RESEARCH ARTICLE

Association of lnc-LAMC2-1:1 rs2147578 and CASC8 rs10505477 Polymorphisms with Risk of Childhood Acute Lymphoblastic Leukemia

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Abstract

Long non-coding RNAs (lncRNAs) are a novel class of non-protein coding RNAs that are involved in a wide variety of biological processes. There are limited data regarding the impact of lnc-LAMC2-1:1 rs2147578 as well as CASC8 rs10505477 T>C polymorphisms on cancer development. Here we examined for the first time whether rs2147578 and rs10505477 polymorphisms are associated with childhood acute lymphoblastic leukemia (ALL) in a total of 110 cases and 120 healthy controls. Genotyping was achieved by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The rs2147578 variant increased the risk of ALL in codominant (OR=4.33, 95%CI=2.00-9.37, p<0.0001, CG vs CC, and OR=5.81, 95%CI=2.30-14.69, p=0.0002, GG vs CC), dominant (OR=4.63, 95%CI=2.18-9.86, p<0.0001, CG+GG vs CC), overdominant (OR=1.74, 95%CI=1.02-2.97, p=0.0444, CG vs CC+GG) and allele (OR=1.91, 95%CI=1.32-2.77, p=0.0008, G vs C) inheritance models tested. No significant association was found between the CASC8 rs10505477 T>C variant and risk of childhood ALL. In conclusion, the present study revealed that the lnc-LAMC2-1:1 rs2147578 polymorphism may be a risk factor for developing childhood ALL. Further studies with larger sample sizes with different ethnicities are now required to confirm our findings.

Keywords: Long non-coding RNA- lnc-LAMC2-1:1- CASC8- acute lymphoblastic leukemia- Polymorphism

Asian Pac J Cancer Prev, **17 (11)**, 4985-4989

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of malignancy diagnosed in children and constitutes about 75% of pediatric acute leukemias (Siegel et al., 2013). Though the etiology of ALL is not completely understood, a great number of genes have been shown to be associated with the development of childhood ALL (Hasani et al., 2014; Bahari et al., 2016a; Bahari et al., 2016b; Tong et al., 2016).

Non-coding RNAs (ncRNAs) divided into microRNAs (~22 nucleotides) and long non-coding RNAs (lncRNAs) which are longer that 200 nucleotides and do not serve as templates for proteins (Rinn and Chang, 2012). LncRNAs as an emerging kind of non-coding RNA have gained extensive attention for their biological regulatory functions (Kung et al., 2013). It has been proposed that lncRNAs can control gene expression at diverse levels including chromatin modification (Gupta et al., 2010), transcription, and post-transcriptional processing (Tripathi et al., 2010; Qi and Du, 2013) and are having many kinds of functions in different physiological as well as pathological processes such as tumorigenesis (Shang et al., 2016). Single nucleotide polymorphisms (SNP) can affect gene expression or protein function. Cumulative evidence shows that SNPs in some lncRNAs are linked to carcinogenesis and chemotherapy response (Shen et al., 2014; Kang et al., 2015; Gong et al., 2016b; Li et al., 2016; Shang et al., 2016).

The rs2147578 polymorphism of lnc-LAMC2-1:1 is located on chromosome 1 at position 183107699 (Gong et al., 2016a). There is only one study regarding the association of this variant and the risk of cancer. For the first time, Gong et al (Gong et al., 2016a) showed that lnc-LAMC2-1:1 rs2147578 polymorphism significantly increased the risk of colorectal cancer.

Cancer susceptibility candidate 8 (CASC8) gene is a lncRNA mapped on chromosome 8 (8q24.21) (Ma et al., 2015). The rs10505477 variant, located in the intron of lncRNA CASC8 gene, has been indicated to be associated with colorectal cancer (CRC) risk (Tomlinson et al., 2007; Zanke et al., 2007; He et al., 2011) and the prognosis of gastric cancer (Ma et al., 2015).

In the present study, for the first time, we examined the impact of lnc-LAMC2-1:1 rs2147578 and CASC8 rs10505477 T>C on risk of childhood ALL in a sample

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of Iranian population.

Materials and Methods

Patients

The current case-control study included 110 children diagnosed with ALL and 120 age- and sex-matched healthy children in Zahedan, southeast Iran. The study design and enrolment process have been described previously (Hasani et al., 2014; Bahari et al., 2016a; Bahari et al., 2016b; Bahari et al., 2016c; Hashemi et al., 2016). The local Ethics Committee of Zahedan University of Medical Sciences approved the project and informed consent was taken from parents of all participants. Extraction of genomic DNA from whole blood was done by using salting out method (Hashemi et al., 2013).

Genotyping

We designed polymerase chain reaction restriction fragment lengths polymorphism (PCR–RFLP) method for detection the variants. For lnc-LAMC2-1:1 rs2147578 polymorphisms, the sequence of forward and reverse primers were 5′- CACGAACTTGTGGTTACTTGCTCAC-3′ and 5′-ATCCAAACCAACATCCACCCC-3′, respectively. Into each 0.20 ml PCR reaction tube, 1 µl genomic DNA (~100 ng/ml), 1 µl (10 µM) forward and reverse primers, 10 µl 2X Prime Taq Premix (Genet Bio, Korea), and 7 µl ddH2O were added. The PCR conditions were as follows: 6 min preheating at 95°C, 30 cycles of 95°C for 30s, 68°C for 30s, and 72 °C for 30s followed by a final extension step for 5 min at 72 °C. Then, 10 µl of amplified product was digested by TaaI restriction enzyme (Fermentas) according to the manufacturer's procedure. The C allele digested and produced two fragments (154-bp and 82-bp), while G allele was undigested (236-bp fragment) (Figure 1).

Regarding CASC8 rs10505477 T>C variant, we designed mismatch PCR–RFLP. The forward and reverse primers were 5′- GGAAGAATTTAAAGGAGAGCAGGGA -3′ and 5′-CTTTGCCCCTTTTCTAAATCTTCATCTgC -3′, respectively. The PCR conditions were as follows: 6 min preheating at 95°C, 30 cycles of 95°C for 30s, 60°C for 30s, and 72 °C for 30 s followed by a final extension step for 5 min at 72 °C. Then, 10 µl of amplified product was digested by PstI restriction enzyme (Fermentas) according to the manufacturer's procedure. The C allele digested and produced two fragments (200-bp and 28-bp), while T allele was undigested (228-bp fragment) (Figure 2).

For quality control, repeated analyses were done for 20% randomly selected samples and the finding showed 100% concordance.

Statistical analysis

Data were summarized using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Statistical analysis of the data was done by statistical package SPSS 22 software. The categorical and continuous data were analyzed using $\chi 2$ and t-test, respectively. Individual SNP associations with childhood ALL risk were calculated using unconditional logistic regression analyses, in which ORs and 95% CIs were estimated. Hardy- Weinberg equilibrium (HWE) was calculated by $\chi 2$ test. The statistical level of significance was defined as $P<0.05$.

Results

A total of 230 subjects including 110 confirmed childhood ALL (65 male, 45 female; age 6.0 ± 3.9 years) and 120 unrelated healthy children (57 male, 63 female; age 5.6 ± 2.1 years) were evaluated. No significant difference was found between the groups regarding sex and age (p=0.087 and p=0.369, respectively).

The genotype and allele distributions of lnc-LAMC2-1:1 rs2147578 C>G polymorphism in ALL and healthy children are displayed in table 1. The finding revealed that rs2147578 variant increased the risk of ALL in codominant (OR=4.33, 95%CI=2.00-9.37, p<0.001, CG vs CC; OR=5.81, 95%CI=2.30-14.69, p<0.001, GG vs CC), dominant (OR=4.63, 95%CI=2.18-9.86, p<0.001, CG+GG vs CC), and overdominant (OR=1.74, 95%CI=1.0-3.0, p=0.044, CG vs CC+GG) inheritance models tested. The G allele was associated with increased risk of childhood ALL (OR=1.9, 95%CI=1.3-2.8 p <0.001) compared to C allele.

Our findings showed that CASC8 rs10505477 T>C

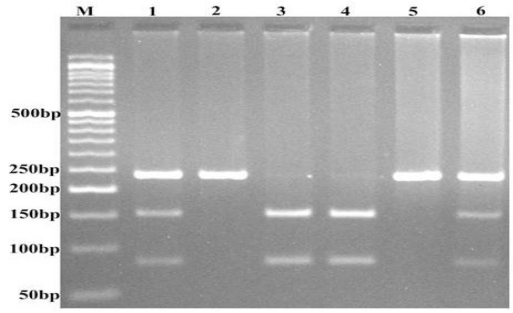

Figure 1. Photograph of Electrophoresis Pattern of the PCR-RFLP Method for Detection of lnc-LAMC2-1:1 rs2147578 C>G polymorphism.
C allele digested by TaaI restriction enzyeme and produces 152 and 82 bp fragments and the G allele undigested (236 bp). M: DNA marker; Lanes 1 and 6: CG; Lanes 2 and 5: GG; Lanes 3 and 4: CC.

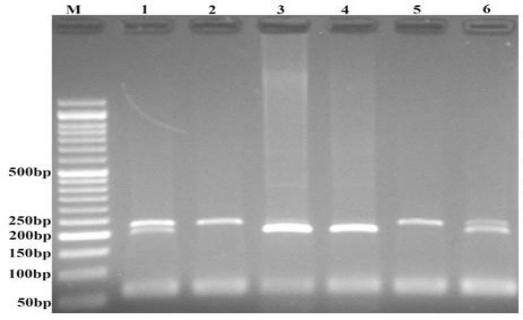

Figure 2. Photograph of Electrophoresis Pattern of the PCR-RFLP Method for Detection of CASC8 rs10505477 T>C.
C allele digested by PstI restriction enzyeme and produces 200 and 28 bp fragments, while the T allele undigested (228 bp). M: DNA marker; Lanes 1 and 6: TC; Lanes 2 and 5: TT; Lanes 3 and 4: CC

Table 1. Association of lnc-LAMC2-1:1 rs2147578 and CASC8 rs10505477 T>C Polymorphism and the Risk of ALL

Polymorphism	Case n (%)	Control n (%)	OR (95%CI)	p
lnc-LAMC2-1:1 rs2147578				
Codominant				
CC	10 (9.1)	38 (31.7)	1.0	-
CG	74 (67.3)	65 (54.2)	4.3 (2.0-9.4)	<0.001
GG	26 (23.6)	17 (14.1)	5.8 (2.3-14.7)	<0.001
Dominant				
CC	10 (9.1)	38 (31.7)	1.0	-
CG+GG	100 (90.9)	82 (68.3)	4.6 (2.2-9.9)	<0.001
Recessive				
CC+CG	84 (76.4)	103 (85.9)	1.0	-
GG	26 (23.6)	17 (14.1)	1.9 (0.9-3.7)	0.089
Overdominant				
CC+GG	36 (32.7)	55 (45.8)	1	-
CG	74 (67.3)	65 (54.2)	1.7 (1.0-3.0)	0.044
Allele				
C	94 (42.7)	141 (58.7)	1.0	-
G	126 (57.3)	99 (41.3)	1.9 (1.3-2.8)	<0.001
CASC8 rs10505477 T>C				
Codominant				
TT	40 (36.4)	35 (29.2)	1.0	-
TC	43 (39.1)	56 (46.6)	0.7 (0.4-1.2)	0.222
CC	27 (24.5)	29 (24.2)	0.8 (0.4-1.6)	0.599
Dominant				
TT	40 (36.4)	35 (29.2)	1.0	-
TC+CC	70 (63.6)	85 (70.8)	0.7 (0.4-1.2)	0.265
Recessive				
TT+TC	83 (75.5)	91 (75.8)	1.0	-
CC	27 (24.5)	29 (24.2)	1.0 (0.6-1.9)	0.976
Overdominant				
TT+CC	67 (60.9)	64 (53.4)	1.0	-
TC	43 (39.1)	56 (46.6)	0.7 (0.4-1.2)	0.287
Allele				
T	123 (60.4)	126 (52.5)	1.0	-
C	97 (39.6)	114 (47.5)	0.9 (0.6-1.3)	0.512

variant may not be associated with the risk of childhood ALL in any inheritance models tested (table 1).

Association between the lnc-LAMC2-1:1 rs2147578 C>G and CASC8 rs10505477 T>C polymorphisms with the patients' clinical characteristics were evaluated. As shown in Table 2, a significant association between rs2147578 C>G and platelet count was found (p=0.023).

The genotype distribution of the lnc-LAMC2-1:1 rs2147578 C>G and CASC8 rs10505477 T>C polymorphisms in control group were consistent with the HWE ($\chi2$=1.66, P=0.198 and $\chi2$=0.496, P=0.481, respectively).

Discussion

Although the functional roles of lncRNAs remained mostly elusive, increasing evidence shows that up to 90% of the non-coding transcripts in the human genome have significant and diverse biological roles (Geisler and Coller, 2013).

It has been proposed that gene expression or protein function is affected by SNPs. Growing evidence validates that SNPs in some lncRNAs are related to tumorigenesis and chemotherapy response (Shen et al., 2014; Kang et al., 2015; Gong et al., 2016b; Li et al., 2016; Ronchetti et al., 2016; Shang et al., 2016). Abnormal expression of lncRNAs in various cancers (Morris, 2009; Han et al., 2012; Hauptman and Glavac, 2013; Rodriguez-Malave et al., 2015; Ricciuti et al., 2016) proposed the potentially tumor suppressor or oncogenic role (Emmrich et al., 2014; Yang et al., 2014; Morlando et al., 2015; Sun et al., 2015; Xing et al., 2015).

It has been shown that overexpression of lncRNA BALR-2 led to increased cell growth and resistance to

Table 2. Association of lnc-LAMC2-1:1 rs2147578 Polymorphism with Demographic and Clinical Features of Patients

Factors	lnc-LAMC2-1:	1 rs2147578	C>G	p	CASC8	rs10505477	T>C	p
	CC	CG	GG		TT	TC	CC	
Sex				0.513				0.189
Male	7.0	41.0	17.0		21.0	30.0.	14.0	
Female	3.0	33.0	9.0		19.0	13.0	13.0	
Age at diagnosis (Years)	4.9±2.1	5.7±3.6	7.2±4.9	0.161	5.9±4.5	6.50±3.53	5.3±3.4	0.469
WBC ($\times 10^6$/mL)	36.1±29.5	33.1±45.1	55.1±71.7	0.177	35.9±40.9	46.23±64.21	30.8±44.3	0.43
Hemoglobin (g/dL)	7.4±2.3	7.1±2.4	7.6±1.6	0.948	7.1±2.2	7.43±2.43	7.0±2.0	0.714
Platelet ($\times 10^6$/mL)	43.8±44.1	65.0±53.0	35.9±31.6	0.023	54.9±50.5	53.54±54.67	62.4±39.0	0.754
Organomegally				0.418				0.816
Positive	9.0	69.0	22.0		36.0	40.0	24.0	
Negative	1.0	5.0	4.0		4.0	3.0	3.0	
Lymphadenopathy				0.066				0.9
Positive	9.0	54.0	14.0		27.0	31.0	19.0	
Negative	1.0	20.0	12.0		13.0	12.0	8.0	
Cerebrospinal fluid involvement				0.527				0.114
Positive	0.0	6.0	3.0		3.0	6.0	0.0	
Negative	10.0	68.0	23.0		37.0	37.0	26.0	

prednisone treatment in B-acute lymphoblastic leukemia (B-ALL) (Fernando et al., 2015). Zeng et al.,(2015) showed that lncRNA PVT1 is upregulated in acute promyelocytic leukemia (APL) cells. LncRNA HOTAIR is upregulated in acute myeloid leukemia (AML) and highly expressed HOTAIR significantly associated with a poor clinicopathological prognostic stratification (Hao and Shao, 2015).

The lnc-LAMC2-1:1 locates on chromosome 1, overlaps with the protein-coding gene LAMC1 and is close to LAMC2. There is only one report concerning the impact of lnc-LAMC2-1:1 rs2147578 variant on cancer risk. For the first time, Gong et al (Gong et al., 2016a) showed that CG and GG genotypes of the rs2147578 variant of lnc-LAMC2-1:1 significantly increased the risk for colorectal cancer (CRC) compared to the rs2147578 CC genotype. Bioinformatics analyses revealed that rs2147578 is located in the transcript of lnc-LAMC2-1:1 and could influence the binding of lnc-LAMC2-1:1/miR-128-3p (Gong et al., 2016a). In the current study we inspected the impact of lnc-LAMC2-1:1 rs2147578 C>G on risk of childhood ALL. Our finding showed that CG, GG and CG+GG genotypes significantly increased the risk of childhood ALL risk. Furtheremore, the rs2147578 G allele significantly increased the risk of childhood ALL compared with the C allele.

Current evidence proposed that CASC8 rs10505477 variant is related to developing of numerous cancers including CRC (Li et al., 2015; Yao et al., 2015), gastric cancer (Zhou et al., 2014; Ma et al., 2015) and ovarian cancer (Ghoussaini et al., 2008).

It has been proposed that CASC8 rs10505477 variant could be used to determine the response and toxicity of platinum-based chemotherapy in lung cancer patients (Hu et al., 2016). In the present study, for the first time we evaluate the possible association between rs10505477 variant and risk of childhood ALL. The findings did not support an association between CASC8 rs10505477 T>C variant and risk/protection of childhood ALL risk.

In summary, the findings of this study proposed that lnc-LAMC2-1:1 rs2147578 C>G polymorphism significantly increased the risk of childhood ALL in a sample of Iranian population. Further studies with larger sample sizes and different ethnicities are needed to confirm our findings.

Acknowledgements

This paper was funded as a research grant from the Deputy for Research, Zahedan University of Medical Sciences.

Conflicts of interest

All of the authors declare that there are no conflicts of interest.

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