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ROLE OF PRI-MIR-34 B/C AND MIR-146A POLYMORPHISM IN THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN EGYPTIAN PATIENTS INFECTED WITH HEPATITIS C

By

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a common trouble all over the world, with highest mortality rate in both males and females. Hepatocarcinogenesis caused by Hepatitis C virus (HCV) results from alterations that may be caused from viral causes or immune mediated as a consequence of chronic inflammation. MicroRNAs (miRNAs) are collections of noncoding RNA contain around 18–25 nucleotides long to influence post-translational gene expression, have been revealed to become involved in HCC outcome.

Objective: To determine the association of pri-miR-34b/c rs4938723 (T>C) and miR-146a rs2910164 (C>G) polymorphisms of the Egyptian patients with the risk of the development of HCC which might serve as biomarkers for early diagnosis/prognosis of HCC.

Patients and Methods: Thirty five HCC patients, thirty five HCV infected patients, and thirty age and gender matched healthy controls included in this work. Pri-miR-34b/c rs4938723 (T>C) and miR-146a rs2910164 (C>G) polymorphisms were assayed with real time-PCR genotyping assays. This study was carried out over a period from January 2019 and April 2020, at Theodor Bilharz research institute (TBRI).

Results: A significant increase in miR-34b/c TT genotype within HCC group and HCV group in comparison to control group was observed (p value = 0.01 and 0.001 respectively). In addition, there was a significant increase in pri-miR-34b/c T alleles in HCC group (p value = 0.03) and HCV group (p value = 0.01) compared to control group.

Conclusion: Pri-miR-34b/c TT genotype might serve as a risk factor for HCC development in HCV infected Egyptian population.

Keywords: Hepatocellular carcinoma; MicroRNA; pri-miR-34b/c; miR-146a.

INTRODUCTION

Despite substantial advances in HCC care over the last few decades, patient survival rates remain poor. As a result, it is critical to investigate new therapies and look for more precise biomarkers for early finding, care and prognosis in HCC *(Xu et al., 2018).*

Hepatitis C infection (HCV) infection is considered a critical danger factor for

liver cirrhosis and cancer *(Dash et al., 2020)*.

MicroRNAs (miRNAs) are fundamental regulators of liver homeostasis, and their dysregulation has been connected to liver disease, including HCC *(Bandiera et al., 2016)*.

The miR-34a and miR-34b/c loci are directly controlled by P53, which induces apoptosis, cell cycle arrest, and senescence *(Navarro and Lieberman, 2015)*.

The rs4938723 C/T polymorphism within the promoter area of pri-miR-34b/c was considered to affect GATA-X binding to its target genes, influencing tumor differentiation and tumorigenesis target gene expression levels *(Gao et al., 2013)*.

Several studies linked miR-146a expression to nuclear factor kappa B (NF-κB) signaling within the innate immune system. It is quickly induced when human monocytes are activated *(Lee et al., 2016)*. It was reported that miR-146a can function as tumor suppressor (TS) in the context of the immune system *(Boldin et al., 2011)*.

Dysregulation of miR146a advances liver inflammation and illness development in hepatitis B infection (HBV) or hepatitis C infection (HCV) diseases, rather than miR146a's ordinary role of suppressing malignancy development and repressing irritation *(Cornett & Lutz, 2014*; *Iacona et al., 2018* and *Peta et al., 2018)*.

Single nucleotide polymorphism (SNP) (rs2910164; G/C) was found on the passenger strand of pre-miR-146a *(Shao et al., 2014)*. The rarer C allele inhibits nuclear pri-miR-146a processing, lowering levels of pre-miR-146a and mature miR-146a and allowing expression of target genes such as tumour necrosis factor receptor associated factor 6 (TRAF6) and interleukin 1 receptor associated kinase 1 (IRAK1) to be unblocked *(Zhang et al., 2018)*. The SNP might decrease the stability of the pri-miR, the effectiveness of processing of pri-miR into pre-miR or the effectiveness of processing the pre-miR into the mature microRNA.

The present work aimed to determine the association of pri-miR-34b/c rs4938723 (T>C) and miR-146a rs2910164 (C>G) polymorphisms of the Egyptian patients with the risk of the development of HCC which might serve as biomarkers for early diagnosis/prognosis of HCC.

PATIENTS AND METHODS

Our study was done at the Tropical Department, Theodor Bilharz Research institute (TBRI), and the procedures used in this study were approved by TBRI ethical committee according to Helsinki Declaration, with a written consent from each subject over a period from January 2019 and April 2020, where 100 subjects were enrolled and separated into 3 groups: Group A included thirty five HCC patients (27 males (77.1%) and 7 females (22.9%), with the age ranged from 48 years to 60 years (mean ± SD = 46.8 ± 15.9), group B contained thirty five patients with active HCV infection without treatment (16 males -45.7% and 19 females -54.3%), with the age ranged from 34 years to 67 years and group C contained thirty subjects with age and sex matched served as a control group (24 males- 80% and 6

females -20%), with age ranged from 32 years to 57.

HBV comorbidity, schistosomiasis, alcohol consumption or antiviral therapy were excluded.

Genomic DNA extraction: The QIA amp DNA Mini Kit was used to collect genomic DNA (Qiagen; catalogue No.: 51104). DNA was extracted from entire blood samples using the enzyme proteinase K.

Amplification of the extracted DNA and detection of polymorphism: An Allelic Discrimination (AD) measure recognizes variations of a single nucleic acid sequence in a multiplexed (more than one primer/probe pair per response) end-point (information was acquired toward the finish of the PCR cycle) test. Since every response contained two primer/probe sets, genotyping of the two potential variants at the single-nucleotide polymorphism (SNP) site in target template sequence is conceivable.

In allelic discrimination assays, each allele has its own fluorescent dye-labeled probe in the PCR assay. To distinguish the amplification of each allele, the probes contained special fluorescent reporter dyes (FAM and VIC®). Each probe anneals to matching sequences between the forward and reverse primer areas during PCR. Only probes that hybridized to the allele were cleaved with AmpliTaq Gold® DNA polymerase. Cleavage distinguished the reporter dye from the quencher dye, allowing the reporter dye to fluoresce more. As a result, the PCR amplification produced fluorescence signal(s). This PCR reaction was done in a thermal cycler using ABI 7500.

Statistical analysis:

Microsoft Excel 2010 and the statistical Package for the social sciences (SPSS version 26.0) for Windows were used to analyse the results (SPSS IBM., Chicago, IL). Qualitative data were presented as frequency and percentage and were compared by Chi2 or Fisher's exact test. P value of less than 0.05 was deemed statistically Significant. Odd-Ratio and logistic regression analysis were used.

RESULTS

Sex and Age distribution of the studied groups: There was a statistically significant difference regarding gender distribution (P value = 0.01) in HCV group compared to control and also, between HCV group and HCC group (P value = 0.01) **(Table 1)**.

Table (1): Descriptive data

Descriptive parameters \ Groups		Control	HCV	HCC	P. Value		
					Control & HCV	Control & HCC	HCV & HCC
Age	**Min-Max**	**32.0 - 57.0**	**34.0 - 67.0**	**48.0 - 60.0**	**0.5**	**0.9**	**0.7**
	Mean ± SD	**46.07 ± 13.3**	**44.3 ± 13.9**	**46.8±15.9**			
Sex	**Male**	**24(80.0%)**	**16(45.7%)**	**27(70.0%)**	0.01	**0.5**	0.01
	Female	**6(20.0%)**	**19(54.3%)**	**7(30.0%)**			

MiR-146a rs2910164 genotypes and alleles distribution among study subjects: By using X2 test we detected that there is no significant difference on comparing all genotypes through all studied groups regarding miR-146a **(Table 2)**.

Pri-miR-34b/c rs4938723 genotypes and alleles distribution among study subjects: There was a significant decrease on comparing HCV and HCC groups with control group regarding pri-miR-34b/c rs4938723 CT genotype (p = 0.01). We also detected that there was a significant increase on comparing HCC group and HCV group with control group regarding pri-miR-34b/c rs4938723 TT genotype (p value = 0.01) and (p value = 0.001) respectively **(Table 2)**.

Table (2): Genotypes frequency of the studied markers among studied groups

Parameters \ Groups		Control N=30	HCV N=35	HCC N=35	P. value		
					HCV Vs Control	HCC Vs Control	HCC Vs HCV
miR-146a (64)	**CC**	6(20.0%)	7(20.0%)	10(28.6%)	0.84	0.08	0.06
	CG	14(46.7%)	16(45.7%)	10(28.6%)	0.81	0.132	0.134
	GG	10(33.3%)	12(34.3%)	15(42.9%)	0.93	0.09	0.457
	C Allele	26(0.433)	30(0.429)	30(0.429)	0.9	0.9	N.A
	G Allele	34(0.567)	40(0.571)	40(0.571)			
miR-34b/c (23)	**CC**	0(0.0%)	1(2.9%)	0(0.0%)	0.08	N.A	0.08
	CT	24(80.0%)	18(51.4%)	18(51.4%)	0.02	0.02	N.A
	TT	6(20.0%)	16(45.7%)	17(48.6%)	0.03	0.001	0.808
	C Allele	24(0.400)	20(0.286)	18(0.257)	0.17	0.083	0.704
	T Allele	36(0.600)	50(0.714)	52(0.743)			

Risk association of the studied markers among HCV patients Vs Control group: There was no risk association in all comparing genotypes among HCV patients and Control group regarding miR-146a and pri-miR-34b/c **(Table 3)**.

Table (3): Risk association of the studied markers among HCV patients Vs Control group

Parameters \ Groups		Control N=30	HCV N=35	[a]P. value	OR	95% C.I	[b]P. value
miR-146a (64)	**CC**	6(20.0%)	7(20.0%)	0.84	1(reference)		
	CG	14(46.7%)	16(45.7%)	0.81	0.933	0.247 - 3.524	0.9
	GG	10(33.3%)	12(34.3%)	0.93	0.972	0.246 - 3.849	0.9
	C Allele	26(0.433)	30(0.429)	0.9	1(reference)		
	G Allele	34(0.567)	40(0.571)		1.009	0.493 - 2.062	0.9
miR-34b/c (23)	**CC**	0(0.0%)	1(2.9%)	0.08	1(reference)		
	CT	24(80.0%)	18(51.4%)	0.02	0.810	0.047 - 13.920	0.8
	TT	6(20.0%)	16(45.7%)	0.03	2.667	0.143 - 49.756	0.5
	C Allele	24(0.400)	20(0.286)	0.17	1(reference)		
	T Allele	36(0.600)	50(0.714)		1.669	0.785 - 3.546	0.2

OR: Odds Ratio; CI: Confidence Interval.

aP. Value was depending on the X2 test, while bP. Value is depending on Logistic Regression analysis.

Risk association of the studied markers among HCC patients Vs Control group: There was no risk association in all comparing genotypes among HCC patients and Control group regarding miR-146a but TT genotype was associated with a 3.667-fold increased risk of HCC when compared with the CT genotype with corresponding adjusted OR (95% CI) was 3.667 (1.190 - 11.300) regarding pri-miR-34b/c **(Table 4)**.

Table (4): Risk association of the studied markers among HCC patients Vs Control group

Parameters \ Groups		Control N=30	HCC N=35	[a]P. value	OR	95% C.I	[b]P. value
miR-146a	CC	6(20.0%)	10(28.6%)	0.08	1(reference)		
	CG	14(46.7%)	10(28.6%)	0.132	0.450	0.119 - 1.703	0.2
	GG	10(33.3%)	15(42.9%)	0.09	0.900	0.248 - 3.270	0.8
	C Allele	26(0.433)	30(0.429)	0.9	1(reference)		
	G Allele	34(0.567)	0(0.0%)		1.009	0.493 - 2.062	0.9
miR-34b/c	CC	0(0.0%)	0(0.0%)	_	_		
	CT	24(80.0%)	18(51.4%)	0.02	1(reference)		
	TT	6(20.0%)	17(48.6%)	0.001	3.667	1.190 - 11.300	0.02
	C Allele	24(0.400)	18(0.257)	0.083	1(reference)		
	T Allele	36(0.600)	52(0.743)		1.941	0.901 - 4.182	0.09

OR: Odds Ratio; CI: Confidence Interval.
aP. Value was depending on the X2 test, while bP. Value is depending on Logistic Regression analysis.

Risk association of the studied markers among HCC Vs HCV patients: There was no risk association in all comparing genotypes among HCC patients and HCV patients regarding miR-146a and Pri-miR-34b/c **(Table 5)**.

Table (5): Risk association of the studied markers among HCC Vs HCV patients

		HCV N=35	HCC N=35	[a]P. value	OR	95% C.I	[b]P. value
miR-146a	GG	12(34.3%)	15(42.9%)	0.457	1(reference)		
	CG	16(45.7%)	10(28.6%)	0.134	1.111	0.306 - 4.037	0.2
	CC	7(20.0%)	10(28.6%)	0.06	0.5	0.154 - 1.624	0.8
	C Allele	30(0.429)	30(0.429)	–	1(reference)		
	G Allele	40(0.571)	40(0.571)		1.009	0.493 - 2.062	0.9
miR-34b/c	CC	1(2.9%)	0(0.0%)	0.08	1(reference)		
	CT	18(51.4%)	18(51.4%)	_	1.2	1.1 - 1.3	0.9
	TT	16(45.7%)	17(48.6%)	0.808	0.941	0.361- 2.453	0.9
	C Allele	20(0.286)	18(0.257)	0.704	1(reference)		
	T Allele	50(0.714)	52(0.743)		1.163	0.542 - 2.494	0.7

OR: Odds Ratio; CI: Confidence Interval.
aP. Value was depending on the X2 test, while bP. Value is depending on Logistic Regression analysis.

DISCUSSION

HCC is a worldwide issue; it is the sixth and fourth most common cancers, respectively, in the world and Egypt *(Rashed et al., 2020)*. Early detection of HCC improves prognosis because it appears to develop slowly and remain confined to the liver *(Abdel-Hafiz et al., 2018)*.

Many tumors are associated with chronic infectious diseases, according to epidemiological reports. Persistent inflammation has been connected to an expanded danger of malignancy and quicker movement of the illness *(Herbest and Reddy, 2012)*.

HCV infection is linked to advanced cirrhosis and hepatic fibrosis, as well as a higher risk of HCC *(Axley et al., 2018)*.

MiRNAs perform significant functions in the regulation of mammalian gene expression via post-transcriptional repression by directly binding to the 3′ untranslated region (UTR) of messenger RNAs (mRNAs), resulting in down regulation of their expression *(O'Brien et al., 2018)*.

In agreement of our results, *Xiong et al. (2017)* did not find any association between miR-146a rs2910164 (G>C) polymorphism and susceptibility to digestive system cancers. Also, *Farokhizadeh et al. (2019)* found that the frequencies of miR-146a G>C polymorphisms did not change among HCC subjects and controls.

A previous study by *Tian et al. (2017)* suggested that the G allele of rs2910164 increases the risk of hepatitis virus-related HCC, specifically for HBV-related HCC and new evidences suggested that miR-146a be able to encourage apoptosis by inhibiting the NF- κB pathway and jamming its effect on cell expansion, angiogenesis and cancer cell survival. Loss of function of miR-146a could promote cancer cell resettlement and invasion. Furthermore, the rs2910164 polymorphism has been linked to a decline in the development of mature miR-146a and resulting in a decline in the repression of its target genes including vascular endothelial growth factor, NF-κB, p65, and HAb18G, which are probably involved in hepatocarcinogenesis *(Zhang et al., 2015)*.

Regarding pri-miR-34b/c TT genotype and T alleles, a significant increase in HCV and HCC groups compared to control was observed, and by using logistic regression analysis we observed that the TT genotype of pri-miR-34b/c rs4938723 had a higher risk of HCC as compared with other alleles in Egyptian population.

Our results agreed with *Zhang et al. (2014)* who found that in the recessive model, CC genotype of pri-miR-34b/c rs4938723 was associated with a significant decreased risk of esophageal squamous cell carcinoma compared with TT allele. The probable cause for diverse outcomes might be that the similar variation in miRNA acting diverse roles in special types of cancers.

Furthermore, *Li et al. (2019)* came in agreement with ours as they found that miR-34b/c rs4938723 were associated with decreased neuroblastoma susceptibility.

In contrast, *Chen et al. (2016)* stated that the TC and CC genotypes of pri-miR-34b/c rs4938723 were correlated with a

higher risk of HCC compared to the TT genotype.

The explanation for the contradictory results may be due to that the roles of the miR-34b/c rs4938723 in cancer susceptibility is tissue dependent as the rs4938723 polymorphism was revealed to notably raise the risk of HCC. Many possibilities can assist to clarify such contradictory circumstances. This T to C change polymorphism is located in the promoter site of pri-miR-34b/c, within a classic CpG island particularly. According to bioinformatics analysis, this SNP may affect predicted GATA-X transcription factors binding to the promoter of pri-miR-34b/c gene so as to alter its expression levels. Given transcription factors control gene expression in a tissue specific way, this SNP may affect different transcription factors binding to the promoter, thereby either up regulating or down regulating transcription in different tissues *(Hashemi et al., 2018* and *Xu et al., 2018).*

CONCLUSION

Pri-miR-34b/crs4938723 TT genotype might serve as a risk factor for HCC development in Egyptian population which could be used as non-invasive diagnostic parameter.

RECOMMENDATIONS

Larger sample sizes with diverse ethnicities are required to validate our findings and studying other factors may affect the result.

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دور تعدد الأشكال الجينية لجين الحمض الريبوزى متناهى الصغر 34 ب/س وجين 146 أ فى نشوء الإصابة بسرطان الكبد الخلوي في المرضي المصريين المصابين بإلتهاب الكبد الفيروسي ج

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خلفيـــة البحـــث: ســرطان الكبــد الخلــوي يعتبــر مــن المشــكلات الشــائعة حــول العــالم و لــه معــدل وفــاة مرتفــع فــي الجنســين. وينــتج الســرطان الكبــدي المســبب بــالفيروس الكبــدي الوبــائي ج بســبب اســباب فيروســية او مناعيــة كنتيجــة للإلتهــاب المــزمن .والأحمــاض الريبوزيــة المتناهيــة الصــغر عبــارة عــن حمــض نــووي ريبــوزى غيــر مشــفر مكــون مــن 18- 25 نيوكليوتيــدات و التــي تــؤثر التعبيــر الجينــي لمــا بعــد الترجمــة، و التــي اصبحت لها دورا واضحا في تطور الإصابة بسرطان الكبد الخلوي.

الهـدف مــن البحــث: اكتشــاف العلاقــة بــين دور تعــدد الأشــكال الجينيــه لجــين الحمــض الريبـــوزى متنـــاهى الصـــغر 34 ب/س وجـــين 146أ فـــي المرضـــي المصـــريين المصابين بالتهاب الكبد الفيروسي ج مع خطر الإصابة بسرطان الكبد الخلوي.

المرضـــي و طـــرق البحـــث: أجــري هــذا البحــث فــي عــام 2020 علــى 100 شــخص بعــد أخــذ الموافقــة المســتنيرة مــنهم. و قــد شــمل البحــث 35 شخصــا يعــانون مــن إلتهــاب الكبــد الوبــائي ســي، 35 شــخص يعــانون مــن ســرطان الكبــد الخلــوي عــلاوة علــي 30 شــخص أصــحاء كمجموعــة ضــابطة . و تــم إجــراء الدراســة فــي الفتــرة مــا بــين ينــاير 2019 حتـــي ابريـــل 2020، و تـــم قيـــاس تعـــدد الأشـــكال الجينيـــة لجـــين الحمـــض الريبـــوزى متنـــاهى الصـــغر 34ب/س وجـــين 146أ بطريقـــة تفاعـــل البـــوليميراز المتسلسل اللحظي.

نتـــائج البحـــث: لـــوحظ وجـــود إخـــتلاف ذو قيمـــة إحصـــائية بـــين مجموعـــة مرضـــي الســـرطان الكبـــدي الخلـــوي و مجموعـــة مرضـــي إلتهـــاب المبـــدي الفيروســـي ج فيمـــا يخـــص الطـــراز الجينـــي CC لجـــين الحمـــض الريبـــوزى متنـــاهى الصـــغر 146أ و كـــذلك وجـــود إخـــتلاف ذو قيمـــة إحصـــائية عنـــد المقارنـــة بـــين مجموعـــة مرضـــي الســـرطان الكبـــدي الخلـــوي، و مجموعـــة مرضـــي الإلتهـــاب الكبـــدي الفيروســـي ج، و بـــين المجموعـــة الضـــابطة فيمـــا يخـــص الطـــراز الجينـــي TT للجـــين الحمـــض الريبـــوزى متنـــاهى الصـــغر 34ب/س. عـــلاوة علـــي ذلـــك لـــوحظ وجـــود إخـــتلاف ذو قيمـــة إحصـــائية عنـــد المقارنـــة بـــين مجموعـــة مرضـــي الســـرطان الكبـــدي الخلـــوي و مجموعـــة مرضـــي الإلتهـــاب الكبـــدي الفيروســـي ج و بـــين المجموعـــة الضـــابطة فيمـــا يخـــص الأليـــل T للجين الحمض الريبوزى متناهى الصغر 34ب/س.

الإســـتنتاج: الطـــراز الجينـــي TT للجـــين الحمـــض الريبـــوزى متنـــاهى الصـــغر 34ب/س يمكـــن أن يمثـــل مؤشـــرا مبكـــرا لأحتمـــال التحـــول الســـرطاني و التوقـــع المبكـــر لسير المرض.

الكلمـــات الدالـــة: ســـرطان الكبـــد الخلـــوي، الحمـــض الريبـــوزى متنـــاهى الصـــغر، 34ب/س، جين 146أ.