Molecular Biology Reports (2020) 47:4209–4214
https://doi.org/10.1007/s11033-020-05548-7

ORIGINAL ARTICLE

Negative associations between the *has-miR-27a* and *hsa-miR-125a* gene variations and prostate cancer susceptibility

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Received: 12 March 2020 / Accepted: 23 May 2020 / Published online: 28 May 2020

Abstract

Micro-RNAs are a novel class of single-strand non-coding RNAs, which play an important role in tumorigenesis. This investigation aimed to evaluate associations between the *hsa-miR-27a* (rs895819 T > C) and *hsa-miR-125a* (rs12976445 C > T) gene variations and the risk of PCa. In the present case–control investigation, we have obtained 300 peripheral blood samples, consisting of 150 subjects with PCa and 150 healthy men. The genotype frequencies of *hsa-miR-27a* and *hsa-miR-125a* gene variations evaluated using the PCR–RFLP technique. Based on our findings, the genotype frequencies did not reveal a significant association between the rs895819T and rs12976445C variations and the risk of PCa in the three heredity models ($P > 0.05$). Minor alleles C and T of rs895819 and rs12976445 did not show an increased risk of PCa progression ($P > 0.05$). Our findings indicated that the *hsa-miR-27a* and *hsa-miR-125a* gene variations are not increased PCa predisposition in the Iranian population.

Keywords Prostate cancer · *Hsa-miR-27a* · *Hsa-miR-125a* · PCa

Introduction

Prostate cancer (PCa) is one of the most common medical problems in men with a high mortality rate worldwide [29]. The molecular investigation indicates that advanced and metastatic cases are the monoclonal PCa and caused by a single colony resulting from the proliferation and development of the tumor [4]. Epidemiological surveys have recommended that multiple genes involved in prostate carcinogenesis [24]. Previous investigations endeavor to the recognition of pathways and genes that plays crucial biology likely roles in the etiology of a PCa. From this reason, many surveys evaluated the associations of specific single nucleotide polymorphism (SNP) or haplotypes groups in reliable candidate susceptibility genes [20, 24] including the androgen receptor, telomere-related genes (*TERT* and *TET*), and microRNAs [1, 6, 12]. *Has-miR-27a* is assumed as an oncogene, found in the 19p13.13 chromosome, involving an exon, which plays an important role in malignancies such as colorectal cancer (CRC) [3]. The presence of rs895819 variation within the *has-miR-27a* gene is located on chromosome 19p13.12, which could change the secondary structure, aberrant expression, and dysfunction of the target gene [28]. *Has-miR-27a* (rs895819) is a stem-loop structure variant, which affects in the mature *has-miR-27a* function. The *has-miR-27a* rs895819 variation is an unusual miRNA-SNP, which due to the location in the coding region of the pre- *has-miR-27a* hairpin in the stem-loop digested by Dicer enzyme in the pre-miRNA maturation procedures [26]. It has shown that the *has-miR-27a* controlled by the Androgen hormone and can create positive feedback with the first loop [8]. Previous investigations have shown that rs895819 variation acts a critical role in cancerogenesis of several cancers such as pancreas, liver, lung, and PCa [30]. The *has-miR*-125a gene located on chromosome 19q13.41, which consisting of *MIR99B* and *MIR7E* genes. Previously, reported that the *has-miR*-125a decreased expression levels in several cancers and disorders including, systemic lupus erythematosus (SLE), breast, gastric, ovarian and verrucous carcinomas [23]. Molecular investigation revealed that the *hsa-miR-125a* rs12976445 variant could lead to a decrease in the level of *hsa-miR-125a* gene expression. The presence rs12976445 variation may interrupt a possible GATA-1 site and generated a truncate *hsa-miR-125a* transcription [15]. Several surveys have shown that the relationship between

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rs12976445 variation and the risk of several disorders such as recurrent pregnancy loss (RPL), breast cancer (BC), autoimmune thyroid disease, chronic periodontitis, and PCa [7, 10, 15, 27]. This study aimed to assess the relationship between *has-miR-27a* (rs895819) and *has-miR*-125a (rs12976445) gene variations and the risk of PCa in Iranian people.

Materials and methods

Patients' selection

We designed a case–control investigation to assess 300 peripheral blood samples, which involving 150 PCa patients and 150 healthy men, ages matched and no history of other malignancies. All subjects were referred to the department of pathology Imam Khomeini Hospital of Tehran, from May 2014 to April 2015. Our survey was approved the Ahar Branch Islamic Azad University of Iran and written informed consent collected from all of the individuals. Before the sample collection, all PCa patients were assessed according to the standard clinical protocol, including digital rectal exam (DRE), abdominal and pelvic ultrasonography, and appraisal prostate-specific antigen (PSA) level of serum. In addition, the biopsies obtained from the PCa patients were confirmed histopathologically. In the control group, we included the healthy men ages matched, who had been normal PSA levels, without historical malignancies and the same geographical region. The individuals with an abnormal PSA level, unusual DRE, self-reported a disorder and family history of PCa were excluded from this study.

Genotyping

To isolation of genomic DNA from white blood cells, we have collected 2 ml peripheral blood from all subjects in the tubes containing anticoagulant EDTA, using the salting-out method [18]. For *has-miR-27a* (rs895819) and *has-miR*-125a (rs12976445) gene amplification were used the primer sequence (Table 1) as described previously [22]. The PCR condition for *has-miR-27a* (rs895819) and *has-miR-125a* (rs12976445) was as follow: the initial denaturation was 94 °C for 5 min, then, repeated 35 cycles in the denaturation 94 °C for 30 s, the annealing temperatures 64 °C and 60.8 °C for 30 s, and 72 °C in 30 s as the extension temperature, respectively.

We were used the PCR–RFLP method for determine genotype frequencies for *has-miR-27a* (rs895819) and *has-miR*-125a (rs12976445). The PCR product for the rs895819 and rs12976445 variations was digested (12 h at 37 °C) using Hpy1881 and BaeG enzymes (Thermo Fisher Scientific company), respectively (Table 1). To separated PCR product digestion used the 4% agarose gel electrophoresis.

Statistical analysis

To the analysis of the genotype and allele distribution of *has-miR-27a* (rs895819) and *has-miR*-125a (rs12976445) variations between groups, were used the multivariate logistic regression and *chi-square* tests. Statistical assessment was performed using SPSS 25.0 software (SPSS Inc. Chicago, IL) and a $P\ value < 0.05$ was considered as statistically significant.

Results

The mean age characteristics of the PCa patients studied were 48.81 ± 12.37 (range 34–56) years and 45.23 ± 5.39 (range 30–52) years for healthy men. In our investigation, we have involved the age-matched subjects and the same ethnicity. The genotype frequencies of the *has-miR-27a* (rs895819) variant were obtained (TT = 33, TC = 71, and CC = 46) and (TT = 34, TC = 72, and CC = 44) in patients and healthy men, respectively ($P = 0.967$). These findings did not show a significant difference between case and control groups (Table 2).

The genotype frequencies of *has-miR*-125a (rs12976445) polymorphism has shown (CC = 41, CT = 81, and TT = 21) and (CC = 40, CT = 77, and TT = 33) in case and control groups, respectively ($P = 0.770$). However, our results revealed no significant association between the rs12976445 variant and the risk of PCa (Table 3). We have evaluated the genotype frequencies in the co-dominant, dominant and recessive heredity patterns in two groups. Importantly,

Table 1 The primer sequences and enzyme digestion were used in PCR–RFLP method

Gene polymorphism	Primer sequences	PCR product (bp)	Enzyme digestion	Lengths fragments
Has-miR-27a-F	5′-GAACTTAGCCACTGTGAACACGACTCGG-3′	182	Hpy188I	C allele:, 182 bp
Has-miR-27a-R	5′-TTGCTTCCTGTCACAAATCACATTG-3′			T allele: 155 bp, 27 bp
Has-miR-125a-F	5′-TTTTGGTCTTTCTGTCTCTGG-3′	247	BaeG I	C allele: 205 bp, 42 bp
Has- miR-125a–R	5′-TGGAGGAAGGGTATGAGGAGT-3′			T allele: 247 bp

Table 2 The allele and genotype frequencies of *hsa-miR-27a* (rs895819 T > C) in case and control subjects in three heredity models

Gene polymorphism	Case n = 150 (%)	Control n = 150 (%)	Total n = 300	OR[a]	CI 95%[b]		*P* value[c]
					Down	Up	
hsa-miR-27a (rs895819 T > C)							
Co-dominant							
T/T	33 (49%)	34 (51%)	67				
T/C	71 (49%)	72 (50%)	143	1.016	0.569	1.815	0.957
C/C	46 (51%)	44 (49%)	90	1.077	0.572	2.028	0.818
Recessive				1.066	0.65	1.746	0.801
C/C	46 (51%)	44 (49%)	90				
T/C + T/T	104 (49%)	106 (51%)	210				
Dominant				0.962	0.559	1.657	0.89
T/T	33 (49%)	34 (51%)	67				
T/C + C/C	117 (51%)	116 (49%)	233				
Allele frequency				1.041	0.755	1.435	0.806
T	137 (49%)	140 (51%)	277				
C	163 (51%)	160 (49%)	323				

[a]Odds ratio; [b]Confidence interval; [c]$p < 0.05$

Table 3 The allele and genotype frequencies of *hsa-miR-125a* (rs12976445 C > T) in case and control subjects in three heredity models

Gene polymorphism	Case n = 150 (%)	Control n = 150 (%)	Total n = 300	OR[a]	CI 95%[b]		*P* value[c]
					Up	Down	
hsa-miR-125a (rs12976445 C > T)							
Co-dominant							
C/C	41 (51%)	40 (49%)	81				
C/T	81 (51%)	77 (49%)	158	1.026	1.754	0.601	0.924
T/T	28 (46%)	33 (54%)	61	0.828	1.611	0.425	0.578
Recessive				0.814	1.43	0.463	0.473
T/T	28 (46%)	33 (54%)	61				
C/T + C/C	122 (51%)	117 (49%)	239				
Dominant				1.034	1.722	0.621	0.897
C/C	41 (51%)	40 (49%)	81				
C/T + T/T	109 (49%)	110 (51%)	219				
Allele frequency				0.923	1.272	0.67	0.623
C	163 (51%)	157 (49%)	320				
T	137 (49%)	143 (51%)	280				

[a]Odds ratio; [b]Confidence interval; [c]$p < 0.05$

there was no positive association between *has-miR-27a* (rs895819) and *has-miR-125a* (rs12976445) gene polymorphisms in three genetic models with the risk of PCa ($P > 0.05$) (Tables 2 and 3).

In addition, we have also assessed the relationship between the allele frequencies of rs895819 and rs12976445 variants and the risk of PCa between groups. Minor alleles C and T of rs895819 and rs12976445 did not show an increased risk of PCa progression ($P > 0.05$). ($P = 0.806$; OR 1.041; 95% CI 0.755–1.435) and ($P = 0.623$; OR 0.923; 95% CI 0.670–1.272), respectively (Tables 2 and 3).

We have also assessed the relationship between the genotype frequencies for *has-miR-27a* (rs895819) and *has-miR-125a* (rs12976445) polymorphisms in the PCa patients with clinicopathological and demographic characteristics including age at diagnosis, tumor stage, Gleason score, the rate of cell growth and PSA serum levels. The findings disclosed that the *has-miR-27a* (rs895819) variant was significantly associated with the PSA ($P = 0.001$) level. Interestingly, the genotype frequencies of the *has-miR-125a* (rs12976445) variant revealed a significant

association with the Gleason score ($P = 0.001$) of the clinical characteristics of the PCa patients (Table 4).

Discussion

The male reproductive system containing the prostate gland, which several environmental factors, such as family history, obesity, the use of some drugs and sexually transmitted diseases, acts a crucial function in cancerogenesis and PCa progression [16]. In addition, a large number of genetic variations and epigenetic changes have recognized as having important roles in the inflammatory prostate and development of PCa [9, 14]. To date, miRNAs have proposed that as diagnostic or prognostic biomarkers in cancer investigations. However, the miRNAs molecules are involved in the cancerogenesis of PCa, as well as the identification of suitable therapeutic targets that are important regulatory molecules for cancer detection pathways [21]. Our investigation is an initial case–control survey on the men Iranian. Since there were no details on the relationship between rs895819 and rs12976445 variations and the risk of PCa, we have also trying to prepare findings related to the developing of PCa. We have analyzed the association between the *has-miR-27a* (rs895819) and *has-miR-125a* (rs12976445) gene polymorphisms with the risk of PCa progression. Several surveys have assessed the potential impact of SNPs miRNA genes with the risk of PCa, which revealed conflicting results. Until now, a single survey by Nikolić et al. has attempted to evaluate the relationship between three miRNA gene polymorphisms including *hsa-miR-499*, *hsa-miR-196a2* and *hsa-miR-27a* (rs895819) with the PCa progression in the Serbian population. They have assessed 355 PCa patients, 353 benign prostatic hyperplasia and 312 healthy individuals as a control group. The findings revealed that the minor allele C of rs895819 was significantly increased the risk of PCa progression. These findings revealed that early manifestation of the positive association between the rs895819 variant and the risk of developing and metastasis of PCa patients [22]. Our findings conflicted with the results referring to the potential roles of genetic variations in the *has-miR-27a* (rs895819) gene with the risk of PCa reported previously. Chen et al. investigated the association between rs11614913 with the risk of cancers. The rs895819 variant was correlated with a reduced tumor risk in Caucasians and BC, whereas a significantly advanced risk of progressing malignancy could be identified in CRC [2]. According to the previous investigation, *has-miR-27a* is implicated in metastasis of many types of malignancy, acting as an oncogene and regulate the target gene expression such as *Forkhead box protein O1* (*FOXO1*), *B-cell translocation gene 2* (*BTG2*), and *human prohibitin gene* (*PHB*) [13, 19, 31]. Surveys have declared that the presence of SNPs in miRNA could be changed miRNA expression levels and miRNA maturation processing. Furthermore, due to the T to C nucleotide change in *pre-has-miR-27a* can lead to decreased *has-miR-27a* gene

Table 4 The relationship between the genotype frequencies of rs895819 T > C and rs12976445 C > T variations with the clinicopathological and demographic characteristics of PCa patents

Parameters	n = 150	*hsa-miR-27a* (rs895819 T > C)			*P* value	*hsa-miR-125a* (rs12976445 C > T)			*P* value
		TT (%)	TC (%)	CC (%)		CC (%)	CT (%)	TT (%)	
Age at diagnosis(y)					0.924				0.806
≤ 55	120	27 (22%)	57 (48%)	36 (30%)		23 (19%)	64 (53%)	33 (28%)	
> 55	30	6 (20%)	14 (47%)	10 (33%)		5 (17%)	18 (60%)	7 (23%)	
Gleason score									
≤ 6	60	11 (18%)	30 (50%)	19 (32%)		11 (19%)	44 (50%)	5 (31%)	
7	71	11 (15%)	40 (56%)	20 (28%)	0.766	14 (20%)	33 (46%)	24 (34%)	0.001
> 7	19	5 (26%)	7 (37%)	7 (37%)	0.576	3(16%)	12 (63%)	4(21%)	0.001
Stage									
PT1	60	12 (20%)	30 (50%)	18 (30%)		15 (25%)	32 (53%)	13 (22%)	
PT2	70	17 (25%)	34 (49%)	19 (27%)	0.830	10(14%)	36 (51%)	24 (34%)	0.153
PT3	20	4 (20%)	7 (35%)	9 (45%)	0.421	3 (15%)	13 (65%)	4 (20%)	0.592
Rate of cell growth					0.797				0.041
Ki—67	102	24 (24%)	47 (46%)	31(30%)		21(21%)	48 (47%)	33 (32%)	
S—shape	48	9 (19%)	24 (50%)	15 (31%)		7 (14%)	33 (69%)	8 (17%)	
PSA (ng/ml)									
≤ 4	32	8 (25%)	15 (47%)	9 (28%)		6 (19%)	19 (59%)	7 (22%)	
4–10	98	21 (21%)	46 (47%)	31 (32%)	0.001	19 (19%)	52 (53%)	27 (28%)	0.787
> 10	20	4 (20%)	10 (50%)	6 (30%)	0.917	3 (15%)	10 (50%)	7 (35%)	0.582

expression levels and increased the susceptibility of the individual to malignancy [22]. However, differences in ethnicity and genetic backgrounds between various populations could have a significant effect on carcinoma susceptibility.

To date, there are little data regarding the possible association between the rs12976445 variant and the risk of PCa. Hence, we have assessed the relationship between the *has-miR-125a* (rs12976445) variant with the risk of PCa. Our results indicated an inverse association between the rs12976445 polymorphism with the risk of PCa in Iranian. There are discrepancies in the reported association between the rs12976445 and the risk of PCa.

Firstly, Feng et al. evaluated the association between rs1434536 C > T nucleotide change in *a has-miR-125b* binding location in the 3′-UTR of bone morphogenetic protein membrane receptor type IB gene (BMPR1B) and PCa susceptibility.

They have assessed 247 PCa patients and 278 healthy men using dual-luciferase reporter assay to evaluate the binding ability of *has-miR-125b* to target transcript. The findings revealed that CT/TT genotype increased the risk of PCa and contributed as a genetic predisposition factor for PCa progression [7].

Recently, Damodaran et al. evaluated several SNPs in *has-miR146a* (rs73318382, rs57095329 and rs2910164), *has-miR-196a2* (rs11614913) and *has-miR-125a* (rs41275794, rs12976445, rs10404453 and rs1297533) in 100 cases with PCa and 100 healthy men. They were shown that the CC genotype of *has-miR-125a* (rs12976445) variant increased risk for PCa progression [5].

The discrepancy to the findings reported formerly [5] may be regarding the differences in genetic backgrounds, sample size, geographical location, different ethnicity, and race and criteria sample selection.

According to previous evidence, the nucleotide change in the *has-miR-125a* (rs12976445) gene related to several malignancies.

Jiao et al. were an assessed correlation between the *has-miR-125a* (rs12976445) with the survival of BC patients. The findings showed that this nucleotide change was significantly associated with survival in three genetically models including co-dominant, recessive, and dominant. However, this finding proposed that the rs12976445 variant applied as a prognostic value for BC patients [11]. In addition, Feng et al. evaluated the relationship between the rs12976445 polymorphism with the risk of intervertebral disc degeneration (IDD) and the findings showed that this polymorphism was significantly increased the risks of IDD [17].

To the best of our education, this is the early investigation in Iranian people exploring the association of *has-miR-125a* and *has-miR27a* polymorphisms with PCa susceptibility. The *has-miR-125* gene family comprising several members including, *has-miR-125a*, *has-miR-125b-1*, and *has-miR-125b-2*, which were located in a different cytogenetic situation [25]. According to previous investigations has been declared that the has-miR-125a gene expression decreased in BC tissues and play as tumor suppressors [17, 23, 25] by affecting to the ETS1 gene through ERBB2 and ERBB3 pathway [17]. Although this is the particular survey which was assessed the association of rs12976445 and rs895819 variations with PCa, we did not reveal significant effects to PCa susceptibility.

The findings contradiction can be impressed by several factors such as diversity between the subjects groups assessed, geographic regions, race, ethnicity, and genetics background or error analysis. In the other hand, the specimen's criteria selection may lead to different results. Alternatively, this controversial result may be due to heterogeneity between patients and the small number of samples assessed in the survey. In addition, environmental factors may be influence in the other geographic region due to the interaction between gene and environmental parameters. However, additional clinical and experimental analyses are obliged to verify the implements of these SNPs on PCa progression.

Conclusion

Our findings indicated that the *hsa-miR-27a* and *hsa-miR-125a* gene variations are not increased PCa predisposition in Iranian population.

Acknowledgements This article was extracted from an MS.c thesis (IR. 952003) at Ahar Branch Islamic Azad University. We would like to appreciate all the participants.

Funding The present survey has no any fund.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

Research involving human participants or animals This article has involving human participants or animals performed by any of the authors.

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