International Journal of Clinical Oncology (2019) 24:1042–1048
https://doi.org/10.1007/s10147-019-01442-w

ORIGINAL ARTICLE

Association of SNPs in the *OBFC1* gene and laryngeal carcinoma in Chinese Han male population

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Received: 6 March 2019 / Accepted: 1 April 2019 / Published online: 23 April 2019

Abstract

Background Laryngeal carcinoma (LC) is one of common diagnosed head and neck malignancies. Telomere length has been reported involved in malignant transformation and tumorigenesis. We speculate that single nucleotide polymorphisms (SNPs) in telomere length-related gene oligonucleotide/oligosaccharide-binding folds containing 1 (*OBFC1*) may have an association with LC in Chinese Han male population.

Methods To prove this hypothesis, we performed a case–control study to analyze the *OBFC1* polymorphisms in 172 LC patients and 180 healthy controls. A total of five SNPs (i.e., rs9325507, rs3814220, rs12765878, rs11191865, rs9420707) were selected for further genotyping.

Results There was a significant difference in rs9325507 T allele frequency (OR = 0.88, 95% CI 0.64–1.21, $P = 0.036$) and rs11191865 A allele frequency (OR = 0.86, 95% CI 0.62–1.18, $P = 0.009$) between patient and control groups. In addition, the rs9325507 T/C genotype, rs3814220 G/A genotype, rs12765878 C/T genotype and rs11191865 A/G genotype had a lower risk of LC based on the results of logistic regression model analysis.

Conclusions The results indicate a potential association between *OBFC1* and LC risk in Chinese Han male population. Further work is required to confirm these results and explore the mechanisms of these effects.

Keywords *OBFC1* · Single-nucleotide polymorphisms · Telomere length · Laryngeal carcinoma

Abbreviations

CLL	Chronic lymphocytic leukemia
HWE	Hardy–Weinberg equilibrium
ILD	Interstitial lung disease
LC	Laryngeal carcinoma
LTL	Leukocyte telomere length
OBFC1	Oligonucleotide/oligosaccharide-binding folds containing 1
SNPs	Single nucleotide polymorphisms
WHO	World Health Organization

Background

Laryngeal carcinoma (LC), as the most prevalent malignancy in the head and neck region with highly invasive and metastatic potential, remains to be a serious health threat and leads to increasing morbidity and mortality. Worldwide, approximately 177,422 new LC cases and 94,771 deaths predicted in 2018 [1]. In China, the incidence of laryngeal carcinoma is only secondary to nasopharyngeal carcinoma among all types of head and neck cancers [2]. According to 2015 Cancer Statistics in China, the estimated incidence and mortality of LC is 26,400 and 14,500, witch the male–female ratio of morbidity and mortality of LC was 9:1 and 6:1, respectively [3]. The mortality rate of the disease remains high, with a 5-year survival rate of approximately 65% [4]. The Han nationality is the largest ethnic group in China, with about 1.2–1.3 billion from the sixth population survey of China. In this study, we focus on the risk of LC in

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Chinese Han population, hoping to provide an early marker for the detection and prevention of LC.

Telomeres, a specialized ribonucleoprotein structures, are made up of variable number of TTAGGG replicative senescences at the end of each chromosome, which are important in preventing chromosome degradation, abnormal DNA repair, and maintaining the integrity of genetic information [5]. Telomere length, structure, and integrity are significant for the cells and the organism as a whole [6]. In the course of somatic cell replication, the telomere length becomes shorter with cellular division and some genetic mutation, leading to the loss of integral genomic DNA, cell cycle checkpoint, genome instability, and predisposition to carcinogenesis [7]. Shorter telomere length is associated with advanced disease stages, such as Richter's transformation and poor patient prognosis [8, 9]. If adequate oncogenic mutations are acquired before reaching replicative senescence, long telomeres and unlimited proliferation may follow and cancer may result [10]. To date, the molecular regulation of telomere length has not been well elucidated.

Twin studies and intra-familial correlation analysis demonstrated that potential genetic loci influence telomere length and contribute to human telomere dynamics in a large sample of unselected individuals [11, 12]. The gene *OBFC1*, as the human homolog of yeast Stn1, plays an important role in the replication, capping of telomeres and telomeres protection via its effect on telomere length regulation [13]. The correlation between the genetic variants in *OBFC1* and chronic lymphocytic leukemia (CLL) [10], adult glioma, prostatic cancer and late-onset alzheimer disease have been identified in a number of studies worldwide.

To the best of our knowledge, the genetic variants of *OBFC1* in the progression and development of LC remains unclear. To overcome these limitations, our study design eliminates whether the variation within *OBFC1* gene is related to in the susceptibility of LC. We carefully choose the SNPs which had minor allele frequencies (MAFs) > 5% in global population based on 1000 Genomes Project (http://www.1000genomes.org/) and dbSNP (https://www.ncbi.nlm.nih.gov/SNP/) databases, and had some previous studies. Finally, a total of five SNPs (i.e., rs9325507, rs3814220, rs12765878, rs11191865, rs9420907) were selected for further genotyping.

Materials and methods

Study participants

A total of 172 unrelated LC patients and 180 healthy controls were recruited for this case–control study. All recruited subjects were unrelated ethnic Chinese Han males. The cases were recently diagnosed with LC for the first time, without any other severe diseases, treated at the First Affiliated Hospital of the Medical College of Xi'an Jiaotong University, the followed-up were included in the study from January 2002 to April 2013, as previously described [14]. LC was diagnosed by at least two senior pathologists at the Department of Pathology based on World Health Organization (WHO) criteria. Control subjects without any clinical signs or medical history of any types of malignancy histories, were selected from the health checkup center of the First Affiliated Hospital of the Medical College of Xi'an Jiaotong University. Collection of blood samples and clinical information were undertaken with fully informed consent from all the participants at the time of initial diagnose and in accordance with the tenets of the Declaration of Helsinki and the Human Research Ethics Committee of the First Affiliated Hospital of the Medical College of Xi'an Jiaotong University.

SNP selection and genotyping

Candidate SNPs in the *OBFC1* gene from the databases of 1000 Genomes Project (http://www.1000genomes.org/) and dbSNP (https://www.ncbi.nlm.nih.gov/SNP/) database with MAFs > 5% in global population, and had some previous studies were chosen. A total of five SNPs (i.e., rs9325507, rs3814220, rs12765878, rs11191865, rs9420707) were selected for further genotyping. These SNPs were analyzed in tumors or other diseases, such as breast and prostate cancer [15], aplastic anemia [13], and late-onset alzheimer disease [16]. Genomic DNA was extracted from peripheral blood of cases and controls using the GoldMag whole blood genomic DNA purification kit (GoldMag Co. Ltd., Xi'an, China), as recommended by the manufacturer's instructions [17]. DNA concentration was determined by the NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA, USA). MassARRAY Nanodispenser (Agena Bioscience, San Diego, CA, USA) was used to design primers for amplification process and single base extension reactions [18]. SNP genotyping was carried out on the MassARRAY iPLEX (Agena Bioscience, SanDiego, CA, USA). Agena Bioscience Typer 4.0 software was used to manage and analyze SNP genotypic data.

Statistical analysis

Statistical analyses were performed using Microsoft Excel and SPSS 17.0 (SPSS, Chicago, IL, USA) software. Deviation from Hardy–Weinberg equilibrium (HWE) was tested for control subjects to measure the distribution of the polymorphism using a Chi-square test [19]. The Haploview software package (version 4.2) and SHEsis software platform (http://analysis.bio-x.cn/myanalysis.php) were used for analyses of linkage disequilibrium, haplotype construction [20, 21]. Associations between haplotypes and LC risk were

Table 1 Characteristics of cases and controls included in this study

Variable	Case (males)	Control (males)	*P*
Total	172	180	
Age (year)	60.78 ± 10.05	60.25 ± 5.49	< 0.0001*
< 60	81	96	
≥ 60	91	84	
Tumor differentiation			
High	31		
Moderate	125		
Low	14		
Unavailable	2		
pT			
T1	40		
T2	62		
T3	50		
T4	18		
Unavailable	2		
pN			
N0	116		
N1	30		
N2	24		
Unavailable	2		
Clinical stage			
I	37		
II	36		
III	61		
IV	36		
Unavailable	2		
Surgery method			
Neck dissection	37		
Non-neck dissection	133		
Unavailable	2		

pT pathologic tumor stage, *pN* pathologic nodal stage

*$P < 0.05$ indicates statistical significance

analyzed by SNPStats (http://bioinfo.iconcologia.net/SNPstats) [22]. We used the unconditional logistic regression analysis adjusted for age and gender to determine the association between the haplotypes and LC. Two-sided *P* value less than 0.05 was considered statistically significant. The risk associated with individual genotypes and allele was calculated as the odds ratios (OR) with their 95% confidence interval (95% CI) based on logistic regression models analysis. The overall survival (OS) was estimated using the Kaplan–Meier method and compared by the log-rank test. Univariate Cox proportional hazards regression models were used to calculate the hazard ratios (HR), and 95% confidence intervals (95% CI) of the effect of *OBFC1* SNPs on the overall survival (OS) of LC patients.

Results

A cohort of 172 unrelated LC patients with a mean age of 60.78 ± 10.05 years and 180 unrelated controls with a mean age of 60.25 ± 5.49 years involved in this case–control study are presented in Table 1. There was a significant difference in age observed between the case and control groups ($P < 0.0001$). Clinical factors in the case group are included in Table 1, which include tumor differentiation status, pathologic tumor stage (pT), pathologic nodal stage (pN), clinical stage, surgery method.

Table 2 shows the basic information and allele frequencies for each SNP in LC patients and healthy controls. It is clear that information obtained from the table with regard to the SNPs and their chromosomal position, allele, minor allele frequency for cases and controls, and HWE test results. None of them were deviated from those expected by the Hardy–Weinberg equilibrium ($P > 0.05$), indicating good SNP genotyping quality. The minor allele frequency in the rs9325507 was 0.287 for cases compared with 0.314 for controls, which had a significant difference in allele frequency between cases and control groups (OR = 0.88, 95%

Table 2 Basic characteristics and allele frequencies of the five SNPs

SNP	Genes	Chr	Position	Allele	Minor allele frequency		HWE *P* value	OR (95% CI)	*P*[a]
					Case	Control			
rs9325507	*OBFC1*	10	105645622	T/C	0.287	0.314	0.0576	0.88 (0.64–1.21)	0.036*
rs3814220	*OBFC1*	10	105647300	G/A	0.289	0.317	0.1198	0.88 (0.63–1.21)	0.052
rs12765878	*OBFC1*	10	105669622	C/T	0.287	0.317	0.1198	0.87 (0.63–1.20)	0.085
rs11191865	*OBFC1*	10	105672842	A/G	0.284	0.317	0.1198	0.86 (0.62–1.18)	0.009*
rs9420907	*OBFC1*	10	105676465	C/A	0.006	0.011	1.0000	0.52 (1.00–2.88)	0.685

SNP single nucleotide polymorphism, *OR* odds ratio, *95% CI* 95% confidence interval, *HWE* Hardy–Weinberg equilibrium

*$P < 0.05$ indicates statistical significance

[a]*P* values were calculated using Pearson's Chi-square test/Fisher's exact test

Table 3 *OBFC1* SNP genotypes and the risk of Laryngeal carcinoma based on the results of logistic regression model analysis

SNP	Genotype	Control	Case	Adjustment analysis		Crude analysis	
		N (%)	*N* (%)	OR (95% CI)[a]	*P*[a]	OR (95% CI)[b]	*P*[b]
Rs9325507							
Codominant	C/C	79 (43.9%)	91 (53.2%)	1.00		1.00	
	T/C	89 (49.4%)	62 (36.3%)	0.61 (0.39–0.95)	0.038*	0.60 (0.39–0.94)	0.036*
	T/T	12 (6.7%)	18 (10.5%)	1.30 (0.59–2.87)		1.30 (0.59–2.87)	
Dominant	C/C	79 (43.9%)	91 (53.2%)	1.00		1.00	
	T/C + T/T	101 (56.1%)	80 (46.8%)	0.69 (0.45–1.05)	0.084	0.69 (0.45–1.05)	0.080
Recessive	C/C + T/C	168 (93.3%)	153 (89.5%)	1.00		1.00	
	T/T	12 (6.7%)	18 (10.5%)	1.64 (0.76–3.52)	0.200	1.65 (0.77–3.53)	0.200
Overdominant	C/C + T/T	91 (50.6%)	109 (63.7%)	1.00		1.00	
	T/C	89 (49.4%)	62 (36.3%)	0.58 (0.38–0.90)	0.014*	0.58 (0.38–0.89)	0.012*
Log-additive	–	–	–	0.88 (0.63–1.22)	0.430	0.88 (0.63–1.21	0.420
Rs3814220							
Codominant	A/A	79 (43.9%)	89 (53.0%)	1.00		1.00	
	G/A	88 (48.9%)	61 (36.3%)	0.62 (0.40–0.97)	0.057	0.62 (0.39–0.96)	0.052
	G/G	13 (7.2%)	18 (10.7%)	1.22 (0.56–2.66)		1.23 (0.57–2.67)	
Dominant	A/A	79 (43.9%)	89 (53.0%)	1.00		1.00	
	G/A + G/G	101 (56.1%)	79 (47.0%)	0.70 (0.46–1.06)	0.094	0.69 (0.46–1.06)	0.090
Recessive	A/A + G/A	167 (92.8%)	150 (89.3%)	1.00		1.00	
	G/G	13 (7.2%)	18 (10.7%)	1.53 (0.72–3.23)	0.260	1.54 (0.73–3.25)	0.250
Overdominant	A/A + G/G	92 (51.1%)	107 (63.7%)	1.00		1.00	
	G/A	88 (48.9%)	61 (36.3%)	0.60 (0.39–0.92)	0.020*	0.60 (0.39–0.92)	0.018*
Log-additive	–	–	–	0.87 (0.63–1.21)	0.420	0.87 (0.63–1.21)	0.420
Rs12765878							
Codominant	T/T	79 (43.9%)	89 (52.7%)	1.00		1.00	
	C/T	88 (48.9%)	63 (37.3%)	0.64 (0.41–1.00)	0.089	0.64 (0.41–0.99)	0.084
	C/C	13 (7.2%)	17 (10.1%)	1.17 (0.53–2.56)		1.16 (0.53–2.54)	
Dominant	T/T	79 (43.9%)	89 (52.7%)	1.00		1.00	
	C/T + C/C	101 (56.1%)	80 (47.3%)	0.71 (0.46–1.08)	0.110	0.70 (0.46–1.07)	0.100
Recessive	T/T + C/T	167 (92.8%)	152 (89.9%)	1.00		1.00	
	C/C	13 (7.2%)	17 (10.1%)	1.44 (0.68–3.07)	0.340	1.44 (0.68–3.06)	0.340
Overdominant	T/T + C/C	92 (51.1%)	106 (62.7%)	1.00		1.00	
	C/T	88 (48.9%)	63 (37.3%)	0.62 (0.41–0.96)	0.030*	0.62 (0.41–0.95)	0.028*
Log-additive	–	–	–	0.87 (0.63–1.21)	0.40	0.87 (0.62–1.20)	0.390
rs11191865							
Codominant	G/G	79 (43.9%)	93 (55.0%)	1.00		1.00	
	A/G	88 (48.9%)	56 (33.1%)	0.55 (0.35–0.86)	0.010*	0.54 (0.34–0.85)	0.009*
	A/A	13 (7.2%)	20 (11.8%)	1.31 (0.61–2.79)		1.31 (0.61–2.79)	
Dominant	G/G	79 (43.9%)	93 (55.0%)	1.00		1.00	
	A/G + A/A	101 (56.1%)	76 (45.0%)	0.64 (0.42–0.98)	0.041*	0.64 (0.42–0.98)	0.037*
Recessive	G/G + A/G	167 (92.8%)	149 (88.2%)	1.00		1.00	
	A/A	13 (7.2%)	20 (11.8%)	1.71 (0.82–3.57)	0.150	1.72 (0.83–3.59)	0.140
Overdominant	G/G + A/A	92 (51.1%)	113 (66.9%)	1.00		1.00	
	A/G	88 (48.9%)	56 (33.1%)	0.52 (0.34–0.81)	0.003*	0.52 (0.34–0.80)	0.003*
Log-additive	–	–	–	0.86 (0.62–1.19)	0.370	0.86 (0.62–1.18)	0.350

SNPs single nucleotide polymorphisms, *OR* odds ratio, *95% CI* 95% confidence interval

*$P < 0.05$ indicates statistical significance

[a]*P* values were calculated by unconditional logistic regression adjusted for age

[b]*P* values were calculated by unconditional logistic regression without adjustment for age

CI 0.64–1.21, $P=0.036$). In addition, the A allele frequency distribution of SNP rs11191865 also existed a significant difference between patients with LC patients and control subjects (OR = 0.86, 95% CI 0.62–1.18, $P=0.009$).

Comparisons of the SNP genotypes and the risk of LC under the genetic models are presented in Table 3. We observed a lower risk of LC in rs9325507 according to the codominant model (OR = 0.61, 95% CI 0.39–0.95, $P=0.038$ for the T/C genotype), overdominant model (OR = 0.58, 95% CI 0.38–0.90, $P=0.014$) analyses adjusted for age. In addition, we also observed a statistically significant association between the lower risk of LC and the rs3814220 G/A genotype (OR = 0.60, 95% CI 0.39–0.92, $P=0.020$) as well as the rs12765878 C/T genotype (OR = 0.62, 95% CI 0.41–0.96, $P=0.030$) under overdominant model with adjustment for age. Furthermore, a statistically significant association between the lower risk of LC and rs11191865 under codominant model (OR = 0.55, 95% CI 0.35–0.86, $P=0.010$ for the A/G genotype), dominant model (OR = 0.64, 95% CI 0.42–0.98, $P=0.041$) and overdominant model (OR = 0.52, 95% CI 0.34–0.81, $P=0.003$) with adjustment for age was observed.

The results for the association between the *OBFC1* haplotype and the risk of LC are shown in Table 4. In the linkage analyses, four *OBFC1* SNPs (rs9325507, rs3814220, rs12765878, and rs11191865) mapped in a 27 kb LD block (Fig. 1), however, there were no significant differences in haplotype frequencies among any of the groups.

Then, we evaluated the effect of *OBFC1* polymorphism on the LC patient overall survival, as shown in Table 5. However, no significant correlations were identified between *OBFC1* polymorphism and the prognosis of LC.

Discussion

Telomere length, structure, and integrity are critical for the cells and the organism as a whole, and telomere function is essential to maintain the physical integrity of linear chromosomes and healthy human aging. Our case–control study aims to determine whether telomere length-related gene *OBFC1* is associated with laryngeal carcinoma risk in Chinese Han population. From our analyses, we found two SNPs (rs9325507, rs11191865) are related to LC at allele frequencies levels and all SNPs within *OBFC1* in our experiment are related to the lower risk of LC.

OBFC1, a human homolog of yeast Stn1, is associated with the replication and capping of telomeres [23]. The SNP rs9325507 and rs11191865 were studied for the association of relative telomere length and prostate, lung, colorectal, and ovarian cancer screening trial using genome-wide genotyping data [15], but no positive results were found. However, rs9325507 and rs3814220 were studied in human leukocyte telomere length (LTL), results produced the P value less than 5×10^{-7}, confirming that these locus are associated with LTL [24]. The connection of rs12765878 and late-onset alzheimer disease in a genetically isolated Dutch population was investigated through genome-wide screen [16]. Rs11191865 is a SNP involvement in systemic sclerosis (SSc)-related interstitial lung disease (ILD) (OR = 1.09, 95% CI 1.00–1.19, $P=0.043$).

In our study, the A/G genotype of rs11191865 was most significantly associated with a lower OR for LC based on the results of logistic regression model analysis (OR = 0.52, 95% CI 0.34–0.81, $P=0.003$). Previous study demonstrated that ectopic expression of the *OBFC1* is involved in telomere elongation and protects telomeres [6, 25]. Thus, we speculate that these mutations within *OBFC1* in our experiment that result of silencing *OBFC1* and overexpression of mutant resulted in shortening telomeres in LC tumor cells. Telomere shortening and its potential correlation with downregulation of cell cycle regulator p16/Rb and p53/p21 pathways were studied from breast cancer patients [26], which are critical in promoting cell cycle progression and proliferation. Silencing *OBFC1* may be a protective factor for LC carcinogenesis and accompanied by a reduced tumorigenic risk. But these speculations were needed to further investigate.

With regard to the mechanism for *OBFC1* regulates telomere length, one possibility is that the *OBFC1* mutants significantly interferes with normal *OBFC1* function and further negatively regulate telomerase recruitment [6]. In human cells,

Table 4 *OBFC1* haplotype frequencies and the association with Laryngeal carcinoma

rs9325507	rs3814220	rs12765878	rs11191865	Freq	Adjusted analysis		Crude analysis	
					OR (95% CI)[a]	P^a	OR (95% CI)[b]	P^b
C	A	T	G	0.6844	1.00	–	1.00	–
T	G	C	A	0.2895	0.83 (0.59–1.17)	0.290	0.83 (0.59–1.16)	0.270

OR odds ratio; *95% CI* 95% confidence interval

[a] *P* values were calculated by unconditional logistic regression adjusted for age

[b] *P* values were calculated by unconditional logistic regression without adjusted for age

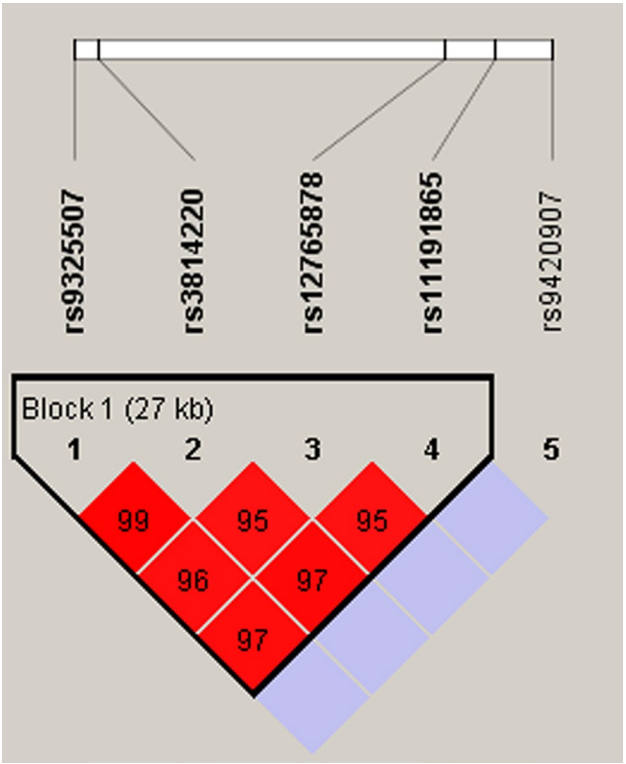

Fig. 1 Haplotype block map for SNPs of the *OBFC1* gene. LD is displayed by standard color schemes with bright red for very strong LD (LOD > 2, $D' = 1$), pink red (LOD > 2, $D' < 1$) and blue (LOD < 2, $D' = 1$) for partial linkage, and white (LOD < 2, $D' < 1$) for complete recombination

OBFC1 is known to interact with telomeric protein TPP1, which has been shown to interact with telomerase and telomere ssDNA-binding protein *POT1* to control telomere homeostasis and integrity [27]. Alternatively, *OBFC1* may complex with other unknown proteins and form the functionally equivalent of yeast CST complex at mammalian telomeres, a complex can bind DNA polymerases via Stn1 to mediate C-strand synthesis of the telomere DNA [28]. Suggesting that *OBFC1* may regulate telomere length through DNA polymerases in a fashion similar to yeast Stn1 [29].

The present study has some limitations. First, small sample size is a major weakness of our study and larger samples would be needed to reach significance after adjustment for multiple testing. Small sample size leads to limited stratified data that is not suitable for further stratified analysis. Second, some other genetic polymorphisms may play a role in the development of LC, but our study only investigated the association between part of the *OBFC1* SNPs and the risk of LC. Third, due to data deficiencies of some exposure information, gene-environment interactions were not detected in current study.

Conclusions

In conclusion, we confirm that genetic loci in our experiment are associated with lower risk for LC in Chinese Han population. Our findings represent an important step for preliminary understanding of the *OBFC1* gene involvement in LC. Future investigations will be identify how these relevant variants within *OBFC1* affect LC and determine the underlying mechanism via cell culture or knock-out mice models, which will provide new evidence that *OBFC1* may be used as a promising marker to better screening and early diagnosis for LC.

Table 5 Univariate analysis of the association between *OBFC1* SNPs and overall survival in LC patients

SNP ID	Genotype	Total	Event	SR (3-/5-year)	Log-rank *p*	HR (95% CI)	*P*
Rs9325507	C/C	91	47	0.602/0.519	0.184	1.00	
	T/C	62	44	0.482/0.353		1.15 (0.59–0.24)	0.676
	T/T	18	11	0.658/–		1.66 (0.85–3.26)	0.138
Rs3814220	A/A	89	47	0.617/0.507	0.407	1.00	
	G/A	61	41	0.523/0.369		1.19 (0.61–2.31)	0.605
	G/G	18	11	0.658/–		1.53 (0.77–3.00)	0.222
Rs12765878	T/T	89	48	0.593/0.492	0.344	1.00	
	C/T	63	42	0.506/0.395		0.75 (0.38–1.49)	0.410
	CC	17	10	0.679/–		1.29 (0.85–1.96)	0.228
rs11191865	G/G	93	49	0.599/0.478	0.117		
	A/G	56	40	0.480/0.362		0.71 (0.37–1.38)	0.315
	A/A	20	11	0.693/–		1.46 (0.96–2.22)	0.077

LC Laryngeal carcinoma, *SR* survival rate, *HR* hazard ratio, *95% CI* 95% confidence interval

Log-rank *P* values were calculated using the Chi-square test

$P < 0.05$ indicates statistical significance

Acknowledgements The authors are grateful to the patients and control individuals for their participation in the study. We thank for the clinicians and hospital staff who contributed to sample and data collection for this study. This study was funded by Natural Science Foundation of China (No. 81803317) and Fundamental Research Funds for the Central Universities, China (No. xjj2018094).

Compliance with ethical standards

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

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