positive**	15	(15.0)	0	(0.0)	
➢ **Anti HCV**					**0.000***
• **Negative**	7	(7.0)	45	(90.0)	
• **Positive**	93	(93.0)	5	(10.0)	

Quantitative data are presented as mean ± SD or median (range), qualitative data are presented as n (%).

Table 2: The genotype distribution of selected MALAT1 SNPs in HCC patients and controls

Polymorphisms	HCC (n=100), n (%)		Controls (n=50), n (%)		p-value
MALATA1 rs4102217					**0.000***
• G-G	20	(20.0)	28	(56.0)	
• C-G	31	(31.0)	10	(20.0)	
• C-C	49	(49.0)	12	(24.0)	
CG+CC vs GG					**0.000***
• GG	20	(20.0)	28	(56.0)	
• CG+CC	80	(80.0)	22	(44.0)	
GG+CC vs CG					0.154
• CG	31	(31.0)	10	(20.0)	
• GG+CC	69	(69.0)	40	(80.0)	
GG+CG vs CC					**0.003***
• CC	49	(49.0)	12	(24.0)	
• GG+CG	51	(51.0)	38	(76.0)	
Allele (G vs C)					**0.000***
• G	71	(35.5)	66	(66.0)	
• C	129	(64.5)	34	(34.0)	

Qualitative data are presented as n (%), Significance defined by $p < 0.05$

Table 3: Logistic regression analysis for HCC risk factors

	B	S.E.	P value	OR	95% C.I. for OR
Dominant mode (CG+CC vs GG)	1.627	0.379	**0.000***	5.09	2.422 – 10.701
Age	0.023	0.023	0.311	1.02	0.978 – 1.071
Sex	0.142	0.458	0.757	1.15	0.470 – 2.829
Smoking	-0.040	0.347	0.908	0.96	0.487 – 1.895
Diabetes	-0.306	0.366	0.402	0.74	0.359 – 1.508
Hypertension	-0.285	0.351	0.417	0.75	0.378 – 1.497
Anti HCV	4.784	0.613	**0.000***	119.57	35.958 – 397.61

B = regression coefficient, SE = standard error, OR= odds ratio, CI =confidence interval, p value is significant ≤0.05

Table 4: Association between the MALTA1 rs4102217 and the laboratory data of HCC cases (n=100)

		Liver functions						
	AFP	**TB**	**DB**	**ALT**	**AST**	**ALP**	**ALB**	**TP**
rs4102217								
• GG	963.33±2022.59	36.98±57.57	20.96±45.32	56.84±29.30	64.30±31.57	221.72±193.20	35.80±4.99	71.38±6.36
• CG	1049.75±3699.24	34.74±64.20	20.85±49.48	91.15±172.85	97.02±187.78	179.45±106.71	33.20±9.36	66.91±14.15
• CC	1038.90±3118.46	47.35±107.71	30.27±79.98	58.24±44.47	83.94±123.24	186.34±205.05	35.81±9.46	74.76±22.04
P value	0.704	0.321	0.221	0.697	0.400	0.473	0.354	0.167
GG vs CG+CC								
• GG	963.33±2022.59	36.98±57.57	20.96±45.32	56.84±29.30	64.30±31.57	221.72±193.20	35.80±4.99	71.38±6.36
• CG+CC	1043.10±3332.47	42.47±93.02	26.62±69.56	70.99±113.17	89.01±150.53	183.67±172.86	34.80±9.45	71.72±19.65
P value	0.727	0.205	0.136	0.396	0.278	0.266	0.997	0.819
CG vs GG+CC								
• CG	1049.75±3699.24	34.74±64.20	20.85±49.48	91.15±172.85	97.02±187.78	179.45±106.71	33.20±9.36	66.91±14.15
• GG+CC	1016.99±2829.98	44.35±95.59	27.57±71.47	57.83±40.45	78.25±105.27	196.59±200.92	35.81±8.37	73.78±18.88
P value	0.549	0.729	0.735	0.757	0.690	0.914	0.175	0.091
CC vs GG+CG								
• CC	1038.90±3118.46	47.35±107.71	30.27±79.98	58.24±44.47	83.94±123.24	186.34±205.05	35.81±9.46	74.76±22.04
• GG+CG	1015.86±3125.22	35.62±61.11	20.89±47.43	77.69±136.15	84.19±147.64	196.03±146.46	34.22±7.98	68.66±11.85
P value	0.404	0.182	0.132	0.694	0.216	0.322	0.208	0.080

Quantitative data are presented as mean ± SD, Significance defined by $p < 0.05$. AFP: alfa fetoprotein, TB: total bilirubin, DB: direct bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, alb: albumin, TP: total protein.

Table 5: Association between the MALTA1 rs4102217 and the imaging studies of HCC cases (n=100)

	MHFL				***P value***	**PVT**				***P value***
	No		**Yes**			**No**		**Yes**		
MALTA1 rs4102217					**0.049***					0.314
• GG	11	(33.3)	9	(13.4)		13	(16.9)	7	(30.4)	
• CG	7	(21.2)	24	(35.8)		26	(33.8)	5	(21.7)	
• CC	15	(45.5)	34	(50.7)		38	(49.4)	11	(47.8)	
GG vs CG+CC					**0.019***					0.232
• GG	11	(33.3)	9	(13.4)		13	(16.9)	7	(30.4)	
• CG+CC	22	(66.7)	58	(86.6)		64	(83.1)	16	(69.6)	
CG vs GG+CC					0.137					0.274
• CG	7	(21.2)	24	(35.8)		26	(33.8)	5	(21.7)	
• GG+CC	26	(78.8)	43	(64.2)		51	(66.2)	18	(78.3)	
CC vs GG+CG					0.619					0.898
• CC	15	(45.5)	34	(50.7)		38	(49.4)	11	(47.8)	
• GG+CG	18	(54.5)	33	(49.3)		39	(50.6)	12	(52.2)	

Qualitative data are presented as n (%), Significance defined by $p < 0.05$ MHFL= Multiple hepatic focal lesions, PVT=Portal vein

Discussion:

Recent researches reported that the human genome encodes more than 28,000 distinct lncRNAs, the aberrant expression and the presence of mutations in a great number of lncRNAs has been documented. Alterations in the expression of lncRNAs and their mutations promote tumorigenesis and metastasis. LncRNAs can function both as oncogenes or tumor-suppressors, regulating proliferation, survival, invasion, metastasis and angiogenesis of cancer cells. Although lncRNAs can be up- or down-regulated in cancer, the majority are up-regulated with respect to their canonical expression in normal tissues [7]. Recently, it has been confirmed that lncRNAs can modulate several pathways relevant for cancer development by interacting with other cellular components such as DNA, protein and RNA [8].

There is an exponential growth of studies on the biological functions of lncRNAs and their roles in human diseases including cancers. Given that lncRNAs possess fundamental roles in cell biology, it is believed that in the future scientists will identify lncRNAs involved in critical stages of cancer development and progression. Currently, studies have identified a few lncRNAs that are frequently associated with different cancer types. Many lncRNAs are known to be dysregulated and have functional roles in HCC as H19, HULC, HOTAIR, MALAT1 and others. Dysregulated HCC-related lncRNAs related to tumor progression through regulation of HCC cell proliferation, invasion, metastasis and apoptosis [9].

In recent years among a large variety of noncoding sequences special attention of researchers was drawn to lncRNA MALAT1. This sequence first was detected in 2003 in non-small cell lung cancer cells. Today the results of numerous experiments revealed that MALAT1 is one of the major genes involved in various types of cancer, including Lung, kidney, colorectal, endometrial and hepatic cancer [10].

In the present case-control study, we found a link between MALAT1 genetic variants (rs4102217) and HCC in the Egyptian population. To our knowledge, this was the first study of the relationship between the MALAT1 (rs4102217) gene variant and HCC patients in Egypt. In our study, the results showed that The GC genotype and the CC (recessive model) of rs4102217 polymorphism showed strong relation with higher HCC risk (P=0.000, odds ratio (OR): 5.09, 95% confidence interval (CI) = 2.422 – 10.701), thus it could be considered as a novel biomarker for HCC as reported by He et al. [11]

There are many other long non coding RNAs were highly expressed in HCC. Such as the four-lncRNA signature, containing LINC01116, DDX11-AS1, LUCAT1 and FIRRE reported by Wu H et al. [12]. Also Zhao et al. identified that eight lncRNAs (TSPEAR-AS1, LINC00511, LINC01136, MKLN1-AS, LINC00506, KRTAP5-AS1, ZNF252P-AS1, and THUMPD3-AS1) were highly expressed in HCC [13].

Another SNPs in MALAT1 gene were studied for their association with HCC risk, Ji et al. study suggested that tagSNPs rs11227209, rs619586, and rs3200401 at MALAT-1 were not significantly associated with HCC risk [14]

The genotyping for MALAT1 rs4102217 polymorphism was performed by many researchers

In harmony with our study Wang et al. found that the risk of HCC increased by 1.23 fold with MALAT1 rs4102217 SNP dominant model [15]. Also He et al. reported that MALAT1 was upregulated in HCC cell lines and clinical tissue samples. In addition inhibition of MALAT1 in HepG2 cells effectively reduced cell viability, motility and invasiveness with increased sensitivity to apoptosis. This explains the role of Malat1 in tumor progression [11].

Chen et al. reported that there was No association between endometrial cancer risk in Chinese population and MALAT1 rs4102217 while MALAT1 rs664589

C>G polymorphism was associated with a significant increase in endometrial cancer risk. [16]

The findings from Li et al. study on Chinese population showed that no evidence of significant association between MALAT1 rs4102217 and Colorectal cancer risk but there was evidence of negative association between lncRNA MALAT1 rs1194338 polymorphism and colorectal cancer risk as for variant genotype (AA) of rs1194338 [17].

This disagreement between our current study and the previously mentioned studies may be attributed to different population composition and different tumor types.

Wang et al. explored the association between SNPs in the promoter of MALAT1 and risk of ischemic stroke. Significant differences were observed in the distribution of the rs1194338 AC/AA genotype and A allele between controls and cases. Further analysis showed that MALAT1 rs1194338 A allele, AA, AC genotype and the dominant model were associated with decreased risk of IS but No significant association was found between rs4102217 and ischemic stroke risk [18].

Zhang et al. indicated rs4102217 SNP were not associated with susceptibility of rheumatoid arthritis [19].

Hu et al. demonstrated that the GC genotype and the recessive model of rs4102217 potentially increased coronary artery disease risk in Chinese population [20], it was reported that MALAT1 considered one of the most up-regulated oxygen deprivation-responsive endothelial lncRNAs. In addition, it has been found to regulate genes that induce proliferation in endothelial cells, through enhancing cell cycle regulatory genes [21].

The results of our study support the important role of lncRNA MALAT1 in HCC risk, development and progression. As reported by prior studies which concluded that MALAT-1 could promote proliferation, invasion, and metastasis of HCC cells [22], and is an independent prognostic factor for HCC recurrence after liver transplantation [23].

More comprehensive and systematic design (large, population-based, and diverse ethnic population) studies are needed to explore the true MALAT-1 pathogenic variants on HCC risk.

Conclusion:

Our data suggest that MALAT1 rs4102217 G>C polymorphism was significantly associated with HCC risk and Progression in Egyptian patients. Further studies are needed to explore clinical applications of SNP detection in early cancer diagnosis, risk prediction for relapse or progression and patient stratification. Eventually, these studies could also lead to identification of novel targets for the development of innovative therapies.

List of Abbreviations:

MALAT: Metastasis associated lung adenocarcinoma transcript 1.

HCC: Hepatocellular carcinoma.

SNP: Single nucleotide polymorphism.

Competing interests:

The authors reported no conflicts of interest associated with this work

Authors' Contributions:

Dr. Hosny Badrawy Hamed has contributed to supervising and revising the work.

Dr. Mohamed Omar Abdelmalek have contributed by helping in sample collection and revising the work.

Dr. Asmaa Mohamed Zahran and Dr. Engy Adel Shafik have contributed to designing the work

Dr. Fatma ELZahraa Mohammed El Saoudy has carried out the collection of samples as well as analysis and interpretation of results and drafted the manuscript.

All Authors have read and approved the final manuscript.

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