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An Evaluation of OGG1 rs1052133C>G Polymorphism in Thyroid Cancer Susceptibility in the Northwestern Region of Iran

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ABSTRACT

Background and Objective: Thyroid cancer is the most common endocrine malignancy in the world. Genetic studies have focused on the role of polymorphisms in genes involved in DNA repair and the risk of cancer susceptibility. The OGG1 gene encodes a key enzyme in the DNA repair pathway. Studies show that the single nucleotide polymorphism rs1052133C>G is associated with an increased risk of developing various types of cancer. The aim of this study is to investigate the association between the aforementioned polymorphism and the risk of thyroid cancer susceptibility in the northwestern region of Iran.

Methods: In this case-control study, 104 patients with thyroid cancer (thyroid cancer tissue confirmed by a pathologist) and 166 controls (healthy individuals with no history of cancer in themselves or their first-degree relatives) were selected. Blood samples were collected and their DNA was extracted by the saturated salt method. OGG1 genotypes were identified and analyzed using the Tetra-ARMS PCR method.

Findings: In this study, the frequencies of CC, CG, and GG genotypes in the patient group were 53.84%, 38.46%, and 7.69%, respectively, and in the control group, 51.2%, 41.56%, and 7.22%, respectively. The frequencies of C and G alleles in the patient group were 73.06% and 26.92%, respectively, and in the control group, 71.98% and 28.01%, respectively. Based on the results obtained, no significant difference was observed between the patient group and the control group in different inheritance models.

Conclusion: The results of the study showed that there is no association between the rs1052133C>G polymorphism of the OGG1 gene and the risk of thyroid cancer in the northwestern region of Iran.

Keywords: *Polymorphism, OGG1 Gene, Thyroid Cancer, rs1052133.*

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Introduction

Thyroid cancer is the most common endocrine malignancy, accounting for 1.2% of all cancer diagnoses worldwide and 2.4% in Iran (1-3). This cancer can occur at any age, but studies show that its incidence is more common after the age of 30, and it is significantly more aggressive in older people (4, 5). Although the mortality rate from thyroid cancer is relatively low, the recurrence or persistence rate of the disease is high (6). Research shows that thyroid cancer is a complex multigenic disorder. In addition, the interaction of genetic and environmental factors also plays a role in the occurrence of this cancer. Based on the conducted studies, a significant relationship has been observed between genetic polymorphisms and an increase or decrease in the susceptibility of individuals to various cancers. Accordingly, genetic association studies have focused on the effect of single nucleotide polymorphisms in candidate genes and the risk of cancer. Among the most important candidate genes are those involved in DNA repair due to their critical role in maintaining genome integrity (7, 8).

One of the most important DNA repair pathways is the base excision repair pathway, which corrects DNA damage caused by oxidation, deamination, and alkylation. In the DNA repair pathway, the base excision repair pathway is initiated by DNA glycosylase. At least 110 distinct DNA glycosylases are known in mammals, each of which recognizes and removes several related lesions (9). The 8-oxoguanine DNA glycosylase-1 (OGG1) gene is a key enzyme in the DNA repair pathway (10). Human oxoguanine glycosylase is encoded by the OGG1 gene and is located on the short arm of chromosome 3 (3.3p26) (11, 12). The most common polymorphism of the OGG1 gene, which is observed with an average frequency of approximately 32% in the population (13), is located in exon 7 of this gene. As a result of this polymorphism, the amino acid serine in codon 326 of this enzyme is converted to the amino acid cysteine (Ser326Cys). This conversion, which occurs due to a C to G nucleotide change, reduces the ability of the OGG1 enzyme to cleave and repair 8-oxoG and leads to an increase in the conversion of GC to AT (14, 15).

Research shows that the single nucleotide polymorphism rs1052133C>G is associated with an increased risk of many cancers, including esophageal, lung, nasopharyngeal, prostate, endometrial, gastrointestinal, and head and neck cancers (16, 17). In addition, other studies have been conducted on the role of this polymorphism in the susceptibility to thyroid cancer in different populations. For example, based on studies conducted in the Spanish population (18), Portuguese population (19), Portuguese-Caucasian population (20), and Indonesian population (21), no significant association was found between the rs1052133C>G polymorphism of the OGG1 gene and thyroid cancer. Based on epidemiological studies, the pattern of cancer incidence can be different in different populations (22), which may be related to differences in the genetic background of the populations and racial differences (23). Therefore, it can be expected that genetic polymorphisms play different roles in the incidence of cancer in different populations (24). Given that no study has been reported on the association between the aforementioned polymorphism and the susceptibility to thyroid cancer in the northwest of Iran, the present study aimed to investigate the association between the OGG1 gene (rs1052133) polymorphism and the risk of thyroid cancer in the northwest of Iran. The results of this study, in addition to determining the allelic and genotypic frequency distribution of this polymorphism in the control and patient groups in the northwest Iranian population, can be analyzed in global meta-analytic studies on the association between this nucleotide polymorphism and thyroid cancer.

Methods

In order to conduct the present case-control study, based on statistical power analysis, 270 participants (5% margin of error with 95% confidence interval) were selected from the population of northwest Iran for as study samples. The sample size included 104 patients with cancer (63 women and 24 men) and 166 healthy individuals (144 women and 22 men). As inclusion criteria, patients who had been hospitalized for thyroid cancer in Imam Reza and Noor Nejat hospitals in Tabriz between 2009 and 2012 and had undergone thyroidectomy were considered as cases, and healthy individuals who had no history of any type of cancer in themselves or their first-degree relatives were included in the study as the control group. Healthy individuals with a previous history of cancer or a family history of cancer, as well as cancer patients who had been hospitalized but had not undergone thyroidectomy, were excluded from the study. It should be noted that the selection of control group members was done carefully by a physician. The study on human samples used in this study was approved by the ethics code number IR.AZARUNIV.REC.1403.004 at Tabriz University of Medical Sciences, and all study subjects have expressed their full consent by signing written consent forms.

Determination of OGG1 rs1052133C>G polymorphic genotypes: The saturated salt method was used to extract DNA and in order to examine the quantity and quality of the extracted DNA, the samples were loaded into a 2% agarose gel. The Tetra-Arms PCR method was used to determine the OGG1 rs1052133 polymorphic genotype. For this purpose, polymerase chain reaction (PCR) primers were designed, which include 4 primers as listed in Table 1.

Table 1. Tetra-Arms PCR primers, products, and conditions for the OGG1 rs1052133C>G gene

Product size	Type of primer	Melting temperature (degrees centigrade)	Sequence	Name of primer
406	control band	65	CAGCCCAGACCCAGTGGACTC	outer forward
406	control band	65	GGTAGTCACAGGGAGGCCCC	outer reverse
252	C	65	CAGTGCCGACCTGCGCCAATG	inner forward
194	G	65	TGGCTCCTGAGCATGGCGGG	inner reverse

The PCR reaction for the OGG1 gene had a final volume of 15 µL and consisted of 7.5 µL of master mix (Ampliqon, Denmark), 4.5 µL of distilled water for injection, 0.5 µL of each of the external primers and 0.5 µL of each of the inner primers, and 1 µL of DNA. The PCR reaction was performed using a thermocycler (Sensoquest, GmbH, Germany), with the following temperature and cycle time specifications: initial reaction for 10 min at 95°C, 30 reaction cycles for 1 min at 95°C, annealing for 1 min at 65°C, extension for 1 min at 72°C, and final extension for 5 min at 72°C. Then, the PCR reaction products were analyzed using 2% agarose gel and stained with Safe Stain (Sinaclon, Iran) using a MaestroGen Gel Documentation System, Taiwan. In this study, the Pearson chi-square test (with odds ratio and 95% confidence interval) was used to examine the differences in genotype and allele frequencies in the two control and patient groups. The study of SNPs using various bioinformatics tools is called In Silico Analysis. Various bioinformatics tools are used to analyze non-synonymous SNPs (non-synonymous single nucleotide polymorphisms= nsSNP), coding or non-coding. Since the rs1052133C>G polymorphism of the OGG1 gene is located in the coding region of the gene, statistical analyses in this study were performed using SIFT, PolyPhen-2, PhD-SNP, SNPs&GO, I-Mutant, and MUpro online websites and software.

Statistical analysis was performed using SPSS version 26. In order to examine the genotype distribution in sick and healthy populations, Hardy-Weinberg Equilibrium (HWE) was performed, which is available at http://www.oege.org/software/hwe-mr-calc.shtml. In addition, in order to examine the possible associations between the studied polymorphisms and the susceptibility to thyroid cancer as well as between clinicopathological features, Chi-square or Fisher's exact test was used. Odds Ratio (OR) was also performed by binary logistic regression. T-test was used for comparison between two groups. Normality of data distribution was determined based on Kolmogorov-Smirnov or Shapiro-Wilk test. Leven's test was also used to assess the homogeneity of variances. A confidence level of 95% and $p<0.05$ were considered significant.

Results

The genotype frequency distribution in the two patient and healthy populations for the rs1052133C> G polymorphism in the OGG1 gene followed Hardy-Weinberg equilibrium. The aforementioned polymorphism was genotyped for 104 patients with thyroid cancer with a mean age of 39±10.72 and 166 healthy individuals with a mean age of 43±6.45 as controls. After genotype determination, all patients and healthy individuals were divided into three genotype groups: GG, CG, and CC. The frequency distribution of the rs1052133C> G polymorphism genotypes in patients with thyroid cancer and controls is shown in Table 2. Based on statistical analysis performed with different models in this study, no significant association was observed between the frequency of GG, CG, and CC genotypes and the frequency of G and C alleles (p=0.78) for the OGG1 rs1052133C>G polymorphism between the patient and control groups. Among the types of thyroid cancer, papillary thyroid carcinoma had the highest prevalence. The risk of thyroid cancer in women was more than 2.5 times that of men (p=0.420). Moreover, the association between the rs1052133C>G polymorphism in the OGG1 gene and patient characteristics such as gender, age, tumor type, tumor size, lymph node involvement, and side of involvement was examined, and no significant association was observed between the genotypes and clinical characteristics of the patients (Table 3).

Table 2. Genotypic and allelic frequency distribution in patient and control samples for the rs1052133C>G polymorphism in different inheritance models

Models	Genotypes	p-value	OR	95% CI for OR	
				lower	Upper
-	GG vs CC	0.98	1.012	0.389	2.632
-	GC vs CC	0.630	0.880	0.526	1.473
Recessive	GG vs CC+CG	0.888	1.068	0.422	2.711
Dominant	GG+CG vs CC	0.672	0.899	0.550	1.470
Codominant	CG+CC+GG	0.613	0.879	0.532	1.451
Allelic	G vs C	0.78	0.95	0.64	1.40

HWE	Chi-squared value	Chi-squared test p-value
Case	0.053	0.82
Control	0.156	0.67
Total	0.028	0.86

Table 3. Association between the rs1052133C>G OGG1 polymorphism and clinical characteristics

Clinical characteristics	GG Number(%)	CG Number(%)	CC Number(%)	Total	p-value
Tumor size (cm)					
<2.5	3(60)	9(37.5)	14(41.18)	26	0.079
≥2.5	2(40)	15(62.5)	20(58.82)	37	
Age					
<38	2(25)	16(51.61)	25(52.09)	43	0.897
≥38	6(75)	15(48.39)	23(47.91)	44	
Gender					
Female	7(87.5)	20(64.51)	36(75)	63	0.420
Male	1(12.5)	11(35.49)	12(25)	24	
Lymph node					
NX	0(0)	4(19.05)	6(20)	10	
N0	4(100)	10(47.62)	17(56.67)	31	0.582
N1	0(0)	7(33.33)	7(23.33)	14	
Pathology					
Papillary carcinoma	3(50)	19(59.38)	34(77.27)	56	
Follicular adenoma	3(50)	9(28.12)	9(20.46)	21	0.232
Hürthle cell carcinoma	0(0)	2(6.25)	1(2.27)	3	
Medullary carcinoma	0(0)	2(6.25)	0(0)	2	
Involved side					
Right	2(40)	14(63.64)	13(38.24)	29	
Left	1(20)	6(27.27)	16(47.06)	23	0.172
Both sides	2(40)	2(9.09)	5(14.70)	9	

The results of the online RNA folding evaluation using the RNA SNP software show that if the wild-type C allele is changed to the G allele, there is no significant change in the secondary structure of the RNA (significance greater than 0.2); both RNA folds are shown in Figure 1.

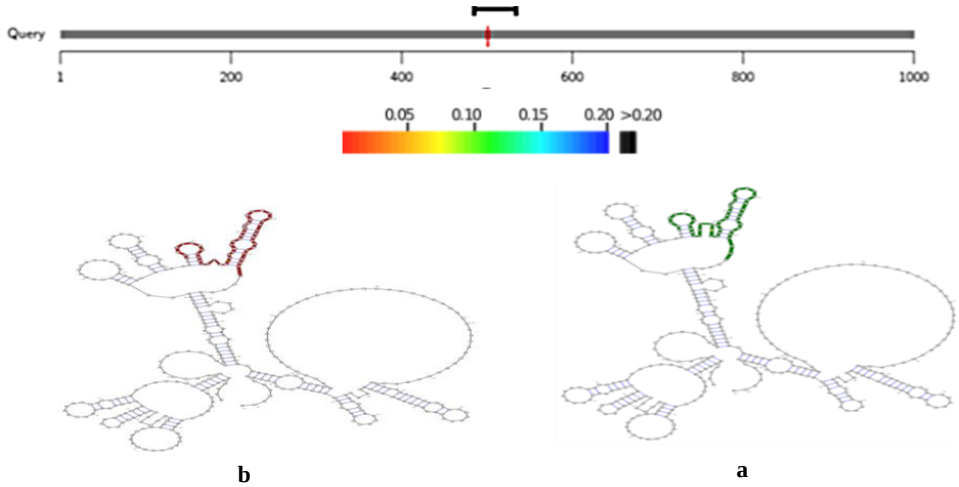

Figure 1. Result obtained from RNA SNP software: Schematic comparison of RNA secondary structure (a) in wild-type and (b) mutant state

The results obtained from the study of protein stability using the I-Mutant and Mupro software show that the rs1052133 polymorphism does not reduce protein stability. The online SNP GO and PHD-SNP software were used to investigate whether the created SNP plays a role in the occurrence of the disease, and the results showed that this SNP does not contribute to the occurrence of the disease. Moreover, the online Polyphen software was used to investigate the effect of amino acid substitution on protein structure and function, and the results showed that the OGG1 rs1052133 gene polymorphism does not affect protein structure and function. The PCR amplification products were electrophoresed on 2% agarose gel. The different genotypes can be seen in Figure 2. The 406 bp band corresponds to the control band.

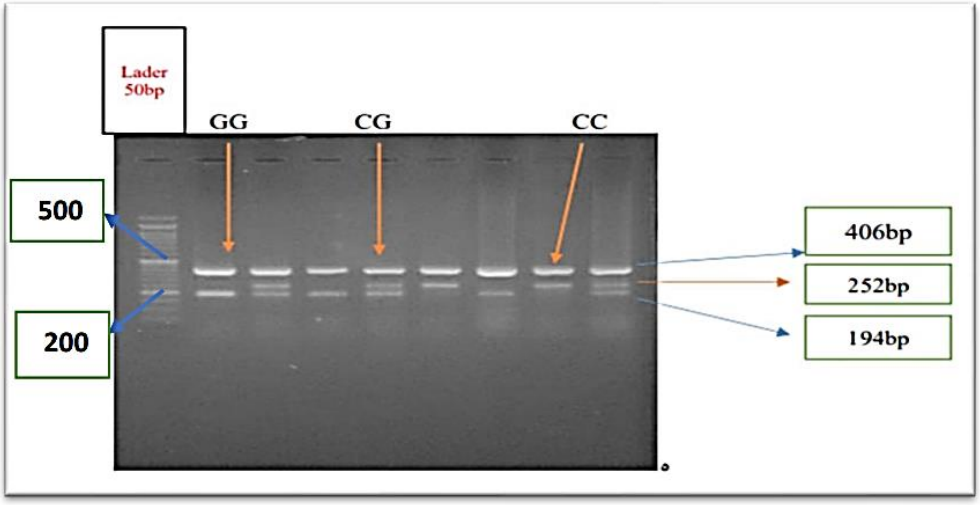

Figure 2. Electrophoresis of PCR products from patients on a 2% agarose gel. The molecular marker (ladder) is 50 base pairs.

Discussion

In this study, no genotypic and allelic association was found for the OGG1 rs1052133 gene polymorphism in thyroid cancer susceptibility in the northwestern region of Iran. In agreement with these results, studies conducted in the Spanish population (18), Portuguese population (19), Portuguese-Caucasian population (20), and Indonesian population (21) also did not find a significant association between this polymorphism and thyroid cancer susceptibility. In contrast, some studies showed an association between this polymorphism and other cancers such as prostate cancer, gastrointestinal system, head and neck cancer, and lung cancer (16). According to the results of the research, it seems that the mentioned polymorphism is not involved in thyroid cancer susceptibility. Furthermore, the results of in silico analysis show that the OGG1 rs1052133 gene polymorphism has no effect on disease development, RNA structure, function, and protein structure. Several studies have been conducted on the association of rs1052133 polymorphisms of the OGG1 gene with an increased risk of various cancers. In a study by Su et al., the association between the OGG1 rs1052133 polymorphism and the risk of colorectal cancer in a Caucasian population was investigated. In this study, a significant association was observed between the OGG1 gene polymorphism and the risk of colorectal cancer in 4103 patients and 5400 controls (25). Moreover, in a study by Floris et al., a relationship between the OGG1 rs1052133 polymorphism and the risk of breast cancer in a Sardinian or northern population was observed in 135 patients with breast cancer and 112 healthy individuals (26). The results of a study conducted by García-Quispes et al., in a group of 881 individuals, 402 of whom had

thyroid cancer and 407 controls, did not show a significant association between the OGG1 gene polymorphism with rs1052133 and thyroid cancer (18). The reason for the inconsistency in the mentioned studies can be explained by the differences in the genetics of different populations, and various factors such as environmental factors, racial differences and nutritional diversity can also be influential. To the best of the authors' knowledge, this study is the first study to investigate the association between the OGG1 gene rs1052133 polymorphism and the risk of thyroid cancer in the northwestern region of Iran. The data of this study showed that the OGG1 rs1052133 polymorphism does not affect the susceptibility to thyroid cancer in the northwestern region of Iran. According to the results, it is suggested that the association between rs1052133 polymorphism and thyroid cancer be studied in more samples and larger statistical populations of sick and healthy individuals and in other parts of Iran and the world.

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