

Reduced Oral Squamous Cell Carcinoma Risk Associated with *MLH1* rs63749795 Polymorphism in the Dominant Genetic Model

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Abstract

Background: Oral squamous cell carcinoma (OSCC) represents the predominant form of cancer affecting the oral cavity, accounting for more than 90% of all oral malignancies. Despite advancements in treatment, the five-year survival rate has remains relatively unchanged, primarily due to late-stage diagnosis. This study aimed to evaluate the genetic variation in *MutL homolog 1 (MLH1)* (rs63749795) in patients with OSCC.

Methods: A cross-sectional case-control study was performed, including a total of 102 patients diagnosed with OSCC and 100 healthy individuals serving as controls. Genotyping of the *MLH1* rs63749795 polymorphism was performed using tetra-primer amplification refractory mutation system-polymerase chain reaction (TP-ARMS-PCR) method, followed by agarose gel electrophoresis.

Results: The predominant genotype observed in both OSCC patients and healthy controls was the CT genotype, with respective frequencies of 45.1% and 55%. The least frequent genotype in both groups was TT, with frequencies of 12.7% in patients and 17% in controls. Most patients were in tumor grade 1 (70.96%) and tumor stage III (35.8%). Among the patients, 53.3% showed lymph node involvement. No statistically significant associations were observed between clinicopathological features and genotypes ($P > 0.05$). The allele frequencies of *MLH1* rs63749795 did not differ significantly between patients and controls. However, the rs63749795 polymorphism was associated with reduced OSCC susceptibility under the dominant genetic model (OR = 0.53, 95% CI = 0.29-0.96, $P = 0.03$ for CT+TT vs. CC genotype).

Conclusions: The *MLH1* rs63749795 polymorphism may be associated with reduced susceptibility to OSCC under the dominant genetic model; however, although further studies involving larger populations are needed.

Keywords: DNA Repair, *MLH1*, Oral Cancer, Polymorphism.

Introduction

Oral squamous cell carcinoma (OSCC) is the most common form of oral malignancy, representing more than 90% of all cases observed in the oral cavity (1). Despite advancements in the treatment of SCC, the

five-year survival rate has remained largely unchanged in recent years, primarily due to late diagnosis (2). OSCC exhibits a higher prevalence in males, potentially attributable to greater involvement in high-risk behaviors (3).

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Tobacco use and alcohol consumption are recognized as the primary risk factors contributing to the development of OSCC. Additionally, infection with high-risk human papillomavirus (HPV) and diets low in fruits and vegetables may also contribute to OSCC development (4).

The mismatch repair (MMR) pathway plays a pivotal role in maintaining genomic integrity by rectifying replication-related mismatches and mutations (5). Dysfunction of the MMR system can lead to the accumulation of DNA damage and increased mutation rates, ultimately impairing the DNA damage response (DDR) system and promoting genomic instability, which is believed to contribute to carcinogenesis (6). The *MutL homolog 1 (MLH1)* gene, located on chromosome 3p22.2, encodes a vital protein of the MMR system and has been reported to have 23 transcripts to date. Interest in MLH1 has increased in recent years, as it is recognized as a key component of the MMR pathway, particularly in relation to microsatellite instability (MSI). MLH1 dysfunction has been correlated with cancer susceptibility. In addition to its established function in the MMR pathway, MLH1 is involved in multiple cellular processes, particularly regulating cell cycle arrest and triggering apoptosis in response to DNA damage induced by specific chemical and physical stressors (7).

Since 2010, genome-wide association studies (GWAS) have uncovered a broad spectrum of single-nucleotide polymorphisms (SNPs) across the human genome, which have been associated with cancer susceptibility, clinical outcomes, and therapeutic response (8). SNPs have been identified in nearly all MMR genes, with *MLH1* and *MSH2* being the most extensively studied (9). Several polymorphisms in the *MLH1* gene have been found, some of which affect the expression of functional MLH1 (10). The role of MSI in oral cancer remains incompletely understood. However, some studies suggest that direct mutations or deletions of *MLH1/MutS homolog 2 (MSH2)* are uncommon in oral cancer (11). In 2006, Demokan et al. analyzed

a cohort of 116 patients with different types of head and neck cancer (HNC) and found MSI in 41% of the samples. Furthermore, in 59% of cases, the promoter regions of *MLH1* or *MSH2* showed hypermethylation, indicating potential regulatory modifications affecting their expression (12).

Various studies highlight the significance of SNPs as key markers connecting phenotypic variations to DNA sequence changes. Recent advancements in this field are expected to enhance the understanding of human physiology and reveal the molecular basis of various diseases. Consequently, this study seeks to examine the association between different clinicopathological factors and OSCC, while analyzing the selected MLH1 gene SNP (rs63749795) in both OSCC patients and healthy individuals.

Materials and Methods

Study Subjects

This case-control study involved 102 patients diagnosed with newly onset OSCC by two independent pathologists, along with 100 healthy individuals who had no history of cancer. The patient group was selected without restrictions on age or gender from Namazi, Khalili, and Madar Va Koodak Hospitals, affiliated with Shiraz University of Medical Sciences. In contrast, the healthy control group consisted of individuals undergoing routine medical screenings in Fars Province during the same period. The study included OSCC patients aged 19-90 years and a group of age- and sex-matched healthy controls. Demographic and clinical parameters such as age, gender, anatomical site of the tumor, lesion dimensions, histological grade, clinical staging, and lymph node involvement were systematically retrieved from patient medical records.

The study received ethical approval from the Ethics Committee of Shiraz University of Medical Sciences, Iran. Participants voluntarily agreed to take part in this study as part of a broader prospective research initiative and provided written informed consent. The criteria for inclusion and exclusion are summarized in Table 1.

Table 1. Participant inclusion and exclusion criteria.

Inclusion (patient)	Exclusion (patient)
1. The initial diagnosis of SCC was based on clinical signs and definitive diagnosis, and the pathology report.	1. Patient's unwillingness to participate in the study
2. Two pathologists confirmed the diagnosis of oral SCC.	2. Simultaneous presence of other tumors and distant metastasis.
3. Determination of clinical staging of cases according to the new TNM staging system (8th edition) staging system of the American Joint Committee on Cancer (AJCC).	3. History of genetic, autoimmune, metabolic, or lichenoid disorders.
4. Determination of the histopathological grade of oral SCC based on World Health Organization (WHO) criteria.	4. Pregnancy or lactation.
5. Age \geq 18 years.	5. Inadequate DNA sample quality or quantity.
Inclusion (control)	Exclusion (control)
1. No history of autoimmune diseases and no history of chronic inflammatory disease	1. History of cancer, genetic, autoimmune, metabolic, or lichenoid disorders.
2. Physical health.	2. Pregnancy or lactation.
3. Age and gender match with the patient population.	3. Inadequate DNA sample quality or quantity.

Table 2. Primers Used for Detection of rs63749795 in *MLH1*.

SNP	Gene	Size (bp)	Primers	Sequence (5' to 3')
<i>rs63749795</i>	Outer primers	392	Forward (0)	AGAACAGACTGATCTTGTGGCCTTCTG
			Reverse (0)	ATGACTGCTTTCTCCATTTCCAAAACCT
	C allele:	204	Forward (1)	GATGTGGAAATGGTGGAAAGATGATTACC
	T allele	241	Reverse (1)	GTACAAGCTGCAGTCATTTCCTTGCA

DNA Extraction and PCR Analysis

Peripheral blood specimens (five mL) were drawn into Ethylenediaminetetraacetic acid (EDTA)-anticoagulated collection tubes for genomic analysis. Genomic DNA was extracted employing the salting-out method with reagents procured from Merck (Germany), ensuring high purity, which was measured via spectrophotometry (Eppendorf Biophotometer, Germany). The genomic sequence of *MLH1* (Gene ID: 4292) was obtained from the NCBI database (<http://www.ncbi.nlm.nih.gov>), and specific primers were designed for TP-ARMS-PCR, a rapid and cost-effective method for detecting SNPs.

PCR assays were assembled in a final reaction volume of 20 μ L, comprising 50 ng of genomic DNA, 0.5 μ M of each primer (Takapoozist, Iran), 1 U of Taq DNA polymerase (Sinaclon, Iran), 250 μ M of dNTPs (Sinaclon, Iran), and 1.5 mM of MgCl₂

(Sinaclon, Iran). The PCR cycling parameters were as follows: an initial denaturation at 95 °C for 5 minutes; followed by 30 amplification cycles comprising denaturation at 95 °C for 45 seconds, annealing at 60 °C for 45 seconds (optimized for the rs63749795 SNP), and extension at 72 °C for 55 seconds; concluding with a final extension phase at 72 °C for 8 minutes.

To validate genotyping quality, 20% of random samples were sequenced, confirming the absence of genotyping errors. Negative control tubes, containing the PCR mixture without DNA templates, were included in each run to monitor contamination. PCR products were separated by electrophoresis on a 2% agarose gel (Sinaclon, Iran), allowing visualization of the amplified regions and confirming the expected PCR product size based on primer predictions.

Statistical Analysis

Descriptive statistics were utilized to compare general characteristics, clinicopathological features, and the *MLH1* variant between OSCC patients and healthy controls. The goodness-of-fit chi-square (χ^2) testing was conducted according to Hardy–Weinberg equilibrium to verify the suitability of the case–control study conditions. Quantitative variables followed a normal distribution, confirmed via the Shapiro-Wilk test, and were analyzed using t-tests and analysis of variance (ANOVA), while chi-square tests were applied for categorical data. To assess associations between clinical characteristics, *MLH1* variant (rs63749795), and OSCC risk, conditional logistic regression analysis was performed, with results presented as odds ratios (OR) and 95% confidence intervals (CI). A statistical significance threshold of $p < 0.05$ was established. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 27.0.

Results

General characteristics

Among the participants diagnosed with OSCC, 56 were male (54.90%) and 46 were female (45.09%), with ages ranging from 18 to 80 years. The mean age of OSCC patients was 61.65 ± 15.49 years, compared to 60.38 ± 13.43

years in the control group. The healthy cohort consisted of 55 males (55.00%) and 45 females (45.00%). Statistical analysis revealed no significant difference in age distribution between the case and control groups ($P > 0.05$). Similarly, gender distribution did not differ significantly across the two groups ($P > 0.05$). Additionally, genotype frequencies in the control group were consistent with the Hardy–Weinberg equilibrium ($\chi^2 = 1.28$, $df = 1$, $P = 0.25$).

Genotyping of *MLH1* rs63749820 variant and the risk of OSCC

The multivariate logistic regression analysis revealed that the risk of OSCC was significantly reduced to 0.53-fold in patients with TT + CT genotypes under the dominant model, relative to CC genotype (OR = 0.53, 95% CI = 0.29–0.96, $p = 0.03$). The rs63749795 T allele was found to be significantly less frequent in OSCC cases compared to the control group. Nonetheless, the analysis revealed no statistically significant difference in the frequency of the *MLH1* rs63749795 C allele between the case and control groups ($P = 0.05$). Additionally, no significant association was observed between the risk of OSCC and the recessive, co-dominant, or over-dominant genotypes of the *MLH1* rs63749795 gene polymorphism ($p \geq 0.05$) (Table 3).

Table 3. Distribution of genotypes and allele frequencies of *MLH1* rs63749795 gene polymorphism in the case and control groups in different genetic models.

rs63749795	Patient group (%)	Control group (%)	OR (95% CI)	P-value
Co-dominant				
CC	43 (42.15)	28 (28.0)	1	
TT	13 (12.74)	17 (17.0)	0.49 (0.20-	0.11
CT	46 (45.09)	55 (55.0)	0.54 (0.29-	0.05
Dominant				
CC	43 (42.15)	28 (28.0)	1	
TT+ CT	59 (57.84)	72 (72.0)	0.53 (0.29-	0.03*
Recessive				
CC+ CT	89 (87.25)	83 (83.0)	1	
TT	13 (12.74)	17 (17.0)	0.71 (0.32-	0.39
Over-dominant				
CC+TT	56 (54.90)	45 (45.0)	1	
CT	46 (45.09)	55 (55.0)	0.67 (0.38-	0.15
Allele				
C	132 (64.70)	111 (55.5)	1	
T	72 (35.29)	89 (44.5)	0.68 (0.45-	0.05

rs10757278 polymorphism and pathological characteristics

Table 4 presents the clinical and pathological characteristics of the patients. The tumor stage was assessed using the TNM staging system, revealing that the majority of patients were classified as grade 1 and stage 3. Grade 4 and stage 1 were the least frequent. Among the patients, 53.3% had lymph node involvement. Information about the tumor site of 3 patients,

the grade of 40 patients, the stage of 21 patients, and lymph node involvement of 36 patients was unavailable. The sole patient classified with tumor grade 4 exhibited the CT genotype. Genotypic distributions were not statistically associated with clinicopathological parameters, including lymph node involvement, tumor type, grading, staging, tumor site, and patient sex or tumor dimensions ($P > 0.05$).

Table 4. Correlation of clinical-pathological characteristics and genotype of the case group.

Genotypes	Variables	CC n (%)	CT n (%)	TT n (%)	P-Value
	Tumor size (Mean ± SD)	6.65±7.70	4.35±5.83	3.81±4.38	0.301
Grade	1	19 (43.2)	19 (43.2)	6 (13.6)	0.709
	2	6 (40)	8 (53.3)	1 (6.7)	
	3	2 (100)	0 (0)	0 (0)	
	4	0 (0)	1 (100)	0 (0)	
Stage	1	5 (31.3)	8 (50)	3 (18.8)	0.817
	2	6 (33.3)	10 (55.6)	2 (11.1)	
	3	15 (51.7)	11 (37.9)	3 (10.3)	
	4	8 (44.4)	8 (44.4)	2 (11.1)	
Tumor site	Oral	10 (41.7)	10 (41.7)	4 (16.7)	0.688
	Tongue	29 (43.9)	30 (45.5)	7 (10.6)	
	Lip	1 (100)	0 (0)	0 (0)	
	Maxilla	0 (0)	1 (100)	0 (0)	
	Nasopharynx	1 (100)	0 (0)	0 (0)	
	Skin	0 (0)	0 (0)	1 (100)	
	Larynx	2 (66.7)	1 (33.3)	0 (0)	
	Thyroid	0 (0)	1 (100)	0 (0)	
Lymph node involvement	+	13 (37.1)	17 (48.6)	5 (14.3)	0.352
	-	17 (54.8)	11 (35.5)	3 (9.7)	
Tumor type	Basal cell carcinoma	0(0)	0 (0)	1 (100)	0.121
	SCC	43 (44.3)	45 (44.3)	11 (11.3)	

Discussion

This investigation evaluated the association between the *MLH1* rs63749795 SNP and susceptibility to OSCC within a southwestern Iranian cohort. The findings indicate that rs63749795 is significantly associated with OSCC risk, though no substantial correlation

was observed between *MLH1* genotypes and clinical characteristics such as gender, lymph node involvement, tumor location, classification, size, grade, or stage. To our knowledge, this investigation represents the first study to explore the association between

the *MLH1* rs63749795 polymorphism and susceptibility to OSCC. Previous research has examined the association between polymorphisms in various genes and OSCC (13-15).

Recent years have seen a growing interest in *MLH1* research, as it has been identified as a crucial component in the MMR system responsible for MSI. Its dysfunction is believed to contribute to cancer susceptibility. Beyond its role in MMR activities, *MLH1* also plays key cellular roles, including cell cycle arrest and the induction of DNA damage-driven apoptosis in response to specific chemical or physical stimuli (7). Several studies have suggested a correlation between *MLH1* polymorphisms and various cancers such as lung, endometrial, and colorectal cancer (16). While the SNPs analyzed in this study are considered clinically pathogenic, there is a lack of sufficient data supporting their direct correlation with cancer. These polymorphisms have been reported across most MMR-associated loci, with *MLH1* and *MSH2* being the most affected (9).

A study conducted by Shakil Malik et al. identified an association between *MLH1* polymorphisms (rs63749795 and rs63749820) and breast cancer risk, although no significant association was found with overall survival or progression-free survival. A reduction in *MLH1* gene expression and the absence of *MLH1* protein were observed in breast cancer cases, suggesting a potential role in disease progression. Furthermore, the lack of *MLH1* protein was associated with higher-grade cancer and lymph node positivity, emphasizing its importance in the MMR system (16). Another study examined five MMR genes, genotyping 614 cases and 614 matched controls across 10 SNPs. Specifically, *MLH1*'s intronic variant rs4647269 was found to be associated with a reduced risk of rectal cancer (17). Conversely, Castrilli et al. reported that *MLH1* and *MSH2* did not play a distinct role in the development and behavior of ameloblastomas (18). Several studies have indicated that most lung cancer patients exhibit normal *MLH1* expression (19, 20). Fernandes

et al. reported no significant variations in *MLH1* expression across different histopathological grades of OSCC (21). Another study demonstrated that MSI in OSCC samples is strongly associated with tumor stage, differentiation grade, and the risk of developing multiple oral cancers (22-24). Additionally, *MLH1* methylation status may be influenced by variations in histological grading among HNSCC patients (25). Variations in sample size and incomplete patient data may account for the discrepancies between this research and previous studies.

The rs63749795 SNP used in the present investigation is deemed clinically harmful. However, data are scarce regarding their correlation with cancer. To the best of our understanding, this investigation is the first report of *MLH1* polymorphism in OSCC patients. The study revealed a significant association between *MLH1* polymorphism (rs63749795) and a decreased risk of OSCC in the dominant genetic model, though no substantial correlation was observed between *MLH1* genotypes and clinical characteristics such as gender, lymph node involvement, tumor location, classification, size, grade, or stage. Similar results have been found in breast cancer. Azimi et al. reported that no significant correlation was observed between this *MLH1* polymorphism and tumor grade, involved side, tumor size, tumor type, and lymph involvement (26). Mutations of MMR genes like *MSH2* and *MLH1* play a significant role in carcinogenesis (27).

This study has several limitations, including the presence of diverse ethnic groups in southwest Iran, a relatively small sample size that may have affected the findings, and the impact of environmental factors. Additionally, the molecular mechanism by which *MLH1* (rs63749795) contributes to OSCC risk was not investigated. Further functional analyses are needed to better understand how *MLH1* (rs63749795) influences OSCC development.

In this study, no significant differences were observed between genotype and clinicopathological characteristics, which included age, gender, tumor size, tumor site,

tumor type, grade, stage, and lymph node involvement. However, a significant association was identified between *MLH1* rs63749795 and OSCC in patients carrying TT+CT genotypes within the dominant model, compared to the CC genotype. Conversely, no correlation was found between OSCC risk and *MLH1* (rs63749795) polymorphism in the co-dominant, over-dominant, or recessive models. Since the molecular mechanism of *MLH1* was not examined in this research, further studies with larger sample sizes are necessary to confirm its role. Expanding future investigations to encompass a more diverse and sizable population may yield a more comprehensive understanding of *MLH1*'s role in OSCC pathogenesis.

Ethics Approval

All participants in this study signed an informed consent form after being informed about all steps of the study, including the publication step. This study was approved by an ethics committee, Faculty of Medicine, Shiraz University of Medical Sciences, with

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Conflicts of Interest

No conflict of interest.

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Authors' contribution

R.Z, N.M, and M.J.M. conceived and planned the presented experiment, R.Z, N.M, M.J.M, M.J.F, and B.K. performed experiments and analyzed the data. R.Z, and M.J.M. supervised the research, designed experiments, and wrote the paper. All authors have read and approved the manuscript.

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