The genetic variants of \textit{LINC-PINT} are related to head and neck squamous cell carcinoma susceptibility in Chinese population

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is the most leading incident tumor worldwide. Genetic factors act crucial role in the HNSCC progression. Our study is intent to explore the correlation of LINC-PINT polymorphism with the risk of HNSCC in Chinese population.

Methods: The case-control study (including 537 HNSCC cases and 533 controls) was performed to determine the relationship between LINC-PINT polymorphisms and HNSCC susceptibility. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the associations.

Results: The current study indicated that rs157916 and rs7781295 in the LINC-PINT gene have a strong significant correlation with HNSCC risk (OR 1.32, \( p = 0.042 \); OR 1.31, \( p = 0.016 \)). Stratification analyses showed that rs157916 is related to the increased risk of HNSCC in age \( \leq 46 \) years (OR 1.56, \( p = 0.029 \)). Rs157916, rs16873842, rs7801029, and rs7781295 exhibited an enhanced risk of HNSCC in men (OR 1.82, \( p = 0.004 \); OR 1.61, \( p = 0.028 \); OR 1.53, \( p = 0.047 \); OR 1.62, \( p = 0.021 \)). Besides, we found that rs16873842 significantly increased the risk of Nasopharyngeal SCC (OR 4.04, \( p = 0.015 \)). Rs157916 (OR 1.39, \( p = 0.028 \)) and rs7781295 (OR 1.30, \( p = 0.028 \)) had a high susceptibility to Thyroid SCC.

Conclusions: This research indicated that polymorphisms in the LINC-PINT gene are significantly associated with an increased susceptibility to HNSCC, which suggest that LINC-PINT polymorphisms have a significant role in prevention and diagnosis of HNSCC.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common solid malignant tumor worldwide (Ferlay, Soerjomataram et al., 2015). There are over 500,000 new confirmed cases every year (Siegel, Ward et al., 2011). HNSCC includes malignant tumors of the oral cavity, pharynx, thyroid, larynx, and other related parts (Leemans, Braakhuis et al., 2011). Due to the limitation of diagnosis and treatment, most patients with HNSCC are in the middle and late stage when they are diagnosed. So far, the key to improve the curative effect of HNSCC is early detection, early diagnosis, and early treatment. This is also one of the main research directions to improve the survival rate of head and neck tumors in the future (Langer, 2012; Yoshizaki, Ito et al., 2012). Although the specific pathogenesis of HNSCC is still unclear, previous studies have confirmed that risk factors including smoking, drinking, virus infection, environmental factors, and genetic factors exhibit a vital role in the pathogenesis of HNSCC (Akhtar, Sheikh et al., 2012; Sabir, Baig et al., 2012; Smith, Rubenstein et al., 2012). However, many people are exposed to these risk factors, but a very small number of people will suffer from HNSCC (Sturgis and Wei, 2002). Besides, a study showed that relatives with a family history of HNSCC will increase the risk (Negri, Boffetta et al., 2009). Taken together, these suggest that heredity factors carry out a promotional role in HNSCC progression. Long noncoding RNAs (lncRNAs) are defined as noncoding RNAs longer than 200 nucleotides. More and more evidence shows that lncRNAs can interact with DNA, RNA and proteins at the transcriptional and post-transcriptional levels, thus regulating protein-coding genes' expression and affecting cell growth, survival, migration, and invasion in human cancer (Zhang, Yin et al., 2017). Besides, growing evidence indicated that lncRNAs contribute to HNSCC progression via regulating biological processes of the tumor cells (Ji, Feng et al., 2020; Jiang, Wu et al., 2020). What's more, genetic variants of lncRNAs such as PTENP1, IncRNA H19, and HOTAIR are associated with the susceptibility of HNSCC (Wu, Liu et al., 2018; Xin, Li et al., 2018; Ghapanchi, Ranjbar et al., 2020).

There is often inactivation of tumor suppressor genes in HNSCC (Arora, Aggarwal et al., 2012; Cadoni, Boccia et al., 2012). To explore the role of tumor suppressor genes in the pathogenesis of HNSCC has become one of the hotspots in the basic research of tumors. At present, with the extensive discovery of polymorphic genetic markers at the molecular level in the whole human genome and the development of the theoretical study of population genetics of related problems, to find and apply molecular genetic markers in the recombination of genetic transmission of HNSCC and to investigate the molecular genetic mechanism has become a new idea for early detection of HNSCC. Long Intergenic Non-Protein Coding RNA, P53 Induced Transcript (LINC-PINT), a tumor suppressor lncRNA, is transcriptionally regulated by P53. Several previous studies showed that LINC-PINT notably downregulates in many human cancers, such as lung squamous cell carcinomas, breast cancer, and endometrial cancer (Marín-Béjar, Mas et al., 2017). A new research demonstrated that LINC-PINT expression is also downregulated in laryngeal tumors, which act a crucial role in the pathology of laryngeal tumors (Yuan, Xiu et al., 2019). Single nucleotide polymorphism (SNP) in gene can impact the gene's
expression and structure, which may lead to the development of human tumors. We speculated that the genetic variants in the LINC-PINT gene have an association with the occurrence of HNSCC. However, there is no report on the association between SNPs in LINC-PINT and the risk of HNSCC.

We performed this study to determine the relationship between LINC-PINT genetic variants and the risk of HNSCC. We firstly obtained four SNPs including rs157916, rs16873842, rs7801029, and rs7781295 in the LINC-PINT gene depending on the 1000 genome with a minor allele frequency (MAF) > 0.05. We further detected the genotyping of all SNPs. Besides, we evaluated the association of SNPs with HNSCC susceptibility. We finally determined the associations stratified by age, gender, and HNSCC types. Our study will provide some candidate biomarkers for the diagnosis of HNSCC.

Materials And Methods

Subjects for study

In this current study, we recruited 537 unrelated HNSCC patients and 533 healthy subjects from Gansu Provincial Cancer Hospital and the First Affiliated Hospital of Xi’an Jiaotong University. Each patient was firstly diagnosed clinically and confirmed as HNSCC by histopathological examination. The controls were selected from healthy people who had been examined in the same hospital. Each subject must meet the following inclusion criteria: 1) without any cancers, 2) without any family history of tumors, 3) without family history of HNSCC. Each subject was informed of the objective of the study and obtained their informed consent. Basic characteristics of the participants including gender, age, BMI (body mass index), clinical stage, status of lymph node metastasis, drinking status and smoking status. All experiments were conducted on the basis of the guiding principles of the Helsinki Declaration. Our research supported by the ethics committee of Gansu Provincial Cancer Hospital and the First Affiliated Hospital of Xi’an Jiaotong University. And all experimental protocols were approved by the ethics committee of Gansu Provincial Cancer Hospital and the First Affiliated Hospital of Xi’an Jiaotong University.

SNP selection and genotyping

We obtained four SNPs in LINC-PINT included rs157916, rs16873842, rs7801029, and rs7781295 from the 1000 Genomes Project with MAF > 0.05. Genomic DNA from peripheral blood samples was extracted by using a whole-blood genomic DNA extraction kit. The purity and concentration of the genomic DNA was detected by a NanoDrop 2000C spectrophotometer. Primers for PCR amplification were designed by Agena Bioscience Assay Design Suite software. We further did the SNP genotyping by Agena MassARRAY iPLEX platform. The Agena Bioscience TYPER software 4 was performed to organize and analyze the genotyping data.

Statistical analyses

The normal distribution of all variables was examined by the Kolmogorov-Smirnov test. The age and clinical characteristics of case and control group were compared by t-test. The \( \chi^2 \) test was used to analyze the gender difference between the case and the control group. The Hardy-Weinberg equilibrium (HWE) of SNPs in the controls was evaluated by a Chi-squared test. The distribution of genotypes and allele from SNPs in cases and controls were detected by the exact test or \( \chi^2 \) test. The impact of LINC-PINT polymorphisms on HNSCC risk was investigated by computing ORs and 95% CIs under allele, dominant, codominant, recessive, and log-additive models by using logistic regression analysis. What’s more, we also detected the associations stratified by age, gender, and HNSCC types.

Result

Characteristics of study subjects

Our study included in 537 patients with HNSCC and 533 healthy controls. The basic characteristics for each participant in cases and controls were showed in Table 1. The average age was 46.87 ± 15.05 years in the cases and 46.62 ± 13.67 years in the controls. No significant variations were observed in gender and age between the cases and the controls (\( p = 0.950; p = 0.782 \), respectively).
Table 1
Characteristic of HNSCC and healthy controls

| Characteristics          | Cases (n = 537) | Controls (n = 533) | p      |
|--------------------------|----------------|-------------------|--------|
| Age, years (mean ± SD)a  | 46.87 ± 15.05  | 46.62 ± 13.67     | 0.782  |
| > 46                     | 299 (56.0%)    | 282 (53.0%)       |        |
| ≤ 46                     | 238 (44.0%)    | 251 (47.0%)       |        |
| Gender b                 |                |                   | 0.950  |
| Male                     | 207 (39.0%)    | 204 (38.0%)       |        |
| Female                   | 330 (61.0%)    | 329 (62.0%)       |        |
| LN metastasis            |                |                   |        |
| Node-positive            | 103 (19.0%)    |                   |        |
| Node-negative            | 82 (15.0%)     |                   |        |
| Missing                  | 352 (66 %)     |                   |        |
| Clinical stage           |                |                   |        |
| II/II                    | 38 (7 %)       |                   |        |
| II/I                     | 140 (26 %)     |                   |        |
| Missing                  | 359 (67 %)     |                   |        |
| Nasopharyngeal carcinoma | 77 (14 %)      |                   |        |
| Thyroid cancer           | 398 (74 %)     |                   |        |
| Laryngeal carcinoma      | 43 (8 %)       |                   |        |
| Parotid gland carcinoma  | 19 (4 %)       |                   |        |
| BMI, kg/m² (mean ± SD)a  |                |                   |        |
| ≤ 24                     | 12 (6 %)       | 247 (46 %)        |        |
| > 24                     | 1 (0.2%)       | 158 (30 %)        |        |
| Missing                  | 515 (93.8 %)   | 128 (24 %)        |        |
| Smoking                  | 90 (17 %)      | 365 (69 %)        |        |
| Drinking                 | 46 (9 %)       | 344 (65 %)        |        |

a Student's t-test is used. b Pearson's X² test is used. p < 0.05 indicates statistical significance.

HNSCC: Head and neck squamous cell carcinoma, LN: Lymph node, BMI: Body mass index.

Association between LINC-PINT polymorphisms and HNSCC susceptibility

Four SNPs including rs157916, rs16873842, rs7801029, and rs7781295 were successfully genotyped. The basic information of each SNP in the current study was showed in Table 2. Each SNP from the controls followed HWE (p > 0.05). We further evaluate the correlation of LINC-PINT genetic variants with HNSCC susceptibility under five genetic models with adjustment for gender and age. Our study indicated that two SNPs (rs157916 and rs7781295) have a strong significant correlation with HNSCC risk (Table 3). Rs157916 could increase the susceptibility of HNSCC (GA: OR 1.32, 95% CI = 1.01–1.73, p = 0.042). Rs7781295 also could significantly increase the susceptibility to HNSCC (A: OR 1.30, 95% CI = 1.05–1.61, p = 0.018; AG-AA: OR 1.32, 95% CI = 1.03–1.70, p = 0.030; log-additive model: OR 1.31, 95% CI = 1.05–1.62, p = 0.016).
Table 2
The distribution of allele frequencies of \textit{LINC-PINT} SNPs in case and control

| SNP ID    | Chromosome position | Function | Alleles (minor/major) | MAF    | O (HET) | E (HET) | p^a-HWE |
|-----------|---------------------|----------|-----------------------|--------|---------|---------|---------|
| rs157916  | chr7: 130884634     | Intron   | G/A                   | 0.429  | 0.401   | 0.449   | 0.481   | 0.149   |
| rs16873842| chr7: 130885731     | Intron   | A/G                   | 0.196  | 0.169   | 0.290   | 0.282   | 0.643   |
| rs7801029 | chr7: 130890856     | Intron   | G/C                   | 0.208  | 0.195   | 0.321   | 0.313   | 0.678   |
| rs7781295 | chr7: 130894403     | Intron   | A/G                   | 0.219  | 0.178   | 0.303   | 0.293   | 0.551   |

HNSCC: Head and neck squamous cell carcinoma, SNP: Single nucleotide polymorphisms, MAF: minor allele frequency, HWE: Hardy–Weinberg equilibrium.

\( p^a \) values were calculated by exact test, \( p^a < 0.05 \) are excluded;

\( p^b \) values were calculated by two–sided \( \chi^2 \), \( p^b < 0.05 \) indicates statistical significance.
## Table 3

**Association of LINC-PINT polymorphism with HNSCC risk**

| SNP ID   | Model      | Genotype | Case N | Control N | With adjusted OR (95% CI) | p     |
|----------|------------|----------|--------|-----------|----------------------------|-------|
| rs157916 | Allele     | A        | 613    | 637       | 1                          |       |
|          |            | G        | 461    | 427       | 1.12 (0.94–1.33)           | 0.190 |
|          | Codominant | AA       | 171    | 199       | 1                          |       |
|          |            | GA       | 271    | 239       | **1.32 (1.01–1.73)**       | **0.042** |
|          |            | GG       | 95     | 94        | 1.18 (0.83–1.68)           | 0.357 |
|          | Dominant   | AA       | 171    | 199       | 1                          |       |
|          |            | AG-GG    | 366    | 333       | 1.28 (1.00–1.65)           | 0.055 |
|          | Recessive  | AA-A G   | 442    | 438       | 1                          |       |
|          |            | GG       | 95     | 94        | 1.00 (0.73–1.37)           | 0.987 |
|          | Log-additive | –     | –      | –         | 1.12 (0.94–1.33)           | 0.191 |
| rs16873842 | Allele    | G        | 863    | 882       | 1                          |       |
|          |            | A        | 211    | 180       | 1.20 (0.96–1.49)           | 0.107 |
|          | Codominant | GG       | 345    | 364       | 1                          |       |
|          |            | GA       | 173    | 154       | 1.19 (0.91–1.54)           | 0.200 |
|          |            | AA       | 19     | 13        | 1.55 (0.75–3.18)           | 0.237 |
|          | Dominant   | GG       | 345    | 364       | 1                          |       |
|          |            | AG-AA    | 192    | 167       | 1.22 (0.94–1.57)           | 0.133 |
|          | Recessive  | GG-AG    | 518    | 518       | 1                          |       |
|          |            | AA       | 19     | 13        | 1.46 (0.72–2.99)           | 0.297 |
|          | Log-additive | –     | –      | –         | 1.21 (0.96–1.51)           | 0.101 |
| rs7801029 | Allele     | C        | 851    | 857       | 1                          |       |
|          |            | G        | 223    | 207       | 1.09 (0.88–1.34)           | 0.450 |
|          | Codominant | CC       | 331    | 343       | 1                          |       |
|          |            | CG       | 189    | 171       | 1.15 (0.89–1.48)           | 0.300 |
|          |            | GG       | 17     | 18        | 0.98 (0.50–1.94)           | 0.959 |
|          | Dominant   | CC       | 331    | 343       | 1                          |       |
|          |            | CG-GG    | 206    | 189       | 1.13 (0.88–1.45)           | 0.337 |
|          | Recessive  | CC-CG    | 520    | 514       | 1                          |       |
|          |            | GG       | 17     | 18        | 0.94 (0.48–1.84)           | 0.850 |

**HNSCC:** Head and neck squamous cell carcinoma, CI: confidence interval; OR: odds ratio; SNP: single nucleotide polymorphism.

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.
| SNP ID   | Model      | Genotype | Case N | Control N | With adjusted OR (95% CI) | p   |
|----------|------------|----------|--------|-----------|---------------------------|-----|
| rs7781295 | Log-additive – – – 1.09 (0.88–1.35) 0.437 |
| Allele   | G          | A        | 834    | 868       | 1.30 (1.05–1.61)          | 0.018 |
| Codominant | GG        | GG       | 324    | 354       | 1.27 (0.98–1.65)          | 0.070 |
|          | GA        | GA       | 186    | 160       | 1.32 (1.03–1.70)          | 0.030 |
|          | AA        | AA       | 24     | 14        | 1.74 (0.89–3.40)          | 0.106 |
| Dominant | GG        | GG       | 324    | 354       | 1.31 (1.05–1.62)          | 0.016 |
|          | AG-AA     | AG-AA    | 210    | 174       | 1.56 (1.05–2.34)          | 0.029 |
|          | AA        | AA       | 24     | 14        | 1.53 (1.05–2.24)          | 0.027 |
| Recessive | GG-AG     | GG-AG    | 510    | 514       | 1.50 (1.13–1.98)          | 0.005 |
|          | AA        | AA       | 24     | 14        | 1.51 (1.14–2.00)          | 0.004 |
| Log-additive – – – 1.57 (1.10–2.23) 0.012 |

HNSCC: Head and neck squamous cell carcinoma, CI: confidence interval; OR: odds ratio; SNP: single nucleotide polymorphism.

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.

**Stratification analyses for the relationship between polymorphisms and HNSCC risk**

We also detected the correlation between *LINC-PINT* polymorphisms and HNSCC risk stratified by age and gender (Table 4). Age-based stratification analyses showed that rs157916 is relevant to the increased susceptibility to HNSCC in age ≤ 46 years (GA: OR 1.56, 95% CI = 1.05–2.34, *p* = 0.029; AG-GG: OR 1.53, 95% CI = 1.05–2.24, *p* = 0.027). When stratified by sex, we observed that four SNPs have a strong association with HNSCC risk in men. Rs157916 showed an increased susceptibility to HNSCC (A: OR 1.51, 95% CI = 1.14–2.00, *p* = 0.004; GA OR 1.74, 95% CI = 1.13–2.68, *p* = 0.011; GG OR 2.06, 95% CI = 1.15–3.70, *p* = 0.016; AG-GG: OR 1.82, 95% CI = 1.21–2.73, *p* = 0.004; log-additive model: OR 1.50, 95% CI = 1.13–1.98, *p* = 0.005). Rs16873842 exhibited an increased susceptibility to HNSCC (A: OR 1.59, 95% CI = 1.10–2.31, *p* = 0.014; AG-AA: OR 1.61, 95% CI = 1.05–2.47, *p* = 0.028; log-additive: OR 1.60, 95% CI = 1.10–2.33, *p* = 0.014). Rs7801029 (CG: OR 1.53, 95% CI = 1.01–2.32, *p* = 0.047) and rs7781295 (A: OR 1.57, 95% CI = 1.10–2.23, *p* = 0.012; AG-AA: OR 1.62, 95% CI = 1.08–2.44, *p* = 0.021; log-additive model: OR 1.61, 95% CI = 1.12–2.33, *p* = 0.010) also presented a strong enhanced risk of HNSCC.
Table 4
The relationship of \textit{LINC-PINT} variants with HNSCC stratified by age and gender

| SNP ID      | Model       | Allele/Genotype | > 46 years | ≤ 46 years | Men | Women |
|-------------|-------------|-----------------|------------|------------|-----|-------|
|             |             |                 | OR (95% CI) | p          | OR (95% CI) | p   | OR (95% CI) | p |
| rs157916    | Allele      | A               | 1.01 (0.80–1.28) | 0.910 | 1.27 (0.98–1.64) | 0.069 | 1.51 (1.14–2.00) | 0.004 | 0.94 (0.76–1.17) | 0.583 |
|             |             | G               | 1.27 (0.98–1.64) | 0.069 | 2.06 (1.15–3.70) | 0.016 | 1.09 (0.77–1.55) | 0.623 |
|             | Codominant  | AA              | 1.12 (0.78–1.62) | 0.546 | 1.56 (1.05–2.34) | 0.029 | 1.74 (1.13–2.68) | 0.011 |
|             |             | GA              | 1.56 (1.05–2.34) | 0.029 | 2.06 (1.15–3.70) | 0.016 | 1.09 (0.77–1.55) | 0.623 |
|             |             | GG              | 0.97 (0.60–1.58) | 0.910 | 1.46 (0.87–2.45) | 0.155 | 2.06 (1.15–3.70) | 0.016 |
|             | Dominant    | AA              | 1.08 (0.76–1.53) | 0.668 | 1.53 (1.05–2.24) | 0.027 | 1.82 (1.21–2.73) | 0.004 |
|             |             | AG-GG           | 1.53 (1.05–2.24) | 0.027 | 2.06 (1.15–3.70) | 0.016 | 1.09 (0.77–1.55) | 0.623 |
|             | Recessive   | AA-AG           | 1.01 (0.80–1.27) | 0.956 | 1.50 (1.13–1.98) | 0.005 | 1.02 (0.73–1.41) | 0.924 |
|             |             | GG              | 0.91 (0.59–1.40) | 0.666 | 1.13 (0.71–1.79) | 0.616 | 1.50 (1.13–1.98) | 0.005 |
|             | Log-additive| –               | 1.01 (0.80–1.27) | 0.956 | 1.50 (1.13–1.98) | 0.005 | 0.84 (0.54–1.32) | 0.450 |
| rs16873842  | Allele      | A               | 1.12 (0.78–1.62) | 0.546 | 1.56 (1.05–2.34) | 0.029 | 1.74 (1.13–2.68) | 0.011 |
|             |             | G               | 1.17 (0.86–1.57) | 0.317 | 1.24 (0.90–1.71) | 0.193 | 1.59 (1.10–2.31) | 0.014 |
|             | Codominant  | GG              | 1.12 (0.78–1.62) | 0.546 | 1.56 (1.05–2.34) | 0.029 | 1.74 (1.13–2.68) | 0.011 |
|             |             | GA              | 1.19 (0.83–1.69) | 0.346 | 1.16 (0.78–1.71) | 0.469 | 1.50 (0.97–2.33) | 0.069 |
|             |             | GG              | 0.97 (0.60–1.58) | 0.910 | 1.46 (0.87–2.45) | 0.155 | 2.06 (1.15–3.70) | 0.016 |
|             | Dominant    | GG              | 1.08 (0.76–1.53) | 0.668 | 1.53 (1.05–2.24) | 0.027 | 1.82 (1.21–2.73) | 0.004 |
|             |             | AG-GG           | 1.53 (1.05–2.24) | 0.027 | 2.06 (1.15–3.70) | 0.016 | 1.09 (0.77–1.55) | 0.623 |
|             | Recessive   | AA-AG           | 1.01 (0.80–1.27) | 0.956 | 1.50 (1.13–1.98) | 0.005 | 0.84 (0.54–1.32) | 0.450 |

HNSCC: Head and neck squamous cell carcinoma.

\textit{p}-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. \textit{p} < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.
| SNP ID     | Model     | Allele/Genotype | > 46 years | ≤ 46 years | Men          | Women        |
|------------|-----------|-----------------|------------|------------|--------------|--------------|
|            |           |                 | > 46 years | ≤ 46 years | Men          | Women        |
| rs7801029  | Allele    | C               | 1          | 1          | 1            | 1            |
|            |           | G               | 0.95       | 0.723      | 0.130        | 0.136        |
|            |           |                 | (0.71–1.27)| (0.65–1.74)| (0.92–1.85)  | (0.75–1.27)  |
|            | Codominant| CC              | 1          | 1          | 1            | 1            |
|            |           | CG              | 1.05       | 0.764      | 0.318        | 0.047        |
|            |           |                 | (0.75–1.49)| (0.83–1.79)| (1.01–2.32)  | (0.69–1.33)  |
|            |           | GG              | 0.48       | 0.182      | 0.241        | 0.931        |
|            |           |                 | (0.16–1.42)| (0.69–4.38)| (0.28–3.19)  | (0.43–2.24)  |
|            | Dominant  | CC              | 1          | 1          | 1            | 1            |
|            |           | CG              | 1.00       | 0.999      | 0.211        | 0.062        |
|            |           |                 | (0.71–1.40)| (0.87–1.84)| (0.98–2.22)  | (0.70–1.32)  |
|            | Recessive | CC-CG           | 1          | 1          | 1            | 1            |
|            |           | GG              | 0.47       | 0.169      | 0.296        | 0.745        |
|            |           |                 | (0.16–1.38)| (0.65–4.07)| (0.25–2.73)  | (0.44–2.25)  |
|            | Log-additive| –              | 0.94       | 0.678      | 0.155        | 0.119        |
|            |           |                 | (0.69–1.27)| (0.92–1.72)| (0.93–1.92)  | (0.74–1.28)  |
| rs7781295  | Allele    | G               | 1          | 1          | 1            | 1            |
|            |           | A               | 1.25       | 0.132      | 0.059        | 0.012        |
|            |           |                 | (0.93–1.68)| (0.99–1.85)| (1.10–2.23)  | (0.88–1.52)  |
|            | Codominant| GG              | 1          | 1          | 1            | 1            |
|            |           | GA              | 1.26       | 0.197      | 0.238        | 0.051        |
|            |           |                 | (0.89–1.79)| (0.86–1.86)| (1.00–2.31)  | (0.82–1.58)  |
|            |           | AA              | 1.71       | 0.312      | 0.106        | 0.061        |
|            |           |                 | (0.61–4.80)| (0.85–5.16)| (0.94–13.49) | (0.64–3.19)  |
|            | Dominant  | GG              | 1          | 1          | 1            | 1            |
|            |           | AG-AA           | 1.29       | 0.146      | 0.119        | 0.021        |
|            |           |                 | (0.92–1.82)| (0.93–1.95)| (1.08–2.44)  | (0.85–1.60)  |
|            | Recessive | GG-AG           | 1          | 1          | 1            | 1            |

HNSCC: Head and neck squamous cell carcinoma.

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.
| SNP ID | Model          | Allele/Genotype | > 46 years | ≤ 46 years | Men         | Women         |
|-------|----------------|-----------------|------------|------------|-------------|---------------|
|       |                | AA              | 1.57       | 1.94       | 3.10        | 1.37          |
|       |                |                 | (0.56–4.40)| (0.80–4.73)| (0.82–11.62)| (0.62–3.03)   |
|       |                |                 | 0.387      | 0.143      | 0.094       | 0.438         |
|       | Log-additive   |                 |            |            |             |               |
|       |                | 1.27            | 1.34       | 1.61       | 1.16        |               |
|       |                | (0.94–1.73)     | (0.98–1.83)| (1.12–2.33)| (0.88–1.52) |               |
|       |                | 0.121           | 0.067      | 0.010      | 0.287       |               |
|       |                |                 |            |            |             |               |
|       |                |                 |            |            |             |               |

HNSCC: Head and neck squamous cell carcinoma.

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.

We further investigated the influence of *LINC-PINT* polymorphisms on Nasopharyngeal SCC and Thyroid SCC risk (Table 5). A significant enhanced association was observed between rs16873842 and Nasopharyngeal SCC susceptibility (codominant model: OR 4.04, 95% CI = 1.31–12.46, *p* = 0.015; recessive model: OR 3.54, 95% CI = 1.17–10.71, *p* = 0.025; log-additive model: OR 1.69, 95% CI = 1.10–2.59, *p* = 0.017). What's more, rs157916 (GA: OR 1.39, 95% CI = 1.04–1.87, *p* = 0.028) and rs7781295 (A: OR 1.30, 95% CI = 1.03–1.63, *p* = 0.028; log-additive: OR 1.29; 95% CI = 1.02–1.63, *p* = 0.037) had a high risk of Thyroid SCC.
Table 5
The relationship of LINC-PINT variants with Nasopharyngeal SCC and Thyroid SCC risk

| SNP ID      | Model       | Allele/Genotype | Nasopharyngeal SCC | Thyroid SCC |
|-------------|-------------|------------------|--------------------|-------------|
|             |             |                  | Case  | Control | OR (95% CI) | p     | Case  | Control | OR (95% CI) | p     |
| rs157916    | Allele      | A                | 87    | 637     | 1.15 (0.82–1.62) | 0.425 | 453   | 637     | 1.13 (0.94–1.36) | 0.200 |
|             |             | G                | 67    | 427     | 1.13 (0.82–1.62) | 0.425 | 453   | 637     | 1.13 (0.94–1.36) | 0.200 |
|             | Codominant  | AA               | 26    | 199     | 1      | 122   | 199     | 1      |
|             |             | GA               | 35    | 239     | 1.13 (0.94–1.36) | 0.200 |
|             |             | GG               | 16    | 94      | 1.13 (0.94–1.36) | 0.200 |
|             | Dominant    | AA               | 26    | 199     | 1      | 122   | 199     | 1      |
|             |             | AG-GG            | 51    | 333     | 1.13 (0.94–1.36) | 0.200 |
|             |             | GG               | 46    | 364     | 1      | 260   | 364     | 1      |
|             | Recessive   | AA-AG            | 51    | 333     | 1.13 (0.94–1.36) | 0.200 |
|             |             | GG               | 46    | 364     | 1      | 260   | 364     | 1      |
| rs16873842  | Allele      | G                | 118   | 882     | 1      | 645   | 882     | 1      |
|             |             | A                | 36    | 180     | 1.13 (0.94–1.36) | 0.200 |
|             | Codominant  | GG               | 46    | 364     | 1      | 260   | 364     | 1      |
|             |             | GA               | 26    | 154     | 1.13 (0.94–1.36) | 0.200 |
|             |             | AA               | 5     | 13      | **4.04 (1.31–12.46)** | 0.015 |
|             | Dominant    | GG               | 46    | 364     | 1      | 260   | 364     | 1      |
|             |             | AG-AA            | 31    | 167     | 1.13 (0.94–1.36) | 0.200 |
|             | Recessive   | GG-AG            | 72    | 518     | 1      | 385   | 518     | 1      |

Nasopharyngeal SCC: Nasopharyngeal squamous cell carcinoma, Thyroid SCC: Thyroid squamous cell carcinoma

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.
| SNP ID | Model     | Allele/Genotype | Nasopharyngeal SCC | Thyroid SCC |
|--------|-----------|-----------------|---------------------|-------------|
|        |           | Case | Control | OR (95% Cl) | p | Case | Control | OR (95% Cl) | p |
| AA     | Log-additive | 5   | 13     | 3.54 (1.17–10.71) | **0.025** | 13   | 13     | 1.36 (0.62–2.98) | 0.445 |
|        |           |      |         |             |    |      |         |             |    |
|        | Log-additive | 5   | 13     | 1.69 (1.10–2.59) | **0.017** | 13   | 13     | 1.12 (0.88–1.43) | 0.358 |
|        |           | rs7801029 | Allele | C | 126 | 857 | 1 | 626 | 857 | 1 |
|        |           | G | 28 | 207 | 0.92 (0.59–1.42) | 0.708 | 170 | 207 | 1.12 (0.90–1.41) | 0.313 |
| Codominant | CC | 51 | 343 | 1 | 242 | 343 | 1 |
|        |           | CG | 24 | 171 | 1.00 (0.59–1.69) | 0.987 | 142 | 171 | 1.19 (0.90–1.57) | 0.226 |
|        |           | GG | 2 | 18 | 0.84 (0.19–3.82) | 0.824 | 14 | 18 | 1.05 (0.51–2.17) | 0.894 |
|        | Dominant | CC | 51 | 343 | 1 | 242 | 343 | 1 |
|        |           | CG-GG | 26 | 189 | 0.98 (0.59–1.64) | 0.944 | 156 | 189 | 1.18 (0.90–1.54) | 0.244 |
| Recessive | CC-CG | 75 | 514 | 1 | 384 | 514 | 1 |
|        |           | GG | 2 | 18 | 0.84 (0.19–3.78) | 0.824 | 14 | 18 | 0.99 (0.48–2.03) | 0.976 |
|        | Log-additive | 5   | 13     | 0.97 (0.62–1.52) | 0.895 | 13 | 19     | 1.13 (0.89–1.43) | 0.317 |
|        | rs7781295 | Allele | G | 119 | 868 | 1 | 617 | 868 | 1 |
|        |           | A | 35 | 188 | 1.36 (0.90–2.04) | 0.141 | 173 | 188 | 1.30 (1.03–1.63) | **0.028** |
| Codominant | GG | 45 | 354 | 1 | 241 | 354 | 1 |
|        |           | GA | 29 | 160 | 1.50 (0.90–2.51) | 0.122 | 135 | 160 | 1.22 (0.92–1.63) | 0.163 |
|        |           | AA | 3 | 14 | 2.32 (0.62–8.74) | 0.213 | 19 | 14 | 1.94 (0.95–3.97) | 0.069 |
| Dominant | GG | 45 | 354 | 1 | 241 | 354 | 1 |

Nasopharyngeal SCC: Nasopharyngeal squamous cell carcinoma, Thyroid SCC: Thyroid squamous cell carcinoma

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.
| SNP ID  | Model     | Allele/Genotype | Nasopharyngeal SCC | Thyroid SCC |  |
|---------|-----------|-----------------|--------------------|-------------|---|
|         |           |                 | Case | Control | OR (95% CI) | p | Case | Control | OR (95% CI) | p  |
| AG-AA   | Recessive | 32               | 174  | 1.55     | (0.94–2.56) | 0.085 | 154  | 174     | 1.28         | (0.97–1.69) | 0.075 |
| GG-AG   |           | 74               | 514  | 1        |             | 0.297 | 376  | 514     | 1.82         | (0.89–3.69) | 0.099 |
| AA      | Log-additive | –               | –    | –        | 1.51        | (0.98–2.33) | 0.065 | –    | –        | 1.29         | (1.02–1.63) | 0.037 |

Nasopharyngeal SCC: Nasopharyngeal squamous cell carcinoma, Thyroid SCC: Thyroid squamous cell carcinoma

*p*-values were calculated by unconditional logistic regression analysis with adjustment for age and gender. *p* < 0.05 indicates statistical significance.

Highlighted in bold indicates the significant association between SNPs and HNSCC risk.

**Discussion**

In the current study, we firstly detected the association of *LINC-PINT* polymorphisms with HNSCC susceptibility in Chinese population. Our findings showed that four SNPs including rs157916, rs16873842, rs7801029, and rs7781295 in *LINC-PINT* are relevant an enhanced susceptibility to HNSCC. Our study may provide new biomarkers for the prevention of HNSCC in Chinese population.

HNSCC is a complicated and multifactorial malignant tumor, which is caused by alcohol consumption, tobacco smoking, environmental and genetic factors. An increasing study indicated that genetic polymorphisms conduce to HNSCC susceptibility. For instance, Li et al showed that rs1801320 polymorphism in the RAD51 gene could significantly enhance the susceptibility to head and neck cancer (Li and Zhang, 2019). Huang's study revealed that interleukin-10 genetic polymorphisms increases head and neck cancer risk (Huang, Song et al., 2017), UGT1A1 genetic polymorphisms were associated with susceptibility to HNSCC (Lacko, Roelofs et al., 2010). Besides, Li found that genetic polymorphisms in NFKB1 are associated with a decreased risk in head and neck cancers (Li and Zhang, 2019). The *LINC-PINT* gene is located on chromosome 7q32.3. *LINC-PINT* plays a suppressor and can affect cell behaviors by regulating the expression of target gene in laryngeal carcinomas. We speculated that polymorphisms in the *LINC-PINT* gene have a strong association with HNSCC susceptibility. However, there is no study focusing on the relationship of *LINC-PINT* genetic variants with the risk of HNSCC. Thus, we tried to determine the influence of *LINC-PINT* polymorphisms on HNSCC risk.

We observed that rs157916 and rs7781295 in the *LINC-PINT* gene have a strong significant correlation with an increased risk of HNSCC. The two SNPs on the *LINC-PINT* gene may affect the expression level of *LINC-PINT*, and then change the expression of target gene, thus changing the risk of HNSCC. However, the exact mechanism is not fully understood and more and deeper functional studies are needed to verify it. Stratified analyses showed that rs157916 is relevant to an enhanced susceptibility of HNSCC in age ≤ 46 years. Rs157916, rs16873842, rs7801029, and rs7781295 exhibited an increased susceptibility to HNSCC in men. Besides, we observed that rs16873842 significantly enhanced Nasopharyngeal SCC risk. Rs157916 and rs7781295 had a high susceptibility to Thyroid SCC. Our results suggest that the association of *LINC-PINT* polymorphisms with the susceptibility to HNSCC may rely on the age, gender, and the subtypes of HNSCC.

Our study had some weakness. First, we detected the correlation between *LINC-PINT* polymorphisms and HNSCC risk, the relationship between *LINC-PINT* polymorphisms and the expression level of this gene in HNSCC should be tested in future. Second, drinking and smoking are the important risk factors for HNSCC, the influence of *LINC-PINT* polymorphisms on HNSCC risk under drinking and smoking subgroups will be tested in next. In spite of its shortcomings, our findings provide the new perspective for the molecular mechanism of HNSCC occurrence.
Conclusion

In conclusion, our present study indicated that LINC-PINT genetic variants have a strong relationship with the HNSCC risk, which suggest that LINC-PINT may carry out an important role in the pathology of HNSCC.

Declarations

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Availability of data and materials

Participant informed consent statements did not seek consent for data to be made publicly available; however, data will be made available to individual researchers upon reasonable request.

Author’s contributions

Quanlin Guan and Jincai Xue designed the study. Tianchang Wang, Qinjiang Liu, Jun Wang, Haixiang Su, and Youxin Tian recruited and collected study samples. Yaqiong Ni and Yunsheng Wang designed the primers and performed the experiments. Fang Dong analyzed the data. Jincai Xue performed the data and wrote the manuscript. Quanlin Guan revised the manuscript.

Ethic approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of Gansu Provincial Cancer Hospital and the First Affiliated Hospital of Xi’an Jiaotong University and the 1964 Helsinki declaration.

Patient consent for publication

No applicable.

Competing interests

All authors declare that they have no competing interests.

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