

Association between genetic polymorphism of *XRCC7* (G6721T) and acute lymphoblastic leukemia risk

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Abstract

Background: One of the most important DNA double-strand break (DSBs) repair genes is *XRCC7* involved in non-homologous end joining (NHEJ). It is supposed that DNA repair gene malfunction is an important risk factor in various malignancies. The *XRCC7* G6721T (rs7003908) polymorphism effect were investigated on the splicing regulation that cause mRNA instability.

Objective: The aim of present hospital-based study was to investigate the association between the G6721T common genetic polymorphism of *XRCC7* and risk of acute lymphoblastic leukemia (ALL).

Methods: This case-control study was performed on 99 ALL patients versus 200 healthy blood donors (children), as the control group. Controls had no history of ALL, and they were frequent-matched by age with cases. The polymorphism of *XRCC7* was determined using an RFLP-PCR method.

Results: The GT (OR= 1.485, 95% CI: 0.765-2.334, $P=0.243$) and TT (OR= 1.655, 95% CI: 0.875-3.128, $P=0.121$) genotypes had no significant effect on risk of ALL, in comparison with the GG genotype. Hence, TT genotype (OR= 1.996, 95% CI: 1.033-3.858, $P=0.04$) after adjusting for parents smoking pattern showed a significant effect.

Conclusion: The presence of the TT genotype may be increase the risk of ALL in children when facing with a Tobacco smoke.

Background

Acute lymphoblastic leukemia (ALL) is the most prevalent type of cancer amongst children [1]. Its etiology is still unknown; however, several factors are involved in the causality of ALL. As risk factor, childhood ALL is related to genetic syndromes, ionizing radiation and genetic susceptibility. Environmental factors can play a part in the accumulation of somatic mutations in children [2].

It is known that genes are involved in DNA repair, crucial in protection against mutations, which preserve the unity of genetic material [3,4]. Decline in DNA repair capacity is related to increased birth defects, cancer, etc. [4]. Although mutations are the main cause of carcinogenesis, defective DNA repair is also a risk factor for many types of cancer [4]. One of the most harmful type of DNA damage is the double-strand break (DSB), which might lead to DNA missing its physical integrity and data content on both strands [5]. The two important pathways for removing the DSBs are homologous recombination (HR) and non-homologous end joining (NHEJ), provided by exogenous and endogenous carcinogens. It is worth mentioning that for DSBs repair, the NHEJ is the main pathway in human cells [5].

The human X-ray repair cross-complementing group 7 (*XRCC7*) (GenBank accession no.: NM_001469) plays a main role in the NHEJ pathway [6]. It encodes the catalytic subunit of DNA-activated protein kinase (DNA-PKcs), which is recruited for the DSBs by the KU70/KU80 heterodimer to create an active

DNA-PK complex. In addition, it is crucial for the progress of the NHEJ pathway [6,7]. The XRCC7 G6721T (rs.7003908) polymorphism is located in intron 8 that might regulate splicing and cause mRNA instability [6]. Although NHEJ is the main pathway for DSBs, only a few studies have investigated the association between XRCC7 G6721T polymorphism and cancers [8–13]. Therefore, the aim of this study was to evaluate the relation between XRCC7 G6721T polymorphism and ALL risk.

Methods

Patient samples

Patients with ALL under 18 years-old (n = 99) from 2016 to 2018 were identified at the Amir Oncology Hospital in Shiraz, Iran. The control group of healthy children without ALL (n = 200) were matched for age and gender in the same period selected for this study. Parents of patients or legal guardians provided a written informed consent form for participation in the study. This study was conducted according to the guidelines by the Declaration of Helsinki and its later amendments. The Institutional Review Board and Human Ethics Committee of Islamic Azad University of Kazerun approved this study.

DNA extraction and genotyping analysis

Genomic DNA was extracted from EDTA peripheral blood leukocytes using the Genomic DNA Purification Kit (QIAGEN, Germany). The G6721T polymorphism of XRCC7 with RFLP-PCR method was analyzed with the primers as described previously [11].

Statistical analysis

The sample groups determined to exhibit Hardy–Weinberg equilibrium for XRCC7 polymorphism with the χ^2 test. The correlation between the genotypes of XRCC7 and ALL risk in cases and controls the odds ratios (OR) and 95% confidence intervals (CIs) were calculated. The multivariate logistic regression were assessed including gender, parents smoking habits and cancer history in the family. Considering the association between the XRCC7 G6721T polymorphism and the risk of ALL cancer, the genotype data were further stratified by subgroups of gender, parents smoking habits, and cancer history in the family. Statistical significance was considered P value < 0.05 and two-tailed for all tests. Statistical analysis was performed using SPSS statistical software package (version 16) for windows (SPSS Inc., Chicago, IL, USA).

Results And Discussion

The frequency distributions of the selected characteristics for the ALL patients and control groups are summarized in Table 1. Their mean age (SD) of the patients and the controls was 5.87 (3.6) and 7.8 (5.2) years. Gender, parent's smoking habits and family cancer history differed significantly between cases and controls (P < 0.05). The cases had a significantly higher percentage of those characteristics in comparison with the controls. Our results showed that cigarette smoking habit of parents to be risk factor

for ALL. However, the age of diagnosis, blood type and T vs. B immune phenotype distribution did not differ significantly between the cases and controls ($P > 0.05$) (data not shown).

Table 1

Frequency distributions of selected variables between the acute lymphoblastic leukemia cases and controls

Variables	Cases (n = 99)	Controls (n = 200)	OR (95% CI)	P value*
	n (%)	n (%)		
Gender				
Male	64 (64%)	96 (48%)	1.00	
Female	36 (36%)	104 (52%)	0.51 (0.31–0.85)	0.009
Parents Smoking habit				
No	52 (52%)	120 (64.2%)	1.00	
Yes	48 (48%)	67 (35.8%)	1.77 (1.68–2.94)	0.027
Family Cancer history**				
No	26 (57.8%)	149 (88%)	1.00	
Yes	19 (42.2%)	42 (22%)	2.608 (1.311–5.385)	0.006
*P associated with either Student's t-test or chi-square test and Fisher's exact test.				
**Family history of Acute lymphoblastic leukemia in the first-degree relatives.				

Table 2 shows genotype distributions of the XRCC7 G6721T (rs7003908) polymorphism among the ALL patients and the control and the associations with the risk of ALL. The genotype frequencies of polymorphism in controls ($\chi^2 = 5.03$, $df = 1$, $P = 0.515$) and patients ($\chi^2 = 2.04$, $df = 1$, $P = 0.165$) were among Hardy-Weinberg equilibrium. The GT (OR = 1.485, 95% CI: 0.765–2.334, $P = 0.243$) and TT (OR = 1.655, 95% CI: 0.875–3.128, $P = 0.121$) in comparison with GG had no significant effect on the risk of ALL (Table 2). The association between ALL cancer risk and XRCC7 G6721T polymorphism was not assessed, although a few studies have analyzed correlation of this polymorphism with the risk of other cancers. The assumption was that dysfunction of human X-ray repair cross-complementing group 7 gene (XRCC7) might be involved in cancer susceptibility. It seems to be possible, based on the function of gene and by product of it, although the investigated intronic XRCC7 G6721T (rs.7003908) polymorphism seems to be controversial. Two studies suggested that XRCC7 G6721T polymorphism might contribute to cancer susceptibility for prostate and renal cell carcinoma [9,12]. On the contrary, Nasiri et al. [10] did not find any correlation between XRCC7 G6721T polymorphism and breast cancer, which was in line with our finding.

Table 2
Association between polymorphisms of XRCC7 and risk of ALL

XRCC 7 Polymorphism	Controls	Cases	OR	95% CI	P value
GG	54	19	1	References	
GT	67	34	1.485	0.765–2.334	0.243
TT	79	46	1.655	0.875–3.128	0.121

Moreover, after adjusting gender and history of family cancer, insignificant results were obtained for GT and TT genotype in comparison with GG (data are not shown). The results in Table 3 shows the distribution of XRCC7 G6721T polymorphism between the ALL and control groups among positive parent's smoking habits. The reference was individuals with negative parents smoking habit and GG genotype. The GT (OR = 1.637, 95% CI: 0.83–3.229, P = 0.155) genotype had no effect on the risk of ALL, but TT (OR = 1.996, 95% CI: 1.033–3.858, P = 0.04) genotype had significant effect on risk of ALL, in comparison with the GG genotype. Overall, there was an interaction between XRCC7 G6721T polymorphism, TT genotype, and positive parents smoking habit with the ALL susceptibility. No statistical significant differences were observed between the XRCC7 G6721T genotypes regarding gender, family history, IPT and TLC (data are not shown).

Table 3
The ALL cancer risk by positive parents smoking habit and the XRCC7 polymorphism

XRCC 7 Polymorphism	Controls	Cases	OR (95% CI) ‡	P value
GG	27	11	1	
GT	22	30	1.637(0.83–3.22)	0.15
TT	18	7	1.996(1.03–3.86)	0.04
‡ORs were adjusted for parents smoking status use in a logistic regression model				

According to the role of the NHEJ pathway in DNA repair, it is a logical possibility that the XRCC7 polymorphism might be regulating the risk of cancer accompanied by environmental risk factors such as smoking habit [11]. Carcinogens might enhance DSBs, leading to the genetic instability by increasing the rate of cancer development. It is known that the XRCC7 gene is responsible for repairing most DSBs [6]. Consequently, the variants of the XRCC7 gene could be expected to have an effect on DSB repair when people are exposed to carcinogens such as a Tobacco smoke.

Conclusions

In summary, to the best of our knowledge, this is the first study to investigate the role of XRCC7 polymorphism in susceptibility to childhood ALL. Interestingly, the TT genotype after adjusted with

positive parents smoking habit was associated with ALL cancer risk. Hence, the hospital-based study could improve the representative power by enlarging the sample size of the cases.

Declarations

Abbreviations: DSBs, double-strand break; NHEJ, non-homologous end joining; XRCC7, X-ray repair cross-complementing group 7; HR, homologous recombination; RFLP, restriction fragment length polymorphism; ALL, acute lymphoblastic leukemia

Ethics approval and consent to participate: Parents of patients or legal guardians provided a written informed consent form for participation in the study. The Institutional Review Board and Human Ethics Committee of Islamic Azad University of Kazerun approved this study.

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- Writing - original draft: Beyzaei Z,
- Writing - review & editing: Beyzaei Z, Ramzi M, Geramizadeh B, Farokhian F, Mokhtari MJ

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