The association of lncRNA *H19* rs217727 polymorphism with oral lichen planus in Shiraz, Iran

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Background: This study aimed to assess the single nucleotide polymorphisms (SNPs) of lncRNA (long non-coding RNA) *H19* rs217727 in patients with oral lichen planus (OLP) compared to controls.

Methods: We collected 270 DNA samples of OLP cases and healthy individuals. We used the ARMS-PCR tetra primer for DNA genotyping and applied specific primer pairs.

Results: The prevalence of the rs217727 C allele was lower in OLP cases than in healthy subjects ($P = 0.005$). The prevalence of TT genotypes of *H19* rs217727 was greater in OLP patients compared with healthy subjects (5.71% vs 1.5%). Also, the TT genotype in the codominant model was associated with a 5.15-fold higher risk of OLP ($P = 0.02$). In the dominant model, the CT+TT genotypes were associated with a 2.09-fold greater risk of OLP ($P = 0.007$). The *H19* rs217727 polymorphism was linked to a 3.95-fold greater risk of OLP in the recessive model ($P = 0.05$) (TT vs. CC+CT). Also, in the over-dominant model, the CT genotypes were related to a 1.78-fold greater risk of OLP ($P = 0.03$).

Conclusion: This study demonstrated a significant link between lncRNA *H19* polymorphism and OLP lesions. Further studies on larger populations are necessary to confirm this relationship.

Keywords: *H19* long non-coding RNA, oral lichen planus, genetics

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INTRODUCTION

Lichen planus (LP) is a mucocutaneous pathology that predominantly affects females in their mid-life. The disease involves all populations; no racial groups have been recognized as more susceptible [1,2]. Oral lichen planus (OLP) is an inflammatory disease with

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a chronic nature and undetermined etiology affecting the oral mucosa. This non-communicable oral lesion affects more than 1-2% of the population in the 4th to 5th decade of life. OLP has various forms including white striae (reticular), white papules (papular), plaque-like, erythematous/atrophic, erosive, or bullous. The buccal mucosa is the most affected site in the oral cavity, but it may involve different parts of the mucosa and can be seen as severe erythema throughout the gingiva with or without genital or skin lesions [1,3-6].

As a possibly cancerous lesion, OLP is associated with a higher risk of oral squamous cell carcinoma (OSCC). Malignant change is expected to arise in 0.5-3% of cases, though no predictive indicators distinguish the forms with an elevated risk. Hence, every patient should be checked thoroughly to identify initial cancerous potentials [7-10].

Long non-coding RNAs (lncRNAs) are RNA particles extending from 200 nt to > 100 kb in size. Considering transcriptional profiling, lncRNA expression varies across human cancers [11]. Cell variation, gene control, chromatin renovation, malignant cell assault, and metastatic tumor development are the main actions performed by lncRNAs. Various surveys have shown the significance of lncRNAs in identifying and predicting many diseases and malignancies [12-15].

As the earliest detected lncRNA, the lncRNA *H19* gene is found on chromosome 11p15.5, coding a polyadenylated, intertwined, and excelled non-coding RNA [16]. LncRNA *H19* is copied from the maternal hereditary alleles and is accountable for managing genome representation at distinct degrees [17]. *H19* can deactivate tumor suppressor proteins by interacting with p53, equally controlling the roles of oncogenes and tumor suppressor genes [18,19].

H19 polymorphism is, according to several distinct surveys, correlated with the presence and growth of tumors [20,21,22]. According to many types of research, single-nucleotide polymorphisms (SNPs) are critical indicators relating phenotypic variations to DNA-sequence modifications [19]. Investigations in this area are anticipated to explain the structural biology and clarify the molecular origin of disorders. Despite the significance of lncRNA *H19* in numerous diseases, its correlation with OLP is yet to be assessed. Hence, we examined the link between susceptibility to OLP and SNPs in the lncRNA *H19* rs217727 gene in an Iranian population.

METHODS

Patients

This cross-sectional study involved 270 subjects recruited between 2018–2019. We had two groups: OLP patients as the case group and healthy subjects as the control group. The patients were examined intraorally by an oral medicine specialist. Cases with clinical signs and histopathological confirmation of OLP were evaluated. Subjects with a history of autoimmune pathology, malignancy, chemotherapy, radiotherapy, or patients using medications related to lichenoid reactions in the past six months and lichenoid contact reactions were excluded from this study. Subjects referred to Shiraz Dental School for routine dental examination were chosen as the control group; they were non-smokers, and all exclusion criteria mentioned for the cases were also considered for controls.

All research participants were Iranian subjects who had no kinship with one another. Patient information was collected in person. All patients participated voluntarily and signed an informed consent. A trained nurse obtained 5 mL of peripheral blood from each participant. The Ethics Committee of Shiraz University of Medical Sciences approved the research protocol under the ethics code IR.SUMS.DENTAL.REC.1399.199.

Single nucleotide polymorphism (SNP) selection

Using the dbSNP database, the region of *H19* and its promoter were selected. A Hardy-Weinberg equilibrium (HWE) value ≥ 0.05 for the Iranian population was selected using Haploview software; finally, the polymorphic site (rs217727) was selected.

Genotyping

DNA was extracted using the salting-out technique. SNP genotyping was carried out using specific primers via the tetra-primer (ARMS-PCR) method (Table 1). The 25 µL mixture for the PCR reaction included 50–100ng of DNA, 12.5 µL of Taq DNA polymerase (Taq Pol) II Master mix Red (Amplicon, Denmark), 0.5 µL of inner and 0.25µL of outer primer pairs (10 pm/µL), and distilled deionized water to reach 25 µL.

Table 1. Primers and rs217727 tetra-primer ARMS-PCR product sizes.

Primer name	Oligo sequence 5'-- > 3'	Product size
OutF1	ATGACTCAGGAATCGGCTCTGGAAGGTG	Product size of two outer primers: 397 bp
OutR1	GGGGAAACAGAGTCGTGGAGGCTTTGA	
inF1	TCATCTTCATGGCCACCCCCTGCTGT	Product size for C allele: 248 bp
inR1	ATATGGTGGCTGGTGGTCAACCGTACG	Product size for T allele: 200 bp

The PCR conditions included an initial denaturing cycle at 95 °C for 5 minutes, after that 30-second cycles of denaturing at 95 °C for 30 seconds, annealing at 65 °C for 30 seconds, and extension at 72 °C for 30 seconds, and a final extension at 72 °C for 5 minutes. Negative controls—tubes containing the PCR mixture without the DNA template—were included in every run to examine for contamination. After that, PCR products were electrophoresed on 3% agarose gel. The genotyping data was checked by conducting conventional PCR in a reaction mixture of 50 µL using primer pairs OutF1 and OutR1 with the abovementioned PCR conditions [20]. After that, Sanger sequencing was performed. The schematic presentation of the tetra-primer ARMS-PCR technique is shown in Figure 1. This methodology was similar to our previous studies on patients with squamous cell carcinoma (SCC) or salivary gland tumors [20,21].

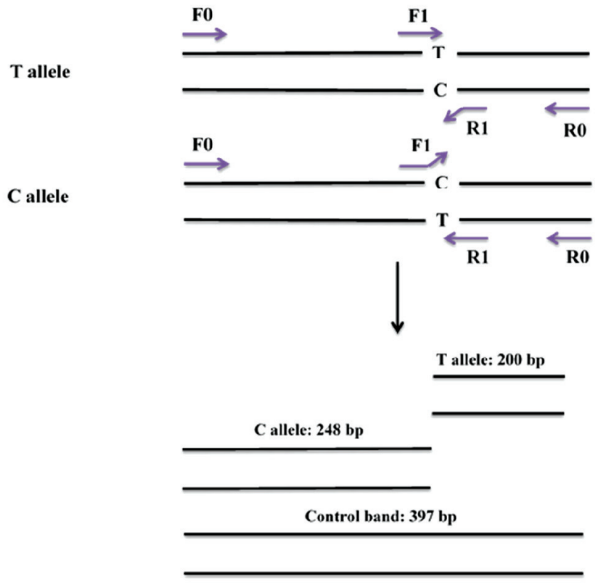

Figure 1. A schematic presentation of the tetra-primer ARMS-PCR method for detecting C/T single-nucleotide polymorphisms (SNPs). Two pairs of primers are used to generate two allele-specific products: one pair (F1 and R0) produced an amplicon representing the C allele, and the other pair (F0 and R1) produced an amplicon representing the T allele. The two outer primers (F0 and R0) were positioned at different distances from the polymorphic nucleotide, so the two allele-specific amplicons differed in length. This allowed them to be discriminated by gel electrophoresis.

Statistical analysis

To evaluate the genotype frequencies among the controls, the HWE was checked by the chi-squared ($\chi 2$) test. The association of *H19* rs217727 genotypes with risk of OLP was calculated by odds ratio (OR) and 95 percent confidence intervals (CI) by logistic regression analysis. In all tests, $P < 0.05$ was regarded as significant.

RESULTS

The OLP patients included 46 females (66%) and 24 males (34%), with an age range of 18–70 and a mean age of 46.4 ± 12.2 years. The control group included 45 females (22.5%) and 155 males (77.5%), with a mean age of 58.79 ± 17.14 (18–85) years.

The product sizes in the PCR test of *H19* rs217727 polymorphism were 248 bp for the C allele, 200 bp for the T allele, and 397 bp for the internal control with 3% agarose gel (Table 1).

The prevalence of the rs217727 SNP genotypes and their correlations with OLP risk are demonstrated in Table 2. The findings illustrate an association between OLP and rs217727 polymorphism in the Iranian population. The prevalence of the rs217727 C allele was lower in OLP patients compared to healthy subjects (C vs. T: OR = 0.53, 95% CI: 0.33–0.83, $P = 0.005$). There was a relationship between rs217727 C allele presentation and a reduced risk of OLP ($P = 0.005$). The prevalence of the TT genotype of *H19* rs217727 was significantly greater in OLP patients compared to healthy subjects (5.71% vs. 1.5%); the TT genotype was associated with a 5.15-fold greater risk of OLP in the codominant model (OR = 5.15, 95% CI = 1.01–28.76, $P = 0.02$), while the CT+TT genotypes were related to a 2.09-fold higher risk of OLP in the dominant model (OR = 2.09, 95%CI = 1.20–3.66, $P = 0.007$). Moreover, the H19 rs217727 polymorphism was associated with a 3.95-

Table 2. Allele and genotype frequencies of *H19* rs217727 in patients with oral lichen planus and controls.

Inheritance model	rs217727 polymorphism	Patients (&)	Healthy subjects (&)	Odd ratio (95% Confidence Interval)	*P*-value
Codominant[a]	Genotype				
	CC	34 (48.57)	133 (66.5)	1	
	CT	32 (45.71)	64 (32)	1.95 (1.10-3.45)	0.01
	TT	4 (5.71)	3 (1.5)	5.15 (1.01-28.76)	0.02
Dominant[b]	CC	34 (48.57)	133 (66.5)	1	
	CT+TT	36 (51.42)	67 (33.5)	2.09 (1.20-3.66)	0.007
Recessive[c]	CC+CT	66 (94.28)	197 (98.5)	1	
	TT	4 (5.71)	3 (1.5)	3.95 (0.79-21.69)	0.05
Over-dominant[d]	CC+TT	38 (54.28)	136 (68)	1	
	CT	32 (45.71)	64 (32)	1.78 (1.01-3.12)	0.03
	Allele				
	T	40 (28.57)	70 (17.5)	1	
	C	100 (71.42)	330 (82.5)	0.53 (0.33-0.83)	0.005

[a] The co-dominant model is defined as the major allele homozygotes vs. heterozygotes.
[b] The dominant model is defined as the major allele homozygotes vs. heterozygotes + minor allele homozygotes.
[c] The recessive model is defined as the major allelehomozygotes + heterozygotes vs. minor allele homozygotes.
[d] The over-dominant model is defined as the major allele homozygotes + minor allele homozygotes vs. heterozygotes.

fold increase in the risk of OLP in the recessive model (OR = 3.95, 95% CI = 0.79–21.69, *P* = 0.05) (TT vs. CC+CT genotypes). Also, in the over-dominant model, the CT genotype was related to a 1.78-fold higher risk of OLP (OR = 1.78, 95% CI = 1.01–3.12, *P* = 0.03) (Table 2). This shows that H19 rs217727 polymorphism positively correlates with the risk of OLP. On the other hand, age, gender, and type of OLP were not significantly related to H19 rs217727 polymorphism.

DISCUSSION

This study assessed *H19* gene polymorphism (rs217727) in OLP patients compared with controls. We applied inheritance models in multiple forms to assess the relationship between SNPs in the *H19* gene and OLP risk. A relation was found between OLP and the *H19* rs217727 polymorphism in dominant, codominant, and over-dominant models. However, age, gender, and type of OLP were not significantly related to H19 rs217727 polymorphism. Regarding the recessive inheritance model, we found no relationship between SNPs and the risk of OLP. Our findings indicate a new diagnostic marker for OLP, possibly reflecting a higher predisposition to this condition. It may also be a criterion for cancer susceptibility in OLP patients, and *H19* gene polymorphisms might discriminate between potentially malignant and non-harmful lesions.

Oral lichen planus (OLP) is the most common oral lesion with a possible malignant change. The etiopathogenesis remains elusive, though it must be promptly diagnosed to facilitate effective care and diminish the seriousness of its influence on the quality of life. Hence, delineating the exact cellular and molecular mechanisms causing OLP development to OSCC is essential [23-25]. Presently, tissue biopsy and histological evaluation is a gold and ideal technique for diagnosing OLP and other malignant and premalignant oral mucosa lesions, but it is costly and may pose risks. Hence, non-invasive techniques, such as assessing certain biomarkers, have been established as alternatives [3,23,26].

Various components, comprising inflammatory cells, cytokines, tumor suppressor genes, and matrix metalloproteinases, can induce OLP advancement. Numerous surveys have concentrated on proteins that control the immune system and autoimmunity [3,7,27-30]. We found that the polymorphism of lncRNA H19 significantly correlated with OLP susceptibility in all forms of the disorder compared to healthy subjects. Because the molecular alterations happen before the morphological variations in precancerous and cancerous cells, lncRNA *H19* may give important evidence on patient prognosis, follow-up, and management.

Long non-coding RNAs (lncRNAs) are supervisory layers in transcriptional and post-transcriptional gene control [13,14,31]. The expression stage, composition, and strength of lncRNA may be altered by a mutation

in the lncRNA, thus leading to the development of several diseases [18,20]. Several studies show that lncRNAs represent an important biomarker in patients with head and neck cancers [15,20,21,32-34]. Jia *et al.* investigated the effect of lncRNAs on the pathogenesis, diagnosis, and prognosis of cancerous changes from dysplasia to SCC in the oral mucosa. They showed that lncRNAs were significantly expressed in both SCC and dysplastic states; the target genes possibly have a crucial effect on the carcinogenesis and expansion of oral cancers [14].

Numerous studies have confirmed the considerable effect of lncRNA *H19* on various tumor cells and carcinogenesis [16,19-21]. Our previous study found that LncRNA H19 rs217727 was statistically related to OSCC susceptibility in an Iranian population [20]. A study indicated that *H19* may improve gastric tumor cell invasion and migration [35]. Elias *et al.* reported that lncRNA *H19* might be a useful diagnostic biomarker for breast tumors. H19 could act as a valuable marker classifying the specimens in typical vs. benign vs. premalignant breast tissues and help to determine aggressive from nonaggressive lesions [36]. A high serum level of H19 was found in cases with certain myelomas and non-small cell lung cancers, and this biomarker appears useful for the early detection and prognosis of such tumors [37-39].

In known cases of malignancy, *H19* represents a predictive factor. Reduced levels of *H19* in tumor tissue can suggest aggressive characteristics, meaning that *H19* levels can influence treatment planning [36]. Some researchers have described the variation in H19 levels found in tissues [11,40]. Chu and colleagues described the relationship between H19 polymorphisms and tumorigenicity [41]. Other studies considered the association linking cancer predisposition and lncRNA *H19* polymorphisms [42,43]. In one study, the rs2839698 G > A polymorphism was accompanied by gastrointestinal tract malignancy [43]. This is in line with our study, which linked the rs217727 C allele with a reduced risk of OLP.

Huang *et al.* assessed the association of the polymorphisms of H19 (rs2839698, rs3741219) with autoimmune disease in Chinese individuals. They found no significant correlation between these diseases and H19 polymorphism in the Han population [44]. This does not align with our work, which showed a significant association of H19 rs217727 polymorphism with OLP as an autoimmune disease in an Iranian population. This discrepancy may be related to differences in study populations and sample sizes. It has been noted that the expression of H19 is associated with hormone receptors [45]; most of our patients who suffered from OLP were females, possibly correlating with a higher serum level of H19.

A study showed that the T allele of rs217727 was more frequently seen in type 2 diabetes in an Iranian population than in healthy controls. Likewise, the rs217727-TT genotype was highly correlated with type 2 diabetes [46]. This finding is in accordance with our study, which showed that the prevalence of the TT genotype was significantly greater in OLP patients compared to controls (5.71% vs 1.5%).

Previous studies showed that lncRNA can dysregulate immune responses and harbor pro-inflammatory cytokines [47-49]. Extensive data indicate that immunologic and inflammatory factors have significant responsibilities in OLP. Furthermore, microRNAs (miRs), small non-coding RNAs, are implicated in OLP. Specifically, miR-155 is upregulated in patients with OLP; miR-155 has various roles and is strongly linked to inflammation and immune system regulation [50].

It is important to note that while earlier surveys have described the role of H19 in a variety of disorders [51], this investigation is the earliest to examine the genetic variation of this gene in relationship with OLP. Our study assessed the serum samples of patients with confirmed OLP. Nonetheless, when talking about limitations, due to COVID-19 pandemic our sample size was chosen as the least size calculated by previous studies. Further studies with lager sample sizes are suggested. Other constraints of the current research were the diverse ethnic population that lives in this region. Further research on single ethnic groups are also suggested.

CONCLUSION

In conclusion, the potential premalignant characteristic of OLP highlights the importance of investigating the underlying mechanism of this disorder. A reliable and objective molecular marker is required to assist clinicians in making appropriate clinical judgments concerning high-risk disorders without undertaking tissue biopsy or alongside the histopathological findings. The present study sought

to address this issue, demonstrating a significant link between lncRNA *H19* polymorphism and OLP lesions. However, our investigation is just the beginning, and further studies are needed to delineate the potential roles of lncRNAs in OLP.

Authors contributions

JG, MZ, MJM, MJF and FR conceived and designed the research and experiments; MJM, MJF and NM Performed the experiments; NM and MZ Analyzed and interpreted the data; MJM, JG and FR wrote the draft of the manuscript. MZ performed the editing and the final manuscript was read and confirmed by all the authors.

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Conflict of Interest: None declared.

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