scientific reports

Check for updates

OPEN

Clinical significance of long non-coding RNA MIR155HG genetic variants and susceptibility to oral cancer

Chiao-Wen Lin[1,2,15], Jeng-Wei Lu[3,4,5,15], Chun-Yi Chuang[6,7], Wang-Yu Hsieh[8], Yun-Jung Tsai[9], Shun-Fa Yang[10,11] & Shu-Hui Lin[12,13,14]✉

Oral cancer is a malignant disease with a notably high incidence rate in Taiwan. Recent reports have revealed that MIR155HG polymorphisms play a crucial role in the development of tumorigenesis in human cancers. The objective of this study was to investigate the role of MIR155HG polymorphisms in susceptibility to oral cancer among individuals in the Taiwanese Han population. In this study, we recruited 1316 oral cancer patients and controls to investigate the allelic discrimination of MIR155HG polymorphisms. Genotyping was performed using a TaqMan allelic discrimination test. The association of MIR155HG polymorphism rs1893650 with oral cancer susceptibility was found to be significant, unlike rs928883, rs767649, rs72014506, and rs4143370. Moreover, when compared to the homozygous TT genotype, the C alleles of rs1893650 polymorphism showed a significant correlation with cell differentiation grade in oral cancer patients ($p = 0.019$). Additionally, in oral cancer patients who chew betel quid, the C alleles of the rs1893650 polymorphism was significantly associated with lymph node metastasis and cell differentiation grade compared to those with the homozygous TT genotype. It was concluded that the rs1893650 polymorphism significantly increased the likelihood of developing oral cancer. Further large-scale studies involving diverse ethnic populations and clinicopathological characteristics are required to confirm these results. This research paves the way for new approaches in the detection and diagnosis of oral cancer, enabling early prevention of this disease.

Keywords MIR155HG, Single nucleotide polymorphism, Betel quid chewers, Oral cancer

Oral cancer stands as one of the most prevalent malignancies worldwide, posing significant challenges to public health[1,2]. It is estimated that oral diseases affect nearly 3.5 billion people globally, with a predominant occurrence among males[3]. According to a previous epidemiological survey, the annual count of new oral cancer cases exceeds 400 thousand worldwide, with a higher incidence observed in Western countries and certain populations in Southern-Eastern Asia[4,5]. In Asian-Pacific countries like Taiwan, the number of oral cancer patients surpasses the global average[6]. Oral cancer arises from various factors, including individual habits such as tobacco, alcohol, and betel nut consumption, as well as smoking, which are among the primary triggers for its development[7–10]. Recently, there has been growing interest in the role of targeted therapy aimed at cancer cell

[1]Institute of Oral Sciences, Chung Shan Medical University, Taichung, Taiwan. [2]Department of Dentistry, Chung Shan Medical University Hospital, Taichung, Taiwan. [3]Department of Bioscience and Biotechnology, National Taiwan Ocean University, Keelung, Taiwan. [4]Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark. [5]The Finsen Laboratory, Faculty of Health and Medical Sciences, Rigshospitalet/National University Hospital, University of Copenhagen, Copenhagen, Denmark. [6]Department of Otolaryngology, Chung Shan Medical University Hospital, Taichung, Taiwan. [7]School of Medicine, Chung Shan Medical University, Taichung, Taiwan. [8]Ming Dao Senior High School, Taichung, Taiwan. [9]Translational pathology core laboratory, Changhua Christian Hospital, Changhua, Taiwan. [10]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan. [11]Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan. [12]Department of Pathology, Changhua Christian Hospital, Changhua, Taiwan. [13]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan. [14]Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung, Taiwan. [15]Chiao-Wen Lin and Jeng-Wei Lu contributed equally to this work. ✉email: 74630@cch.org.tw

markers[11]. Nevertheless, genome-wide and targeted-gene association studies[12,13] have identified relationships between single-nucleotide polymorphisms and carcinogenesis.

Long noncoding RNAs (lncRNAs) lack protein-coding potential and typically consist of more than 200 nucleotides. For a long time, they were considered genetic dark matter. However, recent studies have confirmed that these RNAs play crucial roles in various biological activities, including transcriptional inhibition and post-transcriptional regulation[13–15]. The MIR155HG gene, located on chromosome 21 in humans, is a typical long noncoding RNA (lncRNA) known as the B-cell Integration Cluster (BIC)[16,17]. MIR155HG is an lncRNA identified as a critical regulator of various physiological and pathological processes, encompassing hematopoiesis, inflammation, immunity, and tumorigenesis[18–22]. Studies have confirmed the overexpression of MIR155HG in acute myeloid leukemia, Hodgkin's lymphoma, and chronic lymphoblastic leukemia[23]. Additionally, experimental results have demonstrated that downregulation of MIR155HG inhibits the growth of gliomas in-vitro and in-vivo[24]. Previous studies have suggested that the lncRNA MIR155HG has the potential to serve as a prognostic biomarker in cancer patients[25].

Single nucleotide polymorphisms (SNPs) are the most prevalent genetic variations, commonly observed, that impact disease risk by modifying the expression of associated genes[26,27]. To our knowledge, three studies have reported the relationship between MIR155HG SNPs and multiple sclerosis[28], atopic eczema[29], and epilepsy[30]. The MIR155HG SNP has also been found to be associated with the development of human cancer[23,26,31–35]. The SNPs in MIR155HG, including rs4143370 and rs34904192, were associated with esophageal cancer risk[32]; rs12482371, rs1893650, and rs928883 were significantly linked to colorectal cancer risk[35], with rs12482371 and rs1893650 offering protection against liver cancer while rs928883 increased liver cancer risk[33]; and rs767649 was associated with an increased risk of non-small-cell lung cancer[31], all in the Chinese Han population[31–33,35]. However, the precise relationship between MIR155HG SNPs and the risk of oral cancer remains uncertain.

The objective of the current study is to evaluate whether the distribution of MIR155HG SNPs influences the clinicopathological characteristics of oral cancer in a Taiwanese Han population. Furthermore, the study also analyzed the distribution of MIR155HG SNPs between patients with oral cancer and those without the condition.

Materials and methods

Study patients and sample collection

The Chung Shan Medical University Hospital, located in Taichung, Taiwan, enrolled a total of 1316 oral cancer patients and 1195 controls between 2012 and 2022. For each participant, their medical records were reviewed to gather information on age, betel quid chewing, cigarette smoking, alcohol drinking, stage, tumor T status, lymph node status, metastasis and cell differentiation. Clinical staging was conducted using the TNM staging approach according to the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual for each patient.

Genomic MIR155HG SNPs were detected from peripheral blood samples obtained from oral cancer patients

Genomic DNA was extracted from peripheral blood samples of the research participants using the QIAamp DNA Blood Micro Kit (Qiagen, Valencia, CA, USA). Genomic DNA quality was assessed using the A260/A280 ratio measured by spectrophotometry. For each sample, genotypes for MIR155HG SNPs rs1893650 (assay ID: C__11728421_10), rs928883 (assay ID: C___9498425_10), rs767649 (assay ID: C___2212229_10), rs72014506 (assay ID: C__98195406_10), and rs4143370 (assay ID: C__27357690_10) were identified using TaqMan assay, which included sequence-specific forward and reverse primers and two TaqMan minor groove binder probes with nonfluorescent quenchers. The TaqMan SNP Genotyping Assay was conducted using the ABI StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The PCR reaction was set up in a total volume of 10 µL, consisting of 5 µL of TaqMan Genotyping Master Mix (catalog number: 4371355; Applied Biosystems, Foster City, CA, USA), 0.5 µL of SNP assay (20x), 1 µl of 10 ng/µl genomic DNA, and 3.5 µL of nuclease-free water. The reaction conditions were as follows: initial denaturation at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min. During the PCR amplification, the software collects fluorescence intensity data from the two probes corresponding to each allele of the SNP by using ABI SDS version 3.0 software (Applied Biosystems, Foster City, CA, USA)[36–38].

Statistical analysis

The multiple logistic regression methods were employed to calculate the correlation between genotype and oral cancer risk while controlling for relevant variables. The resulting multiple logistic regression models were utilized to assess adjusted odds ratios (AORs) and their corresponding 95% confidence intervals (CIs) according to previously described[39]. Significant differences in demographic data between male patients and controls in oral cancer cases were evaluated using either the Mann-Whitney U test or Fisher's exact test. All analyses were conducted using Statistical Product and Service Solutions (SPSS, version 17; SPSS, Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant[38].

Results

Characteristics of study participants: controls and male patients with oral cancer

A total of 1316 male oral cancer patients and 1195 controls were included in this study, comprising two groups. Table 1 provides a summary of the characteristics of the recruited individuals. Among them, there were 1195 controls compared to 1136 male patients with oral cancer. Betel quid chewing ($p < 0.001$), cigarette smoking ($p < 0.001$), and alcohol consumption ($p < 0.001$) were significantly associated with male patients with oral cancer

Variable	Controls ($N=1195$)	Patients ($N=1316$)	p value
Age (yrs)			
≦56	644 (53.9%)	664 (50.5%)	$p=0.085$
>56	551 (46.1%)	652 (49.5%)	
Betel quid chewing			
No	996 (83.4%)	391 (29.7%)	
Yes	199 (16.6%)	925 (70.3%)	$p<0.001$*
Cigarette smoking			
No	562 (47.0%)	247 (18.8%)	
Yes	633 (53.0%)	1069 (81.2%)	$p<0.001$*
Alcohol drinking			
No	959 (80.3%)	759 (57.7%)	
Yes	236 (19.7%)	557 (42.3%)	$p<0.001$*
Stage			
I + II		601 (45.7%)	
III + IV		715 (54.3%)	
Tumor T status			
T1 + T2		635 (48.3%)	
T3 + T4		681 (51.7%)	
Lymph node status			
N0		885 (67.3%)	
N1 + N2 + N3		431 (32.7%)	
Metastasis			
M0		1308 (99.4%)	
M1		8 (0.6%)	
Cell differentiation			
Well differentiated		202 (15.4%)	
Moderately or poorly differentiated		1114 (84.6%)	

Table 1. The distributions of demographical characteristics in 1195 controls and 1316 male patients with oral cancer. Mann-Whitney U test or Fisher's exact test was used between healthy controls and patients with oral cancer. *p value < 0.05 as statistically significant.

in terms of their clinical characteristics. Age, stage, tumor T status, lymph node status, metastasis, and cell differentiation were all similar, with no discernible differences.

MIR155HG rs1893650 genotype was associated in male oral cancer patients

The genotype frequencies of all five SNPs (rs1893650, rs928883, rs767649, rs72014506, and rs4143370) were initially assessed in oral cancer patients to investigate potential associations between MIR155HG SNPs and the risk of developing oral cancer. The highest frequencies of these MIR155HG SNPs were observed in the homozygous TT genotype (rs1893650), heterozygous GA genotype (rs928883), heterozygous TA genotype (rs767649), as well as in the homozygous ins/ins genotype (rs72014506) and homozygous GG genotype (rs4143370) in both the control and oral cancer groups. Statistical data indicated a correlation between MIR155HG rs1893650 and the control and oral cancer groups (AOR 95% CI: 1.622 [1.001–2.630], $p=0.049$). However, MIR155HG SNPs rs928883, rs767649, rs72014506, and rs4143370 did not exhibit statistically significant associations with oral cancer, indicating that these variants may play a limited role in the development or progression of oral cancer (Table 2).

Association of MIR155HG rs1893650 genotype with cell differentiation grade in male oral cancer patients

Furthermore, we investigated the associations of MIR155HG genotypes for rs1893650 (T > C) with various clinicopathological characteristics, including clinical stage, tumor size, lymph node metastasis, metastasis, and cell differentiation grade, in all oral cancer patients. Statistical analysis revealed that MIR155HG rs1893650 C allele (TC + CC) was significantly associated at cell differentiation grade (AOR 95% CI: 0.695 [0.512–0.943], $p=0.019$). However, it was not associated with clinical stage (AOR 95% CI: 0.946 [0.755–1.186], $p=0.634$), tumor size (AOR 95% CI: 1.005 [0.802–1.259], $p=0.967$), lymph node metastasis (AOR 95% CI: 0.859 [0.674–1.094], $p=0.219$), or metastasis (AOR 95% CI: 0.585 [0.117–2.924], $p=0.514$) (Table 3).

Variable	Controls ($N=1195$) (%)	Patients ($N=1316$) (%)	AOR (95% CI)[a]
rs1893650			
TT	740 (61.9%)	838 (63.7%)	1.000 (reference)
TC	417 (34.9%)	413 (31.4%)	0.862 (0.704–1.056)
CC	38 (3.2%)	65 (4.9%)	**1.622 (1.001–2.630)[b]**
TC + CC	455 (38.1%)	478 (36.3%)	0.925 (0.761–1.124)
T allele	1897 (79.4%)	2089 (79.4%)	1.000 (reference)
C allele	493 (20.6%)	543 (20.6%)	1.009 (0.856–1.189)
rs928883			
GG	419 (35.1%)	530 (40.3%)	1.000 (reference)
GA	581 (48.6%)	579 (44.0%)	0.815 (0.663–1.003)
AA	195 (16.3%)	207 (15.7%)	1.005 (0.758–1.333)
GA + AA	776 (64.9%)	786 (59.7%)	0.860 (0.708–1.045)
G allele	1419 (59.4%)	1639 (62.3%)	1.000 (reference)
A allele	971 (40.6%)	993 (37.7%)	0.960 (0.837-1.100)
rs767649			
TT	500 (41.8%)	587 (44.6%)	1.000 (reference)
TA	553 (46.3%)	572 (43.5%)	0.918 (0.751–1.122)
AA	142 (11.9%)	157 (11.9%)	1.080 (0.792–1.473)
TA + AA	695 (58.2%)	729 (55.4%)	0.949 (0.784–1.148)
T allele	1553 (65.0%)	1746 (66.3%)	1.000 (reference)
A allele	837 (35.0%)	886 (33.7%)	0.999 (0.868–1.150)
rs72014506			
ins/ins	719 (60.2%)	793 (60.3%)	1.000 (reference)
ins/del	424 (35.5%)	452 (34.3%)	0.848 (0.694–1.036)
del/del	52 (4.3%)	71 (5.4%)	1.083 (0.689–1.703)
ins/del + del/del	476 (39.8%)	523 (39.7%)	0.873 (0.719–1.059)
ins allele	1862 (77.9%)	2038 (77.4%)	1.000 (reference)
del allele	528 (22.1%)	594 (22.6%)	0.927 (0.790–1.088)
rs4143370			
GG	872 (73.0%)	947 (72.0%)	1.000 (reference)
GC	300 (25.1%)	334 (25.4%)	1.001 (0.805–1.244)
CC	23 (1.9%)	35 (2.6%)	1.486 (0.781–2.826)
GC + CC	323 (27.0%)	369 (28.0%)	1.033 (0.837–1.276)
G allele	2044 (85.5%)	2228 (84.6%)	1.000 (reference)
C allele	346 (14.5%)	404 (15.4%)	1.061 (0.881–1.279)

Table 2. Odds ratio (OR) and 95% confidence interval (CI) of oral cancer associated with *MIR155HG* genotypic frequencies. The odds ratio (OR) with their 95% confidence intervals were estimated by logistic regression models. [a] The adjusted odds ratio (AOR) with their 95% confidence intervals were estimated by multiple logistic regression models after controlling for age, betel quid chewing, cigarette smoking, and alcohol drinking. [b] $p=0.049$.

The MIR155HG rs1893650 genotype was found to be associated with lymph node metastasis and cell differentiation grade in male oral cancer patients who chewed betel quid

Next, we further investigated the associations between MIR155HG rs1893650 (T > C) genotypes and various clinicopathological characteristics in male oral cancer patients, both with and without a history of betel quid chewing. In the non-betel quid chewers group, not significant associated were found between rs1893650 genotypes and clinical stage (AOR 95% CI: 1.092 [0.711–1.676], $p=0.688$), tumor size (AOR 95% CI: 1.274 [0.831–1.953], $p=0.267$), lymph node metastasis (AOR 95% CI: 1.214 [0.780–1.889], $p=0.391$), or cell differentiation grade (AOR 95% CI: 0.722 [0.376–1.386], $p=0.328$). In contrast, among betel quid chewers, statistical analysis revealed significant associations between rs1893650 (T > C) and lymph node metastasis (AOR 95% CI: 0.739 [0.552–0.990], $p=0.042$) as well as cell differentiation grade (AOR 95% CI: 0.688 [0.486–0.974], $p=0.035$). However, no significant associations were observed with clinical stage (AOR 95% CI: 0.907 [0.695–1.185], $p=0.476$), tumor size (AOR 95% CI: 0.927 [0.709–1.211], $p=0.476$), or metastasis (AOR 95% CI: 1.104 [0.183–6.654], $p=0.914$) (Table 4).

Discussion

To date, numerous studies have explored the association between genetic polymorphisms and the risk of oral cancer[40], identifying various susceptibility genes and SNPs in different populations[41,42]. However, investigations

Variable	TT (*N* = 838)	TC + CC (*N* = 478)	AOR (95% CI)	*p* value
Clinical stage				
Stage I + II	378 (45.1%)	223 (46.7%)	1.00 (reference)	0.634
Stage III + IV	460 (54.9%)	255 (53.3%)	0.946 (0.755–1.186)	
Tumor size				
≦ T2	404 (48.2%)	231 (48.3%)	1.00 (reference)	0.967
> T2	434 (51.8%)	247 (51.7%)	1.005 (0.802–1.259)	
Lymph node metastasis				
No	553 (66.0%)	332 (69.5%)	1.00 (reference)	0.219
Yes	285 (34.0%)	146 (30.5%)	0.859 (0.674–1.094)	
Metastasis				
M0	832 (99.3%)	476 (99.6%)	1.00 (reference)	0.514
M1	6 (0.7%)	2 (0.4%)	0.585 (0.117–2.924)	
Cell differentiated grade				
Well	113 (13.5%)	89 (18.6%)	1.00 (reference)	**0.019***
Moderate or poor	725 (86.5%)	389 (81.4%)	0.695 (0.512–0.943)	

Table 3. Odds ratio (OR) and 95% confidence intervals (CI) of clinical statuses associated with genotypic frequencies of *MIR155HG* rs1893650 in male oral cancer patients. Cell differentiate grade: grade I: well differentiated; grade II: moderately differentiated; grade III: poorly differentiated. The adjusted odds ratio (AOR) with their 95% confidence intervals were estimated by multiple logistic regression models after controlling for age, betel quid chewing, cigarette smoking, and alcohol drinking. * p value < 0.05 as statistically significant.

Variable	Non-Betel Quid Chewers (*N* = 391)				Betel Quid Chewers (*N* = 925)			
	TT (*N* = 257)	TC + CC (*N* = 134)	AOR (95% CI)	*p* value	TT (*N* = 581)	TC + CC (*N* = 344)	AOR (95% CI)	*p* value
Clinical Stage								
Stage I + II	110 (42.8%)	56 (41.8%)	1.00 (reference)	0.688	268 (46.1%)	167 (48.5%)	1.00 (reference)	0.476
Stage III + IV	147 (57.2%)	78 (58.2%)	1.092 (0.711–1.676)		313 (53.9%)	177 (51.5%)	0.907 (0.695–1.185)	
Tumor size								
≦ T2	122 (47.5%)	57 (42.5%)	1.00 (reference)	0.267	282 (48.5%)	174 (50.6%)	1.00 (reference)	0.576
> T2	135 (52.5%)	77 (57.5%)	1.274 (0.831–1.953)		299 (51.5%)	170 (49.4%)	0.927 (0.709–1.211)	
Lymph node metastasis								
No	173 (67.3%)	85 (63.4%)	1.00 (reference)	0.391	380 (65.4%)	247 (71.8%)	1.00 (reference)	**0.042***
Yes	84 (32.7%)	49 (36.6%)	1.214 (0.780–1.889)		201 (34.6%)	97 (28.2%)	0.739 (0.552–0.990)	
Metastasis								
M0	254 (98.8%)	134 (100.0%)	1.00 (reference)	-	578 (99.5%)	342 (99.4%)	1.00 (reference)	0.914
M1	3 (1.2%)	0 (0.0%)	-		3 (0.5%)	2 (0.6%)	1.104 (0.183–6.654)	
Cell differentiated grade								
Well	25 (9.7%)	18 (13.4%)	1.00 (reference)	0.328	88 (15.2%)	71 (20.6%)	1.00 (reference)	**0.035***
Moderate or poor	232 (90.3%)	116 (86.6%)	0.722 (0.376–1.386)		493 (84.8%)	273 (79.4%)	0.688 (0.486–0.974)	

Table 4. Odds ratio (OR) and 95% confidence intervals (CI) of clinical statuses associated with genotypic frequencies of *MIR155HG* rs1893650 in male oral cancer patients among with betel quid chewers or without betel quid chewers. Cell differentiate grade: grade I: well differentiated; grade II: moderately differentiated; grade III: poorly differentiated. The adjusted odds ratio (AOR) with their 95% confidence intervals were estimated by multiple logistic regression models after controlling for age, cigarette smoking, and alcohol drinking. * p value < 0.05 as statistically significant.

into variants in the MIR155HG gene concerning the occurrence and development of oral cancer are limited. In this study, we conducted the first evaluation of the relationships between five SNPs in the lncRNA MIR155HG and the risk of oral cancer in the Taiwanese Han population. The betel quid chewing, smoking, and alcohol consumption are well-known risk factors associated with impaired DNA repair capacity in oral cancer, contributing to disease development and progression[42]. The majority of oral cancer patients in Taiwan are males who exhibit habits of cigarette smoking as well as betel nut chewing, with over 90% of oral cancer cases being oral squamous cell carcinoma[43].

In our study, we observed statistically significant associations between these risk factors—betel quid chewing, cigarette smoking, and alcohol consumption—and oral cancer among 1315 male patients, when compared with the controls (Table 1). Our results are consistent with previous literature[42]. In addition, our analysis identified a significant association between the MIR155HG SNP rs1893650 and susceptibility to oral cancer, highlighting its potential role in the genetic predisposition to the disease. Previous research also indicates that genetic model analysis revealed an increased risk of colorectal cancer[35], thyroid carcinoma[34] and gastric cancer[26] associated with rs1893650 in the MIR155HG gene. These results are consistent with our data (Table 2). Alternatively, rs1893650 in the MIR155HG gene was associated with a reduced risk of liver cancer[33].

The lncRNA MIR155HG has been identified as a marker of early-stage cancer development[25]. Both in-vitro and in-vivo studies have demonstrated that MIR155HG modulates the malignant phenotype of gastric cancer cells, including enhanced cell proliferation, colony-forming ability, migratory potential, and tumor growth in nude mice. These findings indicate that the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3) signaling pathways are potentially key regulators of these malignant behaviors. Importantly, inhibition of NF-κB and STAT3 signaling pathways effectively attenuates the oncogenic phenotypes driven by MIR155HG overexpression. Moreover, cytotoxicity and apoptosis assays indicate that overexpression of MIR155HG reduces apoptosis in gastric cancer cells induced by cisplatin and 5-fluorouracil (5-FU)[44]. The hypoxia-responsive lncRNA MIR155HG promotes programmed cell death ligand 1 (PD-L1) expression in hepatocellular carcinoma cells by stabilizing hypoxia-inducible factor 1-alpha (HIF-1α) mRNA[45].

Activation of the MIR155HG gene by the MYB transcription factor leads to its upregulation, resulting in the downregulation of numerous tumor suppressor genes[46]. Furthermore, the MIR155HG transcript undergoes processing to produce microRNA-155 (miR-155), which plays diverse roles in immune, inflammatory, and cardiovascular diseases[23]. Additionally, miR-155 has been identified as a negative regulator for tumor protein 53 and DNA mismatch repair genes[47]. In particular, miR-155-5p has been found to be overexpressed in solid tumors of various origins, including colon cancer[48]. Recent studies have indicated that miR-155 may function as a tumor suppressor[49]. Additionally, overexpression of miR-155 has been observed to induce apoptosis and suppress cell proliferation in colon cancer[50].

The silencing of MIR155HG has been shown to inhibit the progression of cervical cancer through its interaction with SRSF1, underscoring its potential as a novel therapeutic target for this malignancy. Additionally, the tumor-promoting effects of MIR155HG in pancreatic cancer cells have been attributed to its negative regulation of miR-802. Collectively, these findings highlight the potential of the lncRNA MIR155HG as a promising diagnostic and therapeutic target across various cancer types[32,35,51]. Hence, we hypothesize that MIR155HG may play a crucial role in promoting the progression of oral cancer, potentially through the production of miR-155. Further functional studies are needed to elucidate the underlying mechanisms of MIR155HG and its role in the pathogenesis of oral cancer.

For years, intron sequences were deemed functionally inert. However, subsequent studies have demonstrated that genes containing introns exhibit higher levels of transcription in mammalian cells compared to intron-less genes. This suggests that introns may serve as enhancers of transcription[52]. The rs1893650 variant is situated within the intronic region of the MIR155HG gene. Given this location and the predicted functions outlined in the database[26,33,35], we postulate that these SNPs might augment the translation of the MIR155HG gene, potentially influencing the susceptibility to oral cancer. In this study, our findings indicated a significant association between MIR155HG rs1893650 (T > C) genotypes and particularly cell differentiation grade in male oral cancer patients (Table 3). Additionally, in male oral cancer patients who chewed betel quid, this association extended to lymph node metastasis ($p = 0.042$) and cell differentiation grade ($p = 0.035$) (Table 4). However, variants of MIR155HG have been linked to susceptibility to various cancers. Notably, a study on colorectal cancer identified the MIR155HG polymorphism rs1893650 as being associated with an increased risk of developing colorectal cancer[35]. In addition, the MIR155HG polymorphism rs1893650 was found to be negatively correlated with susceptibility to papillary thyroid cancer, with TC heterozygotes exhibiting a protective effect. These findings suggest that MIR155HG rs1893650 could serve as a potential risk biomarker for papillary thyroid carcinoma[34]. Our findings also provide new evidence demonstrating that the rs1893650 polymorphism is significantly associated with an increased risk of oral cancer. These clinically significant findings may offer potential avenues for early detection and the development of targeted therapies for oral cancer patients, while this SNP could translate into practical applications or serve as a foundation for guiding future clinical research in cancer patients.

However, our study has several limitations that should be considered. First, the absence of functional validation through in vitro and in vivo experiments limits our ability to establish the biological mechanisms underlying the observed associations. Future studies incorporating molecular and cellular approaches are necessary to elucidate the functional role of these SNPs in the pathogenesis of oral cancer. Second, the study focused exclusively on a single Taiwanese Han population, which may restrict the generalizability of the findings to other ethnic groups. Genetic variations and cancer susceptibility can differ across populations due to diverse genetic backgrounds and environmental exposures. Therefore, further large-scale studies that include diverse ethnic populations with varying clinicopathological characteristics are essential to validate and extend these findings. Expanding the study to include different geographic regions and ethnic groups will enhance our understanding of the broader implications of these genetic markers in oral cancer. Lastly, integrating multi-omics approaches and longitudinal cohort studies could provide deeper insights into the potential clinical applications of these SNPs in early detection, risk stratification, and targeted therapy.

In conclusion, our study first demonstrated the SNPs in MIR155HG has confirmed the relationships between genetic polymorphisms and oral cancer in the Taiwanese Han population. We hope that this research paves the way for new approaches in the detection and diagnosis of oral cancer, enabling early prevention of this disease.

To deepen our understanding of this relationship, further analyses should additional clinical data, and functional experiments. Furthermore, it is essential to conduct repeated studies involving diverse ethnic populations to validate our findings.

Data availability

The data used to support the findings of the present study are available from the corresponding author upon request.

Received: 13 November 2024; Accepted: 17 March 2025
Published online: 22 March 2025

References

1. Valdez, J. A. & Brennan, M. T. Impact of oral cancer on quality of life. *Dent. Clin. North. Am.* **62**, 143–154. https://doi.org/10.1016/j.cden.2017.09.001 (2018).
2. Su, S. C. et al. Oral microbial dysbiosis and its performance in predicting oral cancer. *Carcinogenesis* **42**, 127–135. https://doi.org/10.1093/carcin/bgaa062 (2021).
3. Disease, G. B. D., Injury, I. & Prevalence, C. Global, regional, and National incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* **392**, 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7 (2018).
4. Montero, P. H. & Patel, S. G. Cancer of the oral cavity. *Surg. Oncol. Clin. N Am.* **24**, 491–508. https://doi.org/10.1016/j.soc.2015.03.006 (2015).
5. Lu, H. J. et al. Preoperative prediction model to evaluate salvage surgery in patients with recurrent or second primary oral cavity squamous cell carcinoma. *Oral Oncol.* **131**, 105951. https://doi.org/10.1016/j.oraloncology.2022.105951 (2022).
6. Su, S. C. et al. A novel melatonin-regulated LncRNA suppresses TPA-induced oral cancer cell motility through replenishing PRUNE2 expression. *J. Pineal Res.* **71**, e12760. https://doi.org/10.1111/jpi.12760 (2021).
7. Lin, C. W. et al. IGF2BP2 promotes cell invasion and epithelial-mesenchymal transition through Src-mediated upregulation of EREG in oral cancer. *Int. J. Biol. Sci.* **20**, 818–830. https://doi.org/10.7150/ijbs.91786 (2024).
8. Lu, H. J. et al. Prognostic impact of caspase-8 mutation in oral cavity squamous cell carcinoma. *Oral Dis.* https://doi.org/10.1111/odi.15124 (2024).
9. Yeh, J. C. et al. Interactive effects of CDKN2B-AS1 gene polymorphism and habitual risk factors on oral cancer. *J. Cell. Mol. Med.* **27**, 3395–3403. https://doi.org/10.1111/jcmm.17966 (2023).
10. Su, C. W., Lin, C. W., Yang, W. E. & Yang, S. F. TIMP-3 as a therapeutic target for cancer. *Ther. Adv. Med. Oncol.* **11**, 1758835919864247. https://doi.org/10.1177/1758835919864247 (2019).
11. Tahmasebi, E. et al. The current markers of cancer stem cell in oral cancers. *Life Sci.* **249**, 117483. https://doi.org/10.1016/j.lfs.2020.117483 (2020).
12. Huang, W. et al. Interleukin-10 rs1800896 polymorphism is associated with increased head and neck cancer risk but not associated with its clinical stages. *Oncotarget* **8**, 37217–37224. https://doi.org/10.18632/oncotarget.16660 (2017).
13. Su, S. C. et al. Association of LINC00673 genetic variants with progression of oral cancer. *J. Pers. Med.* https://doi.org/10.3390/jpm11060468 (2021).
14. Yoon, J. H., Abdelmohsen, K. & Gorospe, M. Posttranscriptional gene regulation by long noncoding RNA. *J. Mol. Biol.* **425**, 3723–3730. https://doi.org/10.1016/j.jmb.2012.11.024 (2013).
15. Su, S. C., Reiter, R. J., Hsiao, H. Y., Chung, W. H. & Yang, S. F. Functional interaction between melatonin signaling and noncoding RNAs. *Trends Endocrinol. Metab.* **29**, 435–445. https://doi.org/10.1016/j.tem.2018.03.008 (2018).
16. Tam, W., Ben-Yehuda, D. & Hayward, W. S. bic, a novel gene activated by proviral insertions in avian leukosis virus-induced lymphomas, is likely to function through its noncoding RNA. *Mol. Cell. Biol.* **17**, 1490–1502. https://doi.org/10.1128/MCB.17.3.1490 (1997).
17. Tam, W. Identification and characterization of human BIC, a gene on chromosome 21 that encodes a noncoding RNA. *Gene* **274**, 157–167. https://doi.org/10.1016/s0378-1119(01)00612-6 (2001).
18. Chang, S. et al. Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155. *Nat. Med.* **17**, 1275–1282. https://doi.org/10.1038/nm.2459 (2011).
19. Hu, Y. L., Fong, S., Largman, C. & Shen, W. F. HOXA9 regulates miR-155 in hematopoietic cells. *Nucleic Acids Res.* **38**, 5472–5478. https://doi.org/10.1093/nar/gkq337 (2010).
20. van den Berg, A. et al. High expression of B-cell receptor inducible gene BIC in all subtypes of hodgkin lymphoma. *Genes Chromosomes Cancer.* **37**, 20–28. https://doi.org/10.1002/gcc.10186 (2003).
21. Vargova, K. et al. MYB transcriptionally regulates the miR-155 host gene in chronic lymphocytic leukemia. *Blood* **117**, 3816–3825. https://doi.org/10.1182/blood-2010-05-285064 (2011).
22. Kohlhaas, S. et al. Cutting edge: the Foxp3 target miR-155 contributes to the development of regulatory T cells. *J. Immunol.* **182**, 2578–2582. https://doi.org/10.4049/jimmunol.0803162 (2009).
23. Elton, T. S., Selemon, H., Elton, S. M. & Parinandi, N. L. Regulation of the MIR155 host gene in physiological and pathological processes. *Gene* **532**, 1–12. https://doi.org/10.1016/j.gene.2012.12.009 (2013).
24. Wu, X. et al. Blocking MIR155HG/miR-155 axis inhibits mesenchymal transition in glioma. *Neuro Oncol.* **19**, 1195–1205. https://doi.org/10.1093/neuonc/nox017 (2017).
25. Thiele, J. A. et al. LncRNAs in Non-Malignant tissue have prognostic value in colorectal cancer. *Int. J. Mol. Sci.* https://doi.org/10.3390/ijms19092672 (2018).
26. Zou, W. et al. Analysis of the relationship between MIR155HG variants and gastric cancer susceptibility. *BMC Gastroenterol.* **20** https://doi.org/10.1186/s12876-020-1169-8 (2020).
27. Weng, W. C. et al. Functional variants of the pentraxin 3 gene are associated with the metastasis and progression of prostate cancer. *J. Cell. Mol. Med.* **28**, e70041. https://doi.org/10.1111/jcmm.70041 (2024).
28. Paraboschi, E. M. et al. Genetic association and altered gene expression of mir-155 in multiple sclerosis patients. *Int. J. Mol. Sci.* **12**, 8695–8712. https://doi.org/10.3390/ijms12128695 (2011).
29. Saaf, A. et al. Are BIC (miR-155) polymorphisms associated with eczema susceptibility? *Acta Derm Venereol.* **93**, 366–367. https://doi.org/10.2340/00015555-1466 (2013).
30. Tao, H. et al. Association of Tag SNPs and Rare CNVs of the MIR155HG/miR-155 gene with epilepsy in the Chinese Han Population. *Biomed. Res. Int.* https://doi.org/10.1155/2015/837213 (2015).
31. Zou, Z. et al. Association of miR-155 and MIR155HG polymorphisms with cancer risk: A meta-analysis. *J. Cancer Res. Ther.* **17**, 1209–1218. https://doi.org/10.4103/jcrt.jcrt_913_21 (2021).
32. Jia, Z. et al. The single nucleotide polymorphisms rs4143370 and rs34904192 in MIR155HG were associated with esophageal cancer risk in the Chinese Han population. *Digestion* **104**, 222–232. https://doi.org/10.1159/000527751 (2023).

33. Chao, X. et al. MiRNA155HG polymorphisms influenced the risk of liver cancer among the Han Chinese population. *BMC Med. Genet.* **21**, 134. https://doi.org/10.1186/s12881-020-01064-4 (2020).
34. Karajovic, J. et al. Association of HOTAIR, MIR155HG, TERC, miR-155, -196a2, and – 146a genes polymorphisms with papillary thyroid cancer susceptibility and prognosis. *Cancers (Basel)*. https://doi.org/10.3390/cancers16030485 (2024).
35. Wu, H. et al. Analysis of MIR155HG variants and colorectal cancer susceptibility in Han Chinese population. *Mol. Genet. Genomic Med.* **7**, e778. https://doi.org/10.1002/mgg3.778 (2019).
36. Chang, J. H. et al. Associations of TIMP-3 genetic polymorphisms with EGFR statuses and cancer clinicopathologic development in lung adenocarcinoma patients. *Int. J. Mol. Sci.* https://doi.org/10.3390/ijms21218023 (2020).
37. Yuan, L. T. et al. Genetic variants of LncRNA MALAT1 exert diverse impacts on the risk and clinicopathologic characteristics of patients with hepatocellular carcinoma. *J. Clin. Med.* https://doi.org/10.3390/jcm8091406 (2019).
38. Lin, S. H. et al. Evaluation of the clinical significance of long non-coding RNA MALAT1 genetic variants in human lung adenocarcinoma. *Aging (Albany NY)*. **16**, 5740–5750. https://doi.org/10.18632/aging.205675 (2024).
39. Chen, Y. T. et al. Potential impact of ADAM-10 genetic variants with the clinical features of oral squamous cell carcinoma. *J. Cell. Mol. Med.* **27**, 1144–1152. https://doi.org/10.1111/jcmm.17728 (2023).
40. Shridhar, K. et al. Single nucleotide polymorphisms as markers of genetic susceptibility for oral potentially malignant disorders risk: review of evidence to date. *Oral Oncol.* **61**, 146–151. https://doi.org/10.1016/j.oraloncology.2016.08.005 (2016).
41. Yete, S., Pradhan, S. & Saranath, D. Single nucleotide polymorphisms in an Indian cohort and association of CNTN4, MMP2 and SNTB1 variants with oral cancer. *Cancer Genet.* **214–215**, 16–25. https://doi.org/10.1016/j.cancergen.2017.03.006 (2017).
42. Chen, P. J. et al. The impact of FOXP3 polymorphisms on oral cancer progression and clinicopathological characteristics. *J. Cancer.* **14**, 1195–1201. https://doi.org/10.7150/jca.84470 (2023).
43. Lin, C. W. et al. Lipocalin 2 prevents oral cancer metastasis through carbonic anhydrase IX Inhibition and is associated with favourable prognosis. *Carcinogenesis* **37**, 712–722. https://doi.org/10.1093/carcin/bgw050 (2016).
44. Lin, H. et al. LncRNA MIR155HG overexpression promotes proliferation, migration, and chemoresistance in gastric cancer cells. *Int. J. Med. Sci.* **20**, 933–942. https://doi.org/10.7150/ijms.82216 (2023).
45. Qiu, J. et al. Hypoxia-responsive LncRNA MIR155HG promotes PD-L1 expression in hepatocellular carcinoma cells by enhancing HIF-1alpha mRNA stability. *Int. Immunopharmacol.* **136**, 112415. https://doi.org/10.1016/j.intimp.2024.112415 (2024).
46. Nielsen, C. B. et al. Determinants of targeting by endogenous and exogenous microRNAs and siRNAs. *RNA* **13**, 1894–1910. https://doi.org/10.1261/rna.768207 (2007).
47. Valeri, N. et al. Modulation of mismatch repair and genomic stability by miR-155. *Proc. Natl. Acad. Sci. USA* **107**, 6982–6987. https://doi.org/10.1073/pnas.1002472107 (2010).
48. Zhang, G. J. et al. Upregulation of microRNA-155 promotes the migration and invasion of colorectal cancer cells through the regulation of claudin-1 expression. *Int. J. Mol. Med.* **31**, 1375–1380. https://doi.org/10.3892/ijmm.2013.1348 (2013).
49. Kim, S. et al. Loss of oncogenic miR-155 in tumor cells promotes tumor growth by enhancing C/EBP-beta-mediated MDSC infiltration. *Oncotarget* **7**, 11094–11112. https://doi.org/10.18632/oncotarget.7150 (2016).
50. Liu, J., Chen, Z., Xiang, J. & Gu, X. MicroRNA-155 acts as a tumor suppressor in colorectal cancer by targeting CTHRC1 in vitro. *Oncol. Lett.* **15**, 5561–5568. https://doi.org/10.3892/ol.2018.8069 (2018).
51. Qin, Y., Liu, X., Pan, L., Zhou, R. & Zhang, X. Long noncoding RNA MIR155HG facilitates pancreatic cancer progression through negative regulation of miR-802. *J. Cell. Biochem.* **120**, 17926–17934. https://doi.org/10.1002/jcb.29060 (2019).
52. Vaz-Drago, R., Custodio, N. & Carmo-Fonseca, M. Deep intronic mutations and human disease. *Hum. Genet.* **136**, 1093–1111. https://doi.org/10.1007/s00439-017-1809-4 (2017).

Acknowledgements

We thank the Human Biobank of Chung Shan Medical University Hospital, Taichung, Taiwan for specimen preparation.

Author contributions

CWL, JWL, SFY and SHL conceived and designed this study. CWL, WYH, and SHL performed the experiments. CWL and SHL analyzed the data. CYC, WYH, and YJT helped discuss the results. CWL, JWL, and SHL drafted and edited the manuscript. All authors contributed to the article and approved the submitted version.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Following obtaining fully informed consent from all participants, the study proposal received approval from the Institutional Review Board (IRB) at Chung Shan Medical University Hospital (CS1-21151). We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Additional information

Correspondence and requests for materials should be addressed to S.-H.L.