Evaluation of Association of LOC105371267 Polymorphisms and Breast Cancer Susceptibility

Xiaoli Liu  
Xizang Minzu University

Dandan Li  
Xizang Minzu University

Chunjuan He  
Xizang Minzu University

Linna Peng  
Xizang Minzu University

Shishi Xing  
Xizang Minzu University

Yuhe Wang  
Xizang Minzu University

Yongjun He  (yongjunhe01@163.com)  
Xizang Minzu University

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Abstract

**Background:** LOC105371267 (also known as PR-lnRNA1) was reported to be a p53-regulated lncRNA, which played essential roles in the pathogenesis of breast cancer (BC). We aimed to investigate the potential associations between LOC105371267 polymorphisms and BC risk.

**Method:** Totally, 555 healthy individuals and 561 BC patients were recruited. Five candidate SNPs of LOC105371267 were genotyped with Agena MassARRAY system. Odds ratio (OR) and 95% confidence intervals (CIs) were applied to evaluate the relationship of LOC105371267 with BC susceptibility. Additionally, stratification analyses based on clinical features and haplotype analysis were also conducted.

**Results:** A decreased BC risk was observed rs3931698 GG genotype (OR = 0.30, P = 0.018) and recessive genetic model (OR = 0.30, P = 0.021). Stratified analysis with age also revealed that this SNP was associated with a lower risk at age < 52 years. Meanwhile, multiple clinical characteristics, including ER and PR status and stage were all correlated with SNPs rs6499221, rs3931698, rs3852740 and rs8044565.

**Conclusion:** Four LOC105371267 SNPs (rs6499221, rs3931698, rs8044565 and rs3852740) were found to be correlated with development of BC. Additionally, ER, PR, and stage were also linked to LOC105371267 polymorphisms, providing novel diagnostic and therapeutic targets for of BC management.

Introduction

Breast cancer (BC) has been considered as one of prevailing cancers in the worldwide and the global annual incidence of BC has been continuously increased in the developing countries over the past decades [1, 2]. Although tremendous achievements have been obtained in the diagnosis and treatment for BC [3–5], the underlying molecular mechanisms of BC has not been fully illuminated. Currently, it is well-acknowledged that unfavorable environmental risks, the pattern and lifestyle of individuals and genetic factors such as variants are all presumably associated with the initiation of BC [6].

Many researchers have empathized that genetic variants play essential roles in the cellular signaling of BC [7]. More encouragingly, increasing attention has been concentrated on the investigating the correlation between long noncoding RNAs (lncRNAs) polymorphisms and the BC pathogenesis. Ma et al evaluated the association between BC risk and LncRNA (LINC01585) using a GWAS method and they suggested that this LncRNA probably served as a novel therapeutic target for BC [8]. Moreover, Peng et al pointed out that lncRNA MALAT1 polymorphisms were correlated with the risk of BC based on the association analyses in a Chinese Han population [9].

Notably, overwhelming evidence has demonstrated that tumor suppressor p53 play essential roles in molecular mechanisms of cancer progression [10]. Moreover, p53-regulated IncRNAs were reported to contribute to the occurrence of different types of cancers [11]. For example, Liu et al highlighted that LncRNA loc285194, a p53-regulated IncRNA, served as a tumor suppressor in colon cancer via mediating the expression of miR-211 [12]. LOC105371267 (another p53-regulated IncRNA) might participate in the breast carcinogenesis. Unfortunately, few publications investigated the underlying relationship of p53-regulated IncRNAs and BC prevalence. Here, we carried out a hospital-based case–control study to assess the presumable correlation between LOC105371267 single-nucleotide polymorphisms (SNPs) and the susceptibility to BC in a Chinese population. In addition, we also investigated the association between LOC105371267 polymorphisms and clinical characteristics of BC.

Materials And Methods

**Study population**

In this case-control study, blood samples were collected from 561 patients with BC (cases) and 555 healthy individuals (controls), who were consecutively recruited from Shaanxi Provinical Cancer Hospital. All patients were newly diagnosed as breast carcinoma by the histopathological examination and none of them had undergone chemotherapy or radiotherapy before...
gathering samples. Moreover, those who had other cancer history or suffered from immunological, cardiovascular or hematologic disorders were excluded. The control subjects received from the physical examination center in the same hospital, who had not any medical illness, not family history of BC and were genetically unrelated to the included BC patients. Additionally, the demographic data of participants and the clinical information of BC patients were acquired based on a standard questionnaire, including age, estrogen receptor (ER), progesterone receptor (PR), Ki67 status, tumor status, location and stage, lymph nodes metastasis and distance metastasis. All participants signed informed consent, and this work was approved by the Ethics Committee of Xizang Minzu University. All experiments were conducted in accordance with the World Medical Association Declaration of Helsinki.

SNPs genotyping assay

Total DNA isolation was undertaken from 5 mL of ethylenediamine tetraacetic acid (EDTA) - anticoagulated peripheral blood using GoldMag whole blood genomic DNA purification kit (GoldMag Co. Ltd., Xian, China) according to the manufacturer's protocol and subsequently was stored at −80 °C for the following analysis. Five candidate SNPs of LOC105371267, including rs6499221, rs3931698, rs8044565, rs3852740 and rs111577197, were identified based on two databases the 1000 Genomes Project database (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/) and dbSNP database (http://www.ncbi.nlm.nih.gov/proj cts/SNP/) using with the minor allele frequency (MAF) > 0.05 in Chinese Han population and call rate > 95% [13]. Moreover, functional prediction analysis of these SNPs were performed with web-based HaploReg v4.1 software (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). Subsequently, these SNPs genotyping were carried out with the Agena MassARRAY system (Agena, San Diego, CA, U.S.A.) as described in a previous research [14] by two independent investigators. In addition, 10% of samples were randomly selected as blinded duplicates to evaluate the accuracy of SNP genotyping and exhibited 100% concordance.

Statistical analyses

The differences in demographic and clinical data between cases and controls were assessed by Pearson's χ² test and Student t test. Hardy–Weinberg equilibrium (HWE) analyses for each SNP among controls were conducted by Fisher's exact test. Pearson's χ² test was also used to analyze the difference in allelic and genotype frequencies for each polymorphism between BC patients and healthy subjects. Accordingly, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by logistic regression analysis after the adjustment for age to evaluate the correlation between LOC105371267 polymorphisms and BC risk using PLINK v1.07 software. Meanwhile, several genetic models (dominant, recessive and additive model) were utilized to estimate the relationship of LOC105371267 SNPs with the susceptibility to BC. Moreover, we performed multiple stratified analyses in terms of age, ER, PR, lymph nodes metastasis, stage, Ki67 status, and tumor size. Additionally, the pairwise linkage disequilibrium (LD) were measured by the LD coefficient D′ using the Haploview v4.2 software. Haplotype analysis was conducted by logistic regression analysis using the PLINK v1.07 software. All statistical analyses were carried out by SPSS v 18.0 software (Armonk, New York City, NY, USA) and two-sided P values were considered statistically different.

Results

Characteristics of study population and SNP identification

A total of 1116 participants (561 BC patients and 555 controls) were recruited in the current study and baseline characteristics of these subjects were exhibited in Table 1. We noted that no significant difference was detected between cases and controls (P < 0.05) in terms of age. Five candidate SNPs of LOC105371267 (rs6499221, rs3931698, rs8044565, rs3852740 and rs111577197) were screened according to the criteria described above and successfully genotyped in included samples. The fundamental information of these SNPs was displayed in Table 2 and the genotypes frequency of all SNPs in control groups conformed to HWE (P > 0.05). Moreover, there were no significant differences in allele frequencies between patients and healthy controls (P > 0.05), implying that these SNPs were not correlated with the susceptibility to BC under the allele model.
| Variables                        | Cases (n = 561) | Control (n = 555) | P-value |
|---------------------------------|-----------------|-------------------|---------|
| Age, years (mean ± SD)          | 52.04 ± 9.82    | 51.84 ± 9.76      | 0.738   |
| ER status, n (%)                |                 |                   |         |
| Positive                        | 380 (67.7)      |                   |         |
| Negative                        | 172 (30.7)      |                   |         |
| Unavailable                      | 9 (1.6)         |                   |         |
| PR status, n (%)                |                 |                   |         |
| Positive                        | 328 (58.5)      |                   |         |
| Negative                        | 224 (39.9)      |                   |         |
| Unavailable                      | 9 (1.6)         |                   |         |
| Ki67 status, n (%)              |                 |                   |         |
| High                            | 371 (66.1)      |                   |         |
| Low                             | 154 (27.5)      |                   |         |
| Unavailable                      | 36 (6.4)        |                   |         |
| Tumor size (cm), n (%)          |                 |                   |         |
| > 2                             | 238 (42.4)      |                   |         |
| ≤ 2                             | 206 (36.7)      |                   |         |
| Unavailable                      | 117 (20.9)      |                   |         |
| Tumor location, n (%)           |                 |                   |         |
| Right                           | 267 (47.6)      |                   |         |
| Left                            | 284 (50.6)      |                   |         |
| Bilateral                       | 8 (1.4)         |                   |         |
| Unavailable                      | 2 (0.4)         |                   |         |
| Lymph nodes metastasis, n (%)   |                 |                   |         |
| Positive                        | 277 (49.4)      |                   |         |
| Negative                        | 279 (49.7)      |                   |         |
| Unavailable                      | 5 (0.9)         |                   |         |
| Distance metastasis, n (%)      |                 |                   |         |
| M0                               | 517 (92.2)      |                   |         |
| M1                               | 39 (7.0)        |                   |         |
| Unavailable                      | 5 (0.9)         |                   |         |
| TNM stage, n (%)                |                 |                   |         |
| I-II                             | 366 (65.2)      |                   |         |

Abbreviations: ER, estrogen receptor; RP, progesterone receptor; SD, standard deviation.
### Variables

| Variables                  | Cases (n = 561) | Control (n = 555) | P-value |
|----------------------------|----------------|-------------------|---------|
| III-IV                     | 161 (28.7)     |                   |         |
| Unavailable                | 34 (6.1)       |                   |         |

#### Primary or recurrent, n (%)

|                        | Cases (n = 561) | Control (n = 555) | P-value |
|------------------------|----------------|-------------------|---------|
| Primary                | 424 (75.6)     |                   |         |
| recurrent              | 22 (3.9)       |                   |         |
| Unavailable            | 112 (20.5)     |                   |         |

Abbreviations: ER, estrogen receptor; RP, progesterone receptor; SD, standard deviation.

### Table 2

**Basic characteristics about LOC105371267 candidate SNPs and relationship with risk of breast cancer in allele model.**

| SNPs         | Chr      | Position | Type      | Variants (minor/major) | MAF (case/controls) | HWE a | OR (95% CI) | P-value b | Haploreg                                      |
|--------------|----------|----------|-----------|------------------------|---------------------|-------|-------------|-----------|-----------------------------------------------|
| rs6499221    | 16q12.2  | 53036124 | Intron    | A/G                    | 0.19/0.19           | 0.49  | 1.02 (0.83–1.26) | 0.872     | Enhancer histone marks, motifs changed        |
| rs3931698    | 16q12.2  | 53036913 | Intron    | G/T                    | 0.14/0.16           | 0.64  | 0.80 (0.64–1.02) | 0.074     | Enhancer histone marks, DNAase, motifs changed |
| rs8044565    | 16q12.2  | 53040078 | Intron    | C/T                    | 0.25/0.24           | 1.00  | 1.01 (0.83–1.22) | 0.961     | Motifs changed                                |
| rs3852740    | 16q12.2  | 53044259 | Intron    | G/C                    | 0.20/0.20           | 0.69  | 0.98 (0.80–1.21) | 0.874     | Promoter histone marks, enhancer histone marks, DNAase, proteins bound, motifs changed |
| rs111577197  | 16q12.2  | 53049243 | Intron    | T/C                    | 0.22/0.21           | 0.80  | 1.09 (0.89–1.33) | 0.433     | Enhancer histone marks, motifs changed        |

SNP: single-nucleotide polymorphism; MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium; OR: odds ratio; 95% CI: 95% confidence interval.

**a** P-values for the Hardy–Weinberger equilibrium (HWE) test.

**b** P-values were calculated with logistic regression analysis with adjustments for age.

**Associations between LOC105371267 polymorphisms and BC risk**
The logistic regression model was employed to evaluate the associations between LOC105371267 SNPs and the risk of BC based on the adjustment with age (Table 3). Our findings demonstrated that GG homozygote in rs3931698 had a 0.3-fold decreased BC risk compared with TT genotype (OR = 0.30, 95% CI: 0.11–0.82, \( P = 0.018 \)). Similarly, a 0.3-fold reduced risk was also observed for rs3931698 under the recessive model (OR = 0.30, 95% CI: 0.11–0.84, \( P = 0.021 \)). However, there was no dramatically statistical difference between BC risk and remaining SNPs (rs6499221, rs8044565, rs3852740 and rs111577197) in any genetic model (\( P > 0.05 \)).
Table 3
Associations of genetic polymorphisms of LOC105371267 and breast cancer susceptibility.

| SNPs          | Model     | Genotype | Cases (%) | Controls (%) | OR (95% CI) a | P value a |
|---------------|-----------|----------|-----------|--------------|---------------|-----------|
| rs6499221     | Genotypes | AA       | 18 (3.2%) | 23 (4.1%)    | 0.79 (0.42–1.49) | 0.469     |
|               |           | AG       | 182 (32.4%) | 166 (29.9%) | 1.11 (0.86–1.43) | 0.422     |
|               |           | GG       | 361 (64.3%) | 366 (65.9%) | 1.00          |          |
|               | Dominant  | AA + AG  | 200 (36.0%) | 189 (34.0%) | 1.07 (0.84–1.37) | 0.582     |
|               |           | GG       | 361 (64.3%) | 366 (65.9%) | 1.00          |          |
|               | Recessive | AA       | 18 (3.2%) | 23 (4.1%)    | 0.77 (0.41–1.43) | 0.403     |
|               |           | AG + GG  | 543 (96.8%) | 532 (95.8%) | 1.00          |          |
|               | Additive  | -        | -         | -            | 1.02 (0.83–1.26) | 0.851     |
| rs3931698     | Genotypes | GG       | 5 (0.9%) | 16 (2.9%)    | **0.30 (0.11–0.82)** | **0.018** |
|               |           | GT       | 141 (25.1%) | 148 (26.7%) | 0.89 (0.69–1.17) | 0.430     |
|               |           | TT       | 415 (74.0%) | 391 (70.5%) | 1.00          |          |
|               | Dominant  | GG + GT  | 146 (26.0%) | 164 (29.6%) | 0.84 (0.65–1.09) | 0.189     |
|               |           | TT       | 415 (74.0%) | 391 (70.5%) | 1.00          |          |
|               | Recessive | GG       | 5 (0.9%) | 16 (2.9%)    | **0.30 (0.11–0.84)** | **0.021** |
|               |           | GT + TT  | 556 (99.1%) | 536 (97.2%) | 1.00          |          |
|               | Additive  | -        | -         | -            | 0.80 (0.63–1.01) | 0.064     |
| rs8044565     | Genotypes | CC       | 38 (6.8%) | 33 (5.9%)    | 1.13 (0.69–1.84) | 0.635     |
|               |           | CT       | 199 (35.4%) | 205 (36.9%) | 0.95 (0.74–1.22) | 0.682     |
|               |           | TT       | 324 (57.8%) | 317 (57.1%) | 1.00          |          |
|               | Dominant  | CC + CT  | 237 (42.2%) | 238 (42.8%) | 0.97 (0.77–1.24) | 0.827     |
|               |           | TT       | 324 (57.8%) | 317 (57.1%) | 1.00          |          |
|               | Recessive | CC       | 38 (6.8%) | 33 (5.9%)    | 1.15 (0.71–1.86) | 0.571     |
|               |           | CT + TT  | 523 (93.2%) | 522 (94.0%) | 1.00          |          |
|               | Additive  | -        | -         | -            | 1.01 (0.83–1.22) | 0.961     |
| rs3852740     | Genotypes | GG       | 23 (4.1%) | 20 (3.6%)    | 1.12 (0.60–2.08) | 0.720     |
|               |           | GC       | 175 (31.2%) | 182 (32.8%) | 0.94 (0.73–1.21) | 0.612     |
|               |           | CC       | 363 (64.7%) | 353 (63.6%) | 1.00          |          |
|               | Dominant  | GG + GC  | 198 (35.3%) | 202 (36.4%) | 0.66 (0.75–0.22) | 0.709     |

SNPs: single-nucleotide polymorphisms; OR: odd ratio; 95% CI: 95% confidence interval.

Bold values are statistically significant.

a $P$ values, OR and 95% CI were computed by logistic regression analysis with adjustments for age.

* indicates statistical significance (p < 0.05).
| SNPs             | Model     | Genotype | Cases (%) | Controls (%) | OR (95% CI)   | P value |
|------------------|-----------|----------|-----------|--------------|---------------|---------|
|                  | CC        | 363 (64.7%) | 353 (63.6%) | 1.00         |               |         |
|                  | Recessive | GG       | 23 (4.1%) | 20 (3.6%)    | 1.14 (0.62–2.11) | 0.666   |
|                  |           | GC + CC  | 538 (95.9%) | 535 (96.4%) | 1.00         |         |
|                  | Additive  | -        | -         | -            | 0.98 (0.80–1.21) | 0.865   |
| rs111577197      | Genotypes | TT       | 30 (5.3%) | 25 (4.5%)    | 1.22 (0.71–2.13) | 0.472   |
|                  |           | TC       | 188 (33.5%) | 180 (32.4%) | 1.06 (0.83–1.37) | 0.630   |
|                  |           | CC       | 343 (61.1%) | 350 (63.1%) | 1.00         |         |
|                  | Dominant  | TT + TC  | 218 (38.8%) | 205 (36.9%) | 1.08 (0.85–1.38) | 0.515   |
|                  |           | CC       | 343 (61.1%) | 350 (63.1%) | 1.00         |         |
|                  | Recessive | TT       | 30 (5.3%) | 25 (4.5%)    | 1.20 (0.70–2.07) | 0.515   |
|                  |           | TC + CC  | 531 (94.6%) | 530 (95.5%) | 1.00         |         |
|                  | Additive  | -        | -         | -            | 1.08 (0.89–1.32) | 0.435   |

SNPs: single-nucleotide polymorphisms; OR: odd ratio; 95% CI: 95% confidence interval.

Bold values are statistically significant.

V values, OR and 95% CI were computed by logistic regression analysis with adjustments for age.

* indicates statistical significance (p < 0.05).

**Stratification analysis**

The stratified analyses were subsequently performed to explore the correlation of BC susceptibility and multiple clinicopathologic indicators. As indicated in Table 4, the G allele of rs3931698 exhibited significant association with BC risk at age < 52 years in GG genotype (OR = 0.26, 95% CI: 0.71–0.97, P = 0.045) and additive model (OR = 0.68, 95% CI: 0.48–0.95, P = 0.025). We also found that AG genotype of rs6499221 was associated with BC risk under the age of 52 (OR = 1.48, 95% CI: 1.01–2.09, P = 0.046) For other SNPs, no significant associations were detected between age and the susceptibility to BC.
Table 4
Stratification analysis between LOC105371267 polymorphisms and breast cancer risk by age.

| SNPs       | Model     | Genotype | ≥ 52 years |              |              | < 52 years |              |              |
|------------|-----------|----------|------------|--------------|--------------|------------|--------------|--------------|
|            |           |          | Cases      | Controls     | OR (95% CI)  | P value a  | Cases        | Controls     | OR (95% CI)  | P value a  |
| rs6499221  | Genotype  | AA       | 9          | 12           | 0.70 (0.29–1.71) | 0.434      | 9            | 11           | 0.89 (0.36–2.19) | 0.792      |
|            |           | AG       | 98         | 104          | 0.89 (0.63–1.26) | 0.520      | 84           | 62           | 1.48 (1.01–2.19) | 0.046*     |
|            |           | GG       | 188        | 177          | 1.00          | 1.00       | 173          | 189          | 1.00          | 1.00       |
|            | Dominant  | AA + AG  | 107        | 116          | 0.87 (0.63–1.22) | 0.424      | 93           | 73           | 1.39 (0.96–2.02) | 0.079      |
|            | GG        | 188      | 177        | 1.00         | 1.00         | 173        | 189          | 1.00         | 1.00         | 1.00      |
| rs3931698  | Genotypes | GG       | 2          | 6            | 0.33 (0.07–1.67) | 0.183      | 3            | 10           | 0.26 (0.71–0.97) | 0.045*     |
|            | GG + GT   | 79       | 79         | 0.99 (0.69–1.43) | 0.958      | 67          | 85           | 0.71 (0.48–1.02) | 0.063      |
|            | TT        | 216      | 214        | 1.00         | 1.00         | 199        | 177          | 1.00         | 1.00         | 1.00      |
|            | Recessive | GG       | 2          | 6            | 0.33 (0.07–1.65) | 0.178      | 3            | 10           | 0.28 (0.77–1.04) | 0.058      |
|            | GT + TT   | 293      | 287        | 1.00         | 1.00         | 263        | 252          | 1.00         | 1.00         | 1.00      |
| Additive   |           | -        | -          | -            | 0.94 (0.67–1.31) | 0.696      | -            | -            | 0.68 (0.48–0.95) | 0.025*     |

SNPs: single-nucleotide polymorphisms; OR: odd ratio; 95% CI: 95% confidence interval.

Bold values are statistically significant.

*P values, odd ratios and their 95% CI were estimated by logistic regression models with the adjustment for age.

* indicates statistical significance (p < 0.05).
| SNPs         | Model         | Genotype | ≥ 52 years | Controls | OR (95% CI) | P value | < 52 years | Controls | OR (95% CI) | P value |
|--------------|---------------|----------|------------|----------|-------------|---------|------------|----------|-------------|---------|
|             |               |          | (n = 295) | (n = 293) |             |         | (n = 266) | (n = 262) |             |         |
| rs8044565   | Genotypes    | CC       | 18         | 17       | 0.95        | 0.882   | 20         | 16       | 1.33        | 0.418   |
|             |               | CT       | 106        | 123      | 0.78        | 0.141   | 93         | 82       | 1.22        | 0.292   |
|             |               | TT       | 171        | 153      | 1.00        |         | 153        | 164      | 1.00        |         |
|             | Dominant     | CC + CT  | 124        | 140      | 0.80        | 0.170   | 113        | 98       | 1.24        | 0.230   |
|             |               | TT       | 171        | 153      | 1.00        |         | 153        | 164      | 1.00        |         |
|             | Recessive    | CC       | 18         | 17       | 1.05        | 0.879   | 20         | 16       | 1.24        | 0.533   |
|             |               | CT + TT  | 277        | 276      | 1.00        |         | 246        | 246      | 1.00        |         |
|             | Additive     | -        | -          | -        | 0.87        | 0.904   | -          | -        | 1.18        | 0.230   |
| rs3852740   | Genotypes    | GG       | 14         | 11       | 1.26        | 0.584   | 9          | 9        | 0.98        | 0.965   |
|             |               | GC       | 93         | 97       | 0.95        | 0.775   | 82         | 85       | 0.93        | 0.697   |
|             |               | CC       | 188        | 185      | 1.00        |         | 175        | 168      | 1.00        |         |
|             | Dominant     | GG + GC  | 107        | 108      | 0.98        | 0.914   | 91         | 94       | 0.93        | 0.708   |
|             |               | CC       | 188        | 185      | 1.00        |         | 175        | 168      | 1.00        |         |
|             | Recessive    | GG       | 14         | 11       | 0.28        | 0.552   | 9          | 9        | 1.00        | 0.995   |
|             |               | GC + CC  | 281        | 282      | 1.00        |         | 257        | 253      | 1.00        |         |
|             | Additive     | -        | -          | -        | 1.02        | 0.904   | -          | -        | 0.95        | 0.747   |
| rs111577197 | Genotypes    | TT       | 15         | 14       | 1.10        | 0.805   | 15         | 11       | 1.38        | 0.433   |

SNPs: single-nucleotide polymorphisms; OR: odds ratio; 95% CI: 95% confidence interval.

Bold values are statistically significant.

a P values, odds ratios and their 95% CI were estimated by logistic regression models with the adjustment for age.

* indicates statistical significance (p < 0.05).
### SNPs Model Genotype ≥ 52 years < 52 years

|      | Cases (n = 295) | Controls (n = 293) | OR (95% CI) | P value | Cases (n = 266) | Controls (n = 262) | OR (95% CI) | P value |
|------|----------------|--------------------|-------------|---------|----------------|--------------------|-------------|---------|
| TC   | 100            | 94                 | 1.09 (0.77–1.54) | 0.630   | 88             | 86                 | 1.03 (0.71–1.49) | 0.878    |
| CC   | 180            | 185                | 1.00        |         | 163            | 165                | 1.00        |         |
| Dominant TT + TC | 115          | 108                | 1.09 (0.78–1.52) | 0.609   | 103            | 97                 | 1.07 (0.75–1.52) | 0.709    |
| CC   | 180            | 185                | 1.00        |         | 163            | 165                | 1.00        |         |
| Recessive TT | 15           | 14                 | 1.07 (0.51–2.26) | 0.863   | 15             | 11                 | 1.37 (0.62–3.04) | 0.441    |
| TC + CC | 280          | 279                | 1.00        |         | 251            | 251                | 1.00        |         |
| Additive | -            | -                  | 1.07 (0.81–1.41) | 0.626   | -              | -                  | 1.09 (0.82–1.46) | 0.553    |

SNPs: single-nucleotide polymorphisms; OR: odd ratio; 95% CI: 95% confidence interval.

*Bold values are statistically significant.*

*P values, odd ratios and their 95% CI were estimated by logistic regression models with the adjustment for age.

*indicates statistical significance (p < 0.05).

In addition, rs3582740 was associated with a lower risk of ER-positive BC (OR = 0.73, 95% CI: 0.53–0.99, P = 0.043; Table S4) while rs6499221 raised the incidence of ER-positive patients under the additive genetic model (OR = 1.43, 95% CI: 1.02–2.02, P = 0.041; Table S1). The G allele of rs3931698 was correlated with a higher risk of PR-positive BC (GT vs TT: OR = 1.52, 95% CI: 1.01–2.29, P = 0.043; Table S2) whereas there was no correlation between other LOC105371267 polymorphisms and PR status (Table S1 and 3–5).

Afterwards, we further evaluated the impact of LOC105371267 SNPs on the severity of BC according to TNM staging (III-IV/I-II). The results revealed that GT genotype of rs3921698 was overrepresented in patients with clinical III-IV stage compared to those with I-II stage (OR = 1.58, 95% CI: 1.04–2.40, P = 0.033; Table S2) and there was no correlation between other SNPs and TNM stage (Table S1 and 3–5). Additionally, no statistical difference was estimated between selected five SNPs in LOC105371267 and tumor size, Ki-67 status and lymph nodes metastasis based on the stratification analyses (Table S1-5).

### Haplotype analysis of LOC105371267 polymorphisms

The linkage disequilibrium (LD) and corresponding haplotypes of LOC105371267 SNPs were further investigated by Haploview software. Our findings implied that SNPs rs3931698 and rs8044565 were in high LD block and formed three haplotypes (TC, GT and TT) (Fig. 1). Furthermore, none of haplotypes was related to the incidence of BC (P > 0.05, Table 5).
Table 5

| Haplotype | Frequency  | $\chi^2$ | $P$ value | Adjusted by age |
|-----------|------------|----------|-----------|-----------------|
|           | (case/control) |          | $P$ value | OR (95% CI) $P$ value |
| TT        | 0.62/0.59   | 1.66     | 0.198     | 1.00            |
| TC        | 0.25/0.24   | 0.00     | 0.958     | 0.96 (0.79–1.17) 0.690 |
| GT        | 0.13/0.16   | 3.36     | 0.067     | 0.79 (0.62–1.01) 0.058 |

OR: odds ratio; CI: confidence interval.

Haplotypes were identified with the order of rs3931698 and rs8044565.

$P$ values, odd ratios and their 95% CI were estimated by logistic regression models with the adjustment for age.

Discussion

Recently, numerous researchers have concentrated on elucidating the correlations between IncRNAs and the susceptibility to BC. For example, Li et al. carried out a GWAS-based association analysis between IncRNAs and BC prevalence, which suggested that IncRNAs polymorphism was linked to a higher BC risk probably via influencing microRNA-mediated regulation in cell processes[15]. In this work, we performed the association analyses between LOC105371267 polymorphisms and the risk of BC based on a Chinese population. Five candidate SNPs (rs6499221, rs3931698, rs8044565, rs3852740 and rs111577197) were successfully genotyped. We found that carriers with rs3931698-G allele might have a lower incidence of BC. Stratified by age, rs6499221 increased BC risk while rs3931698 reduced the risk at age < 52 years. Meanwhile, a higher risk was observed between rs3931698SNP and other two clinical indicators (PR status and stage). Rs6499221 and rs3852740 polymorphisms showed a decreased risk in ER-positive patients. Therefore, we speculated that LOC105371267 with SNPs (rs6499221, rs3931698, rs8044565 and rs3852740) might be responsible for the occurrence and development of BC. However, no significant relationship was found between LOC105371267 rs111577197 and BC prevalence.

LOC105371267 (also known as PR-lncRNA1) was reported to be a p53-regulated IncRNA. Sánchez et al. highlighted that LOC105371267 could enhance cell apoptosis and cell cycle arrest by promoting the p53 signaling activation. Specifically, they argued that PR-lncRNA1 regulated the p53 transcriptional network by the efficient binding of p53 to some of its target genes[16]. Furthermore, Li et al. previously also pinpointed that PR-lncRNA1 interacted with a sequence-specific RNA binding protein Sam68 and this complex could promote the p53-mediated transcription in human colon carcinoma cell lines [17]. These lines of evidence have led us to formulate the hypothesis that PR-lncRNA1 could be of pathogenic importance in BC. Our results firstly revealed that LOC105371267 polymorphisms were associated with the susceptibility to BC.

Age has been identified as a prominent risk factor in the BC initiation [18]. An early study suggested that BC patients with the oldest age were more vulnerable to rapid deterioration [19]. Moreover, Unlu et al. highlighted that older women tend to have a higher BC risk compared with those younger women [20]. In the study, we found that PR-lncRNA1 SNP rs6499221 and rs3931698 were related to the risk of BC patients at age < 52 years. Additionally, several clinicopathological characteristics, including ER, PR, Ki-67, metastasis, stage and tumor size were also observed to participate in the BC pathogenesis [21–23]. Our study found that LOC105371267 polymorphisms might be associated with ER, PR, and stage of BC.

Although the association of four SNPs in PR-IncRNA1 with BC risk and several clinicopathological characteristics have been identified in the present work, there are still limitations. On the top of that, due to all participants were all enrolled in the same hospital and were Chinese Han population, the inherent selection bias cannot be excluded and our results cannot permit extrapolation of the results to other ethnic groups. In addition, the comprehensive clinical information and environmental factors should be included. Moreover, the precise molecular mechanisms of PR-IncRNA1 polymorphisms in BC progression remain to be deciphered. Despite the limitations mentioned above, the results of our study might provide evidence for the future studies about LOC105371267 with BC.
Conclusion

In summary, four LOC105371267 polymorphisms (rs6499221, rs3931698, rs8044565 and rs3852740) were found to be associated with the risk of BC. Additionally, ER, PR and stage were also correlated to LOC105371267 SNPs. However, further larger well-designed studies will be needed to validate our results.

Abbreviations

BC, breast cancer; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence intervals; ER, estrogen receptor; PR, progesterone receptor; MAFs, minor allele frequencies; HWE, hardy–weinberg equilibrium; LD, linkage disequilibrium.

Declarations

Ethics approval and consent to participate

All participants signed informed consent, and this work was approved by the Ethics Committee of Xizang Minzu University. All experiments were conducted in accordance with the World Medical Association Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and material

All the data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author.

Competing interests

The authors declare that they have no conflict of interest.

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Authors’ contributions

The work presented here was carried out in collaboration between all authors. Xiaoli Liu and Dandan Li carried out the molecular genetic studies and drafted the manuscript. Chunjuan He and Linna Peng designed the methods and experiments, performed the statistical analyses and interpreted the results. Shishi Xing and Yuhe Wang designed primers and performed the SNP genotyping experiments. Yongjun He conceived of the study, worked on associated data collection and their interpretation, participated in the design and coordination of the study, and funded the study. All authors read and approved the final manuscript.

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Figures
Figure 1
The haplotype block map for SNPs in the LOC105371267 gene.

**Supplementary Files**

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