RESEARCH PAPER

GENETIC ASSOCIATION OF IL-17A GENE POLYMORPHISM (rs2275913) WITH SUSCEPTIBILITY TO ORAL CANCER - A CASE CONTROL STUDY IN SOUTH INDIAN POPULATION

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ABSTRACT

Background

Interleukin-17A (IL-17A), encoded by the IL-17A gene on chromosome 6p12, is a pro-inflammatory cytokine that plays a crucial role in immune regulation, inflammation, and carcinogenesis. The rs2275913 (G>A) polymorphism in the promoter region of the IL-17A gene has been implicated in susceptibility to various inflammatory and malignant conditions, including oral cancer. Oral squamous cell carcinoma represents one of the most common malignancies worldwide, and genetic predisposition may contribute to its development.

Aim

To determine the genotype and allele frequencies of IL-17A gene polymorphism (rs2275913) and to evaluate its association with susceptibility to oral cancer in a South Indian population.

Materials and Methods

A case-control study was conducted including 50 participants (25 oral cancer cases and 25 healthy controls). Genomic DNA was extracted from peripheral blood samples and genotyping was performed using PCR-RFLP analysis. The amplified product size was 102 bp, with digestion patterns identifying AA (102 bp), AG (68 + 34 bp), and GG (102 + 68 + 34 bp) genotypes. Statistical analysis was carried out using the Chi-square test, and Hardy–Weinberg equilibrium (HWE) was assessed.

Results

Among cases, the genotype distribution was AA (28%), AG (24%), and GG (48%), while in controls it was AA (24%), AG (20%), and GG (56%). The allele frequencies in cases were A (0.40) and G (0.60), and in controls were A (0.44) and G (0.56). No statistically significant association was observed between IL-17A rs2275913 polymorphism and oral cancer susceptibility ($p > 0.05$). Allele frequencies were comparable to those reported in the South Indian population.

Conclusion

The present study found no significant association between IL-17A rs2275913 polymorphism and oral cancer risk in the studied South Indian population. Although genotype distributions were assessed with respect to HWE, larger sample sizes are required to draw definitive conclusions regarding the role of this polymorphism in oral carcinogenesis.

Keywords: disease; polymorphism; genotype; oral cancer; carcinogenesis, autoimmune diseases; inflammation; health.

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INTRODUCTION

Oral cancer continues to be a public health concern and one of the most common malignancies involving the head and neck region. Oral squamous cell carcinoma (OSCC) accounts for the majority of oral cancers according to GLOBOCAN estimates and contributes to cancer related morbidity and mortality. India carries a substantial burden of oral cancer mainly due to widespread use of tobacco, alcohol and betel quid(1). However, oral cancer does not develop in all individuals exposed to these factors suggesting the important role of genetic susceptibility in disease development.

An important factor now considered in carcinogenesis is chronic inflammation. Persistent inflammation promotes cellular proliferation, inhibition of apoptosis, angiogenesis and genomic instability hence creating a favourable environment for tumour initiation and progression(2,3). Among different molecular pathways involved, activation of nuclear factor-kappa B (NF-κB) has shown to regulate the expression of a wide variety of inflammatory mediators that promotes cancer development and progression(4). Recent evidence has also highlighted the role of necroptosis in the progression and biological behaviour of oral squamous cell carcinoma (5).

A pro-inflammatory cytokine Interleukin-17A (IL-17A) encoded by the IL17A gene located on chromosome 6p12. It is produced mainly by T helper 17 (Th17) cells(6). It was the primarily identified member of the IL-17 cytokine family. IL-17A plays a vital role in host immunity and inflammatory processes. Studies have shown the potential of IL17A to promote tumor growth through angiogenesis, activation of downstream signaling pathways like NF-κB and MAPK pathways and stimulating inflammatory cell recruitment(7-9). This demonstrates that IL-17A may contribute to the development and progression of different cancers including oral cancer.

Genetic polymorphism within cytokine genes can alter cytokine production and function, thereby influencing an individual's susceptibility to disease. Among such polymorphisms is rs2275913 (-197G>A), located in the promoter region, which has gained significant attention due to its functional potential(10). Previous studies have investigated the association of this polymorphism with several inflammatory disorders and malignancies. Variations in this promoter region may affect its expression and influence inflammatory responses in carcinogenesis(11).

Eventhough the association between IL17A polymorphisms and Cancer susceptibility has been investigated in different populations, studies regarding oral cancer in the Indian population is limited. The available studies have been conducted in East Asian populations and these may not be aligning with South Indian populations due to genetic variation and environmental exposure. Hence evaluation of this polymorphism in a South Indian population may provide vital information regarding their possible role in oral cancer susceptibility.

Therefore, the present study was undertaken to determine the genotype and allele frequencies of IL17A gene polymorphism (rs 2275913) and to evaluate its association with oral cancer in a South Indian population.

AIM AND OBJECTIVE

- To determine the genotype and allele frequencies of *IL-17A* gene polymorphism *(rs2275913).*
- To determine an association between the genotypes with susceptibility to oral cancer.

MATERIALS AND METHODS

Materials and methods :

Study Design:

This study was in the laboratory in Saveetha dental college and hospitals chennai , adopted a case-control design to explore the potential genetic link between the *IL-17A* gene polymorphism *(rs2275913).*and the susceptibility to oral cancer.

Case Group:

Samples were collected and DNA was extracted

Clinical Data:

Comprehensive clinical data, including demographic particulars, history of tobacco and alcohol consumption, and familial cancer history, were gathered through structured interviews and scrutiny of medical records.

Genotyping:

Genomic DNA extraction from peripheral blood samples was extracted from peripheral blood samples. Genotyping of IL17A rs2275913 polymorphism was performed using PCR-RFLP analysis.

Statistical Analysis:

Statistical analyses were conducted using Chi square test. Descriptive statistics were utilized for summarizing demographic and clinical characteristics.

The association between IL17A rs2275913 polymorphism and oral cancer susceptibility was assessed via chi-square tests.

Quality Control:

To ensure genotyping result reliability, a subset of samples underwent random duplicate analysis. Rigorous quality control procedures were implemented throughout the genotyping process to minimize errors and uphold data accuracy.

Data Availability:

Datasets generated and analyzed during this study are accessible from the corresponding author upon reasonable request.

Sample collection and DNA extraction
Genotyping by PCR-RFLP
Statistical analysis: Chi square test
Hardy-Weinberg equilibrium
Amplification size: 102 bp
Annealing temperature: 66 degree C for 30 second

RESULTS

Demographic Details

The study comprised 50 participants, including 25 oral cancer cases and 25 age- and gender-matched healthy controls. All participants belonged to the South Indian population and were enrolled after obtaining informed consent. The age of the subjects ranged between 40 and 60 years. The demographic and clinical characteristics, including history of tobacco and alcohol consumption, were recorded through structured interviews and review of medical records. The control subjects were clinically healthy and free from any oral lesions, including potentially malignant disorders.

Genotype Analysis of IL-17A (rs2275913)

Genotyping of the IL-17A gene polymorphism (rs2275913) was performed using PCR-RFLP analysis. The amplified product size was 102 bp. Following restriction enzyme digestion, the genotypes were identified as follows: AA (102 bp), AG (68 + 34 bp), and GG (102 + 68 + 34 bp).

In the case group (n = 25), the genotype distribution was AA – 7 (28%), AG – 6 (24%), and GG – 12 (48%). In the control group (n = 25), the genotype distribution was AA – 6 (24%), AG – 5 (20%), and GG – 14 (56%). The allele frequencies among cases were A = 0.40 and G = 0.60, whereas in controls, A = 0.44 and G = 0.56. Hardy–Weinberg equilibrium (HWE) analysis showed p-values of 0.0124 for cases and 0.0103 for controls. The genotype distributions in both cases and controls deviated from Hardy-Weinberg equilibrium. Comparison of genotype and allele frequencies between the case and control groups using the Chi-square test revealed no statistically significant association between IL-17A (rs2275913) polymorphism and susceptibility to oral cancer ($p > 0.05$).

The allele frequency observed in the present study was comparable to that reported in the South Indian population.

Comparison with Population Data

The comparison of allele frequencies of the IL-17A gene polymorphism (rs2275913) observed in the present study with different global populations was performed using data retrieved from the Ensembl database. All allele frequency values are represented as percentages (Graph 1).

In the present study, the frequency of the G allele was 60% in the case group (N = 25) and 56% in the control group (N = 25), while the A allele frequency was 40% in cases and 44% in controls. The control group demonstrated a comparatively higher frequency of the A allele (44%) when compared to cases (40%).

According to global population data, the G allele frequency was found to be 71% and the A allele 29%. Among African populations, the G allele predominated with a frequency of 95%, whereas the A allele frequency was only 5%. In the American population, the G allele frequency was 78% and the A allele 22%. The East Asian population showed nearly equal distribution, with G allele frequency of 51% and A allele frequency of 49%. In Europeans, the G allele frequency was 62% and A allele 38%. Similarly, the South Asian population demonstrated a G allele frequency of 62% and A allele frequency of 38%.

The allele frequency observed in the present study is comparable to that reported in the South Asian population, particularly with respect to the predominance of the G allele. However, variations are evident when compared to African and American populations, where the G allele frequency is markedly higher.

Although the findings of the present study are in agreement with South Asian population data, validation using a larger sample size and expanded datasets is required to confirm the association and establish population-specific genetic patterns.

Table 1: Genotype frequencies of *IL17A* gene polymorphism *(rs2275913)* among the cases and ,controls

Groups	AA	AG	GG	A	G	HWE (p value)*
Case (N=25)	7	6	12	0.40	0.60	0.0124

Control (N=25)	6	5	14	0.44	0.56	0.0103

Figure 1: Agarose gel electrophoretogram showing partial amplification of *IL17A* gene polymorphism *(rs2275913)* spanning site run along with standard DNA ladder [Lane M = 100 bp DNA marker].

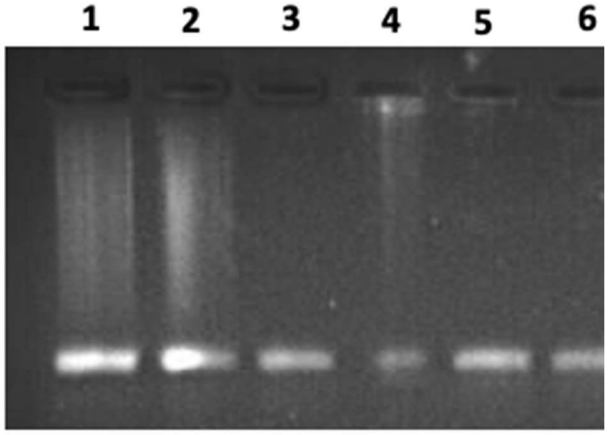
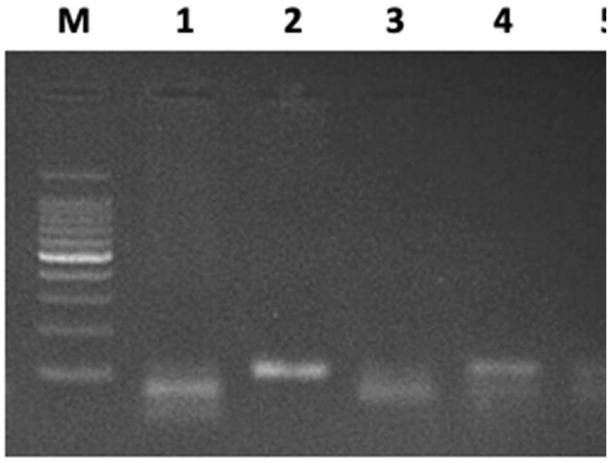
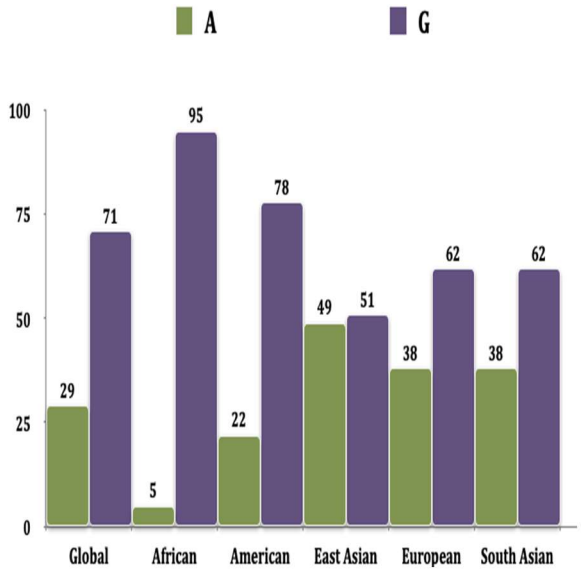


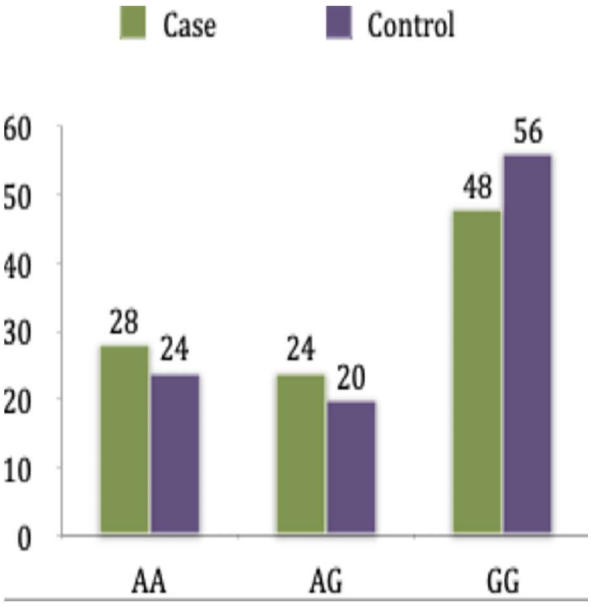
Figure 2: Agarose gel electrophoretogram showing *XagI* digested amplicon of *IL17A* amplicon at (Homozygous: AA-102 bp; Heterozygous: AG-68+34 bp; Homozygous: GG-102+68+34 bp) [Lane M = 100 bp DNA marker]

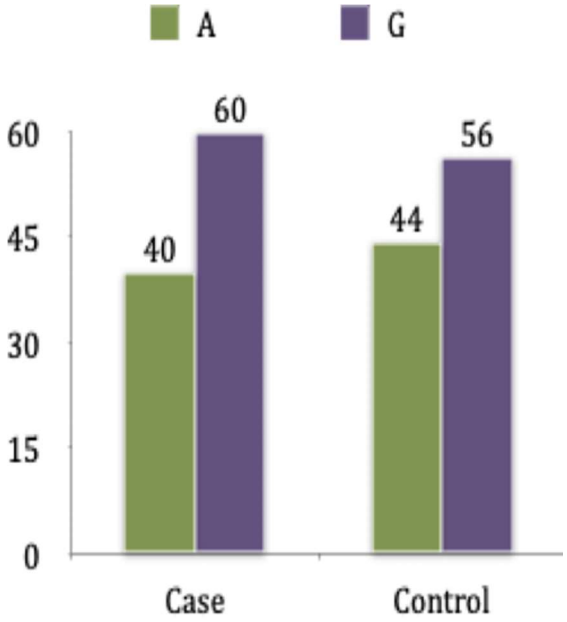


Graph 1: The graph depicts the allele frequency of polymorphism in various study population (Ensembl database)



Graph 2: The graph depicts the (a) genotype and (b) allele frequency of polymorphism in the present study group expressed as percentage.





DISCUSSION

The present study was done to analyse the association between IL17A gene polymorphism rs 2275913 and susceptibility to oral cancer in a South Indian population. Allele frequencies and genotype were analysed and compared between healthy controls and oral cancer patients. There is no statistically significant difference in either genotype distribution or allele frequency between the two groups, signifying that rs 2275913 may not be associated with oral cancer susceptibility in the studied population.

IL-17 A is a pro-inflammatory cytokine linked with immune regulation and chronic inflammation. Numerous studies show the contribution of IL-17 A in tumour progression. Since chronic inflammation is an important factor in oral carcinogenesis, genetic variation affecting IL17A expression has gained attention as potential susceptibility markers.

Previous studies have reported significant association between IL 17 A rs 227 5913 polymorphism and susceptibility to various malignancies. Espinzo et al. demonstrated that the rs 2275913 promoter polymorphism is associated with altered IL-17 A expression, suggesting a possible basis for disease susceptibility(11). Previous studies have reported association between rs2275913 polymorphism and susceptibility to several cancers, but the results varied across different populations. This indicates that this variant can influence risk of malignancy through modulation of inflammatory responses. These findings support the hypothesis that IL17A polymorphisms may contribute to carcinogenesis in genetically susceptible individuals(12).

However, the findings of the present study are not in agreement with the previously done study by Li et al., who demonstrated a significant association between IL17A rs2275913 polymorphism and oral squamous cell carcinoma susceptibility in a Chinese(13). The difference in ethnicity, environmental factors, lifestyle, habit, sample size, and study design may account for the inconsistent finding(14). The allele frequencies observed in the present study are comparable to those reported in South Asian populations. Furthermore, no significant difference in genotype distribution was observed in cases and controls. This suggests that rs 2275913 may not independently influence oral cancer susceptibility in the studied South Indian population.

There are certain limitations in the present study. Various genetic markers are investigated in OSCC, but their clinical significance varies across populations and requires further validation(12). A relatively small sample may have reduced statistical power to detect weak genetic association. Moreover, gene-environment interactions were not evaluated. Since oral cancer is influenced by a variety of environment and genetic factors, larger multicentric studies are required to validate the findings.

Conclusively, the findings of the study suggest that IL17A rs 2275913 polymorphism is not significantly associated with oral cancer susceptibility, in the studied South Indian population. Further investigations comprising larger cohorts and additional inflammatory gene polymorphisms are necessary to clarify the role of IL17A in oral cancer.

CONCLUSION

The present study demonstrated no significant association between IL17A rs2275913 polymorphism and oral cancer susceptibility in the studied South Indian population . The allele frequencies were comparable to those reported in South Asian populations. Due to the relatively small sample size and deviation from Hardy-Weinberg equilibrium demands careful evaluation of the findings. Further studies in larger multicentric populations are required to demonstrate the role of IL17A polymorphisms in oral carcinogenesis.

Additional information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Vijayashree J. Abilasha

Acquisition, analysis, or interpretation of data: Vijayashree J. Abilasha, Uma Maheswari

Drafting of the manuscript: Vijayashree J. Abilasha, Uma Maheswari

Critical review of the manuscript for important intellectual content: Vijayashree J. Abilasha

Supervision: Vijayashree J. Abilasha

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Human Ethical Committee (IHEC) issued approval IHEC/SDC/UG-2014/22/MICRO/223. The pilot study was conducted after obtaining an institutional human ethical committee approval (No: IHEC/SDC/UG2014/22/MICRO/223). . Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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