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Original Article

The impact of pri-miR-218 rs11134527 on the risk and prognosis of patients with esophageal squamous cell carcinoma

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Abstract: MicroRNA-218 (miR-218) acts as a tumor suppressor in numerous types of cancer by regulation of the expression of target genes. The aim of this study was to investigate whether polymorphisms in miR-218 LAMB3 pathway were associated with the risk and prognosis of esophageal squamous cell carcinoma (ESCC). Pri-mir-218 rs11134527 and LAMB3 rs2566 were genotyped in ESCC patients and 745 controls to assess their associations with cancer risk and overall survival. Pri-mir-218 rs11134527 was significantly associated with a decreased risk of ESCC under codominant, recessive and additive models. Although there was a significant association between rs11134527 and better survival of ESCC patients under codominant, recessive and additive models, the association disappeared after adjustment for TNM and LNM. However, further stratified analysis revealed that the association remained significant in patients with TNM stages I and II or non-LNM. Our data suggest that pri-miR-218 rs11134527 may contribute to the genetic susceptibility and prognosis for ESCC in Chinese Han population.

Keywords: Esophageal squamous cell carcinoma, miR-218, laminin 5, single nucleotide polymorphism, susceptibility

Introduction

Esophageal cancer is the third most common form of cancer of the digestive tract and the fifth leading cause of cancer-related death worldwide [1]. The incidence rates vary greatly worldwide, with the highest being in Southern and Eastern Africa and Eastern Asia [1]. Esophageal squamous cell carcinomas (ESCC) is the most common type, accounting for over 90% of esophageal cancer [2]. The prognosis of ESCC is uniformly poor despite the significant improvements in diagnosis and therapy in last ten years [3]. Although environmental risk factors for ESCC have been identified, the molecular mechanisms underlying carcinogenesis remain poorly understood.

Dysregulation of microRNAs (miRNAs) has been implicated in the development of various types of cancer [4-6]. miRNAs are a class of small, single-stranded, non-coding RNAs that normally negatively regulate expression of approximately 90% human genes at the post-transcriptional level [7]. A single miRNA can regulate hundreds of target genes, whereas one gene can be targeted by multiple miRNAs [7, 8]. Much evidence has clearly demonstrated that miRNAs are involved in various diseases, including cancer [9]. miRNAs function as oncogenes and tumor suppressors in cancer initiation, progression and metastasis [5, 6]. Therefore, changes in miRNA expression or miRNA dysfunction may affect cancer initiation and progression. Accumulating evidence reveals that genetic variation in miRNA genes affect the processing and expression of mature miRNAs and target mRNA-binding activity, leading to the changed expression of target genes [10-13]. Accordingly, func-

Table 1. Clinical characteristics of cases and controls

Characteristics	Cases (%)	Controls (%)	*P* values
Total	706	745	
Age (years)	61.2±9.2	60.6±9.9	0.177
Sex, % male	495 (70.1)	502 (67.4)	0.282
Pathologic type			
medullary	268 (38.0)		
ulcerative	278 (39.4)		
others	113 (16.0)		
unknown	47 (6.7)		
Histologic grade			
well	60 (8.5)		
moderate	378 (53.5)		
poor	247 (35.0)		
unknown	21 (3.0)		
Tumor size (cm)			
> 4.5	235 (33.3)		
≤ 4.5	340 (48.2)		
unknown	131 (18.6)		
TNM			
I	35 (5.0)		
II	304 (43.1)		
III	252 (35.7)		
IV	78 (11.0)		
unknown	37 (5.2)		
LNM			
yes	379 (53.7)		
no	294 (41.6)		
unknown	33 (4.7)		

tional single nucleotide polymorphisms (SNPs) not only contribute to the susceptibility to human diseases [10, 13-19], but also can affect prognosis and response to treatment [11, 14, 20].

Many studies have demonstrated that miRNA SNPs are associated with the risk and prognosis of cancer [11, 21]. So far, few studies have mentioned the relationship between miRNA SNPs and the risk and prognosis of ESCC. Previous studies found that pri-miR-218 rs11134527 was related to the risk of cervical carcinoma [17, 18]. In the present study, we assessed the relationship between Pri-mir-218 rs11134527 and rs2566 in miR-218 target gene laminin 5 β3 (LAMB3), and the risk and prognosis of ESCC in Chinese Han.

Materials and methods

Patients

The study protocol was approved by the ethics committee of Taizhou People's Hospital. A total of 706 pathologically confirmed ESCC patients and 745 controls were recruited at Taizhou People's Hospital. All subjects were genetically-unrelated ethnic Han Chinese and lived within the same geographic region (Jiangsu Province). Patients with a prior diagnosis of cancer, other than ESCC, were excluded from this study. Furthermore, no individual had a blood transfusion in the last 6 months. Three ml of peripheral blood was collected from each participant after written informed consent was obtained from all subjects.

Genotyping

Genomic DNA was extracted from the peripheral leucocytes using the Universal Genomic DNA Extraction Kit Version 3.0 (Takara, Dalian, China) according to the manufacturer's instructions. The concentration and quality of genomic DNA was measured by NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, DE, USA) and then stored at -20°C for later use. The genotypes of rs11134527 and rs2566 were determined using polymerase chain reaction-ligation detection reaction (PCR-LDR) method as described previously [22].

Statistical analyses

The differences between cases and controls were assessed using Pearson's χ^2 test and t-tests, as appropriate. The Hardy-Weinberg equilibrium (HWE) was tested by a χ^2 test to compare the expected genotype frequencies with observed genotype frequencies in controls. The differences in frequencies of SNPs between cases and controls were analyzed using χ^2 test or Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate and multivariable logistic regression model. Survival analyses were carried out using the Kaplan-Meier method, and the differences in overall survival were examined using log-rank tests. Hazard ratios (HRs) were estimated by Cox proportional hazard regression model. The SPSS 19.0 software (IBM Corporation, Armonk, NY, USA) was used

Table 2. Associations between 2 SNPs and ESCC risk

SNP	Genotype	Case	Control	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
rs11134527	AA	273 (38.7)	268 (36.0)	1		1	
	AG	344 (48.7)	348 (46.7)	0.970 (0.775-1.215)	0.794	0.976 (0.773-1.234)	0.842
	GG	89 (12.6)	129 (17.3)	0.677 (0.493-0.931)	0.016	0.669 (0.480-0.932)	0.018
	Dominant model			0.891 (0.720-1.103)	0.289	0.894 (0.716-1.115)	0.321
	Recessive model			0.689 (0.514-0.923)	0.012	0.678 (0.500-0.919)	0.012
	Additive model			0.855 (0.736-0.993)	0.041	0.853 (0.729-0.997)	0.046
	Allele A	890 63.0)	884 (59.3)	1		1	
	Allele G	522 (37.0)	606 (40.7)	0.856 (0.737-0.994)	0.041	0.866 (0.744-1.007)	0.062
rs2566	GG	305 (43.2)	310 (41.6)	1		1	
	AG	290 (41.1)	327 (43.9)	1.109 (0.887-1.387)	0.363	1.105 (0.881-1.386)	0.386
	AA	111 (15.7)	108 (14.5)	0.957 (0.703-1.303)	0.781	0.940 (0.687-1.286)	0.698
	Dominant model			1.067 (0.867-1.314)	0.54	1.060 (0.835-1.294)	0.591
	Recessive model			0.909 (0.682-1.212)	0.515	0.894 (0.668-1.197)	0.451
	Additive model			0.993 (0.858-1.148)	0.922	1.000 (0.863-1.160)	0.995
	Allele A	512	543	1		1	
	Allele G	900	947	0.992 (0.853-1.154)	0.919	0.997 (0.855-1.162)	0.971

to perform all statistical analyses. A $P < 0.05$ was considered statistically significant.

Results

Characteristics of ESCC patients and controls

The demographic characteristics of the 704 ESCC cases and 745 cancer-free controls were summarized in **Table 1**. The mean age of cases and controls were 61.2 and 60.6 years, respectively. There were no significant differences between cases and controls in terms of age and sex.

Association of rs11134527 and rs2566 with the risk of ESCC

The genotype and allele frequency distributions for rs11134527 and rs2566 in 704 cases and 745 controls were presented in **Table 2**. The genotype distributions of these two SNPs were in agreement with the Hardy-Weinberg equilibrium among controls ($P > 0.05$). We carried out association analysis with codominant, dominant, recessive and additive models using conditional logistic regression model. In the codominant model, rs11134527 GG genotype was significantly associated with a decreased risk of ESCC compared with AA genotype (OR=0.677, 95% CI: 0.493-0.931, *P*=0.016) (**Table 2**). The difference remained significant even after adjusted for age and sex (adjusted OR=0.669, 95% CI: 0.480-0.932, *P*=0.018). Furthermore, rs11134527 was significant protect factor for ESCC under both recessive (adjusted OR=0.678, 95% CI: 0.500-0.919, *P*=0.012) and additive models (adjusted OR=0.853, 95% CI: 0.729-0.997, *P*=0.046). In the dominant model, rs11134527 showed no significant association with ESCC risk ($P > 0.05$). There was no significant association between rs2566 and the risk of ESCC in our study population.

Effects of rs11134527 and rs2566 on ESCC survival

In the univariate analysis of various clinicopathological parameters for overall survival, LNM (HR=1.883, 95% CI: 1.500-2.364, $P < 0.001$), TNM stages III and IV (HR=2.055, 95% CI: 1.644-2.569, $P < 0.001$), rs11134527 GG genotype (GG *vs.* AA, HR=0.630, 95% CI: 0.434-0.914, *P*=0.015; GG *vs.* AA+AG, HR=0.652, 95% CI: 0.461-0.923, *P*=0.016) were significantly associated with prognosis in ESCC patients (**Table 3**, **Figure 1**). Furthermore, rs11134527 was also associated with better survival in ESCC patients under additive model (HR=0.838, 95% CI: 0.713-0.985, *P*=0.032). In the multivariate analysis, TNM was the only independent prognostic factor for ESCC (adjusted HR=1.775, 95% CI: 1.136-2.773, *P*=0.012). The rs2566 did not show any significant correlation with overall survival (**Table 3**).

Table 3. Univariate and multivariate Cox regression analysis of overall survival in ESCC patients

Features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years), > 60 *vs.* ≤ 60	1.029 (0.830-1.275)	0.797		
Sex, male *vs.* female	0.870 (0.686-1.104)	0.252		
Tumor size (cm), > 4.5 vs. ≤ 4.5	0.813 (0.639-1.034)	0.092		
Tumor differentiation, poor *vs.* well, moderate	0.937 (0.834-1.053)	0.274		
Pathologic type	0.984 (0.848-1.142)	0.829		
LNM, yes vs. no	1.883 (1.500-2.364)	< 0.001	1.118 (0.713-1.754)	0.626
TNM stage, III+IV *vs.* I+II	2.055 (1.644-2.569)	< 0.001	1.775 (1.136-2.773)	0.012
rs11134527				
AA	1			
AG	0.943 (0.749-1.186)	0.614	0.987 (0.783-1.243)	0.910
GG	0.630 (0.434-0.914)	0.015	0.725 (0.497-1.057)	0.095
Dominant model	0.870 (0.697-1.086)	0.219		
Recessive model	0.652 (0.461-0.923)	0.016	0.731 (0.514-1.039)	0.080
Additive model	0.838 (0.713-0.985)	0.032	0.893 (0.758-1.052)	0.177
rs2566				
GG	1			
AG	1.205 (0.953-1.523)	0.119		
AA	1.279 (0.934-1.750)	0.125		
Dominant model	1.224 (0.984-1.523)	0.070		
Recessive model	1.166 (0.873-1.557)	0.298		
Additive model	0.873 (0.753-1.013)	0.073		

The association between rs11134527 and overall survival was further evaluated by stratification of clinicopathological parameters. We found that when compared with rs11134527 AA genotype, GG genotype was more prominent in patients with TNM stages I and II (adjusted HR=0.419, 95% CI: 0.238-0.738, *P*= 0.003) or non-LNM (adjusted HR=0.532, 95% CI: 0.295-0.960, *P*=0.036) (**Figure 1**). Compared with subjects with rs11134527 AA+GG genotypes and with TNM stages III and IV or LNM, patients with GG genotype and with TNM stages I and II or non-LNM had a significantly lower mortality rate (adjusted HR=0.580, 95% CI: 0.338-0.996, *P*=0.048).

Discussion

In the present study, we found that rs11134527 GG genotype was related to a significantly decreased risk of ESCC. Furthermore, a significantly increased survival time was observed in ESCC patients with GG genotypes. The effect was even stronger in those with TNM stages I and II or non-LNM. This is the first report to evaluate the relationship between SNPs in the LAMB3-miR-218 pathway and clinical outcome of ESCC patients.

miR-218 functions as a tumor suppressor [23-25] and is downregulated in various types of cancer, such as colorectal cancer [25], cervical squamous cell carcinoma [26] and head and neck squamous cell carcinoma [27]. Overexpression of miR-218 inhibits cancer cell proliferation, migration and invasion [24, 26, 27], and promotes colon cancer cell apoptosis [28]. In addition, miR-218 can enhance the sensitivity of cervical cancer cell to cisplatin [29] and radiotherapy [23]. The expression level of miR-218 is associated with cancer progression and poor prognosis [25, 30, 31]. Previous study has demonstrated that rs11134527 G allele in pri-miR-218 region leads to hairpin structure change, which increases the expression of mature miR-218 [12]. Therefore, tissue with rs11134527 GG genotype might have a higher level of miR-218, leading to the decreased risk of carcinogenesis. In this study, we found that rs11134527 GG genotype was relate to a reduced risk of ESCC, which was in agreement with previous observations that rs11134527 GG genotype was associated with decreased

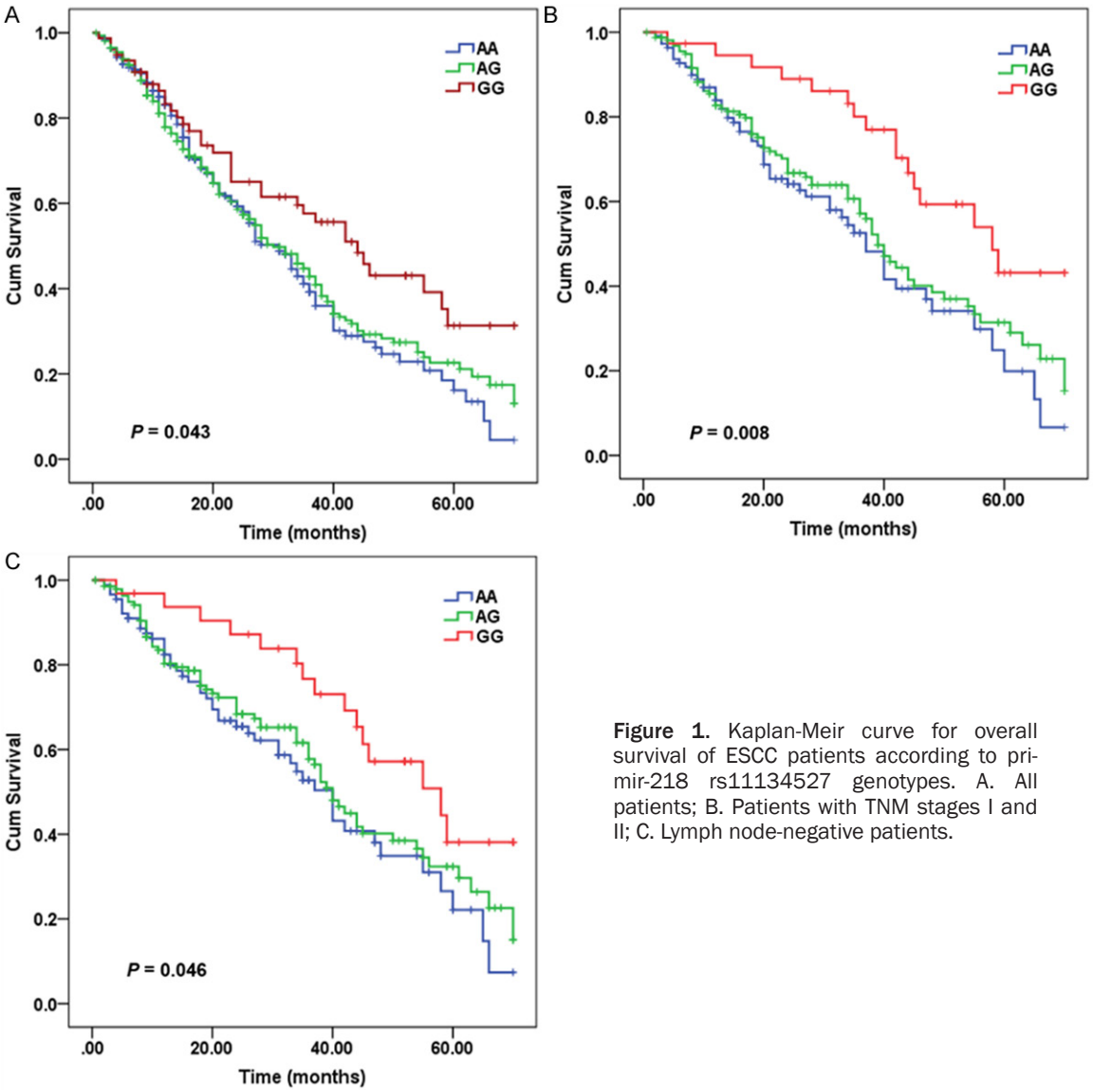

Figure 1. Kaplan-Meir curve for overall survival of ESCC patients according to pri-mir-218 rs11134527 genotypes. A. All patients; B. Patients with TNM stages I and II; C. Lymph node-negative patients.

risk of cervical carcinoma [17, 18]. However, Zhang et al. [32] found no association between rs11134527 and the risk of ESCC. One of the reasons for the contradiction may be genetic heterogeneity among different population samples. Moreover, ESCC patients with rs11134527 GG genotype had a better prognosis, especially in those with early-stage disease. This indicated that the level of miR-218 in early-stage ESCC may be higher than that in later stage. Further studies are required to confirm involvement of pri-miR-218 rs11134527 with the risk and prognosis of ESCC.

Several target genes of miR-218 have been identified, including BMI1 [28], LAMB3 [26, 27] and LASP1 [24]. LAMB3 encodes β3 chain of laminin-5 that is abundant in the basal membrane and regulates important biological processes including cell differentiation, migration, adhesion and angiogenesis [33]. The level of LAMB3 is upregulated in ESCC and high LAMB3 expression is correlated with invasion and worse prognosis [34]. These imply that LAMB3-miR-218 pathway may be involved in the development of ESCC. Zhou et al. [17] reported that rs2566 CT and TT genotypes in the 3'UTR of LAMB3 was associated with increased risk of cervical carcinoma. However, Shi et al. [18] found no association between rs2566 and the risk of cervical carcinoma. Additionally, in this study, rs2566 was not related to the risk as

well as prognosis of ESCC. Rs2566 may not affect miRNA binding and mRNA splicing.

In conclusion, our study revealed that pri-miR-218 rs11134527 GG genotype might decrease the risk of ESCC and be also associated with better survival in ESCC patients, especially in those with early-stage disease. Larger well-designed epidemiological studies and functional evaluations are warranted to confirm these initial findings.

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Disclosure of conflict of interest

None.

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