The Association between LINC00511 Variants and Breast Cancer Susceptibility among the Han Chinese Population

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Abstract: Objective LINC00511 has been considered an oncogene for breast cancer, however, the association between LINC00511 Single nucleotide polymorphisms (SNPs) and breast cancer risk remains unclear. **Methods** A total of 504 breast cancer patients and 505 cancer-free controls were genotyped for 12 LINC00511 SNPs. A logistic regression analysis was conducted to explore the association between LINC00511 SNPs and breast cancer susceptibility, adjusting for reproductive factors. A haplotype analysis and interaction analysis were applied to assess the role of LINC00511 in breast cancer. **Results** LINC00511 SNPs were significantly correlated with breast cancer. The TT genotype of rs11657109 reduced the risk of breast cancer (OR: 0.454, 95%CI: 0.212-0.970), while the AG and GG genotypes of rs17780195 played a protective role (OR: 0.723, 95%CI: 0.539-0.970; OR: 0.398, 95%CI: 0.184-0.860, respectively). The mutation of rs9906859 may also lead to a reduction in breast cancer susceptibility (OR: 0.682, 95%CI: 0.520-0.894). Furthermore, LINC00511 SNPs (rs4432291, rs1558535, rs17780195 and rs9906859) are associated with the HER-2 status ($P < 0.05$ for all). The interaction of rs9906859, breastfeeding and age increased the breast cancer risk by 4.318 (OR: 5.318, 95%CI: 2.214-12.774). **Conclusions** LINC00511 SNPs were associated with the risk of breast cancer. There was an association between LINC00511 SNPs and the HER-2 status. There were interactions between LINC00511 SNPs and reproductive factors that affected the risk of breast cancer.

Key words: LINC00511; SNPs; Breast cancer; Haplotype

Introduction

Breast cancer ranks first among all causes of cancer mortality in women worldwide according to GLOBOCAN 2018[1]. Breast cancer also has the highest incidence among cancers in women, with an estimated 268,000 new breast cancer patients per year in China [2]. It is known that multiple factors are involved in the risk of breast cancer, including the current age, age at menarche, age at first live birth, pregnancy, parity, breast-feeding and family history [3]. Beyond that, emerging epidemiological studies have highlighted the role of hereditary factors, and single nucleotide polymorphisms (SNPs) are being considered as new biomarkers for breast cancer [4].

Long noncoding RNAs (lncRNAs) possess more than 200 nucleotides and do not encode any known proteins

[5]. The role of lncRNAs in carcinogenesis has attracted wide discussion and it is generally accepted that different lncRNAs play a role in a variety of human cancers. Recent studies revealed that several lncRNAs, such as ANRIL, CASC2c and LOC285629, were aberrantly expressed in cancer patients and were considered to be an indicator of a poor prognosis [6-8]. Moreover, lncRNA variants are believed to play an indispensable role in carcinogenesis [9, 10]. Molecular studies uncovered significant associations between cancer susceptibility and lncRNAs SNPs, including rs619586 of MALAT1, rs4801078 of linc-ROR and rs114020893 of NEXN-AS1 [11-13].

Long intergenic non-protein RNA 00511 (LINC00511), a recently reported form of long noncoding RNA located on chromosome 17q24.3, is considered to be related to multiple cancers [14]. It has been suggested that LINC00511 may function as competitive endogenous RNA, thus mediating the induction or progression of various cancers, including breast cancer [15]. A recent study demonstrated the clinical diagnostic value of LINC00511 in breast cancer [16].

The associations between LINC00511 and breast cancer have been confirmed in the general Chinese population. Lu et al. reported that the competitive binding between LINC00511 and miR-185 affects the prognosis of breast cancer among Chinese patients [17]. Liu et al. found that

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there was an association between LINC00511 and breast cancer growth and invasion in China [18]. However, the correlation between LINC00511 SNPs and breast cancer susceptibility remains ambiguous. In this study, we examined whether LINC00511 SNPs influence breast cancer susceptibility by performing a case-control study in a Han Chinese population.

Materials and Methods

Subjects

A total of 504 newly-diagnosed breast cancer patients were recruited from two Henan third-level first-class hospitals. After frequency matching (age $\pm$ 2 years), a total of 505 control samples were randomly selected from the chronic diseases program of Henan Province. All of the reproductive and pathological data were obtained from structured questionnaires. This study was approved by the Ethical Review Committee of Zhengzhou University Committee for Medical and Health Research Ethics.

DNA Extraction, SNP Selection and SNP Genotyping

A DNA Extraction Kit (Shanghai Lifefeng Biotech Co., Ltd) was applied to extract DNA from the blood samples of all subjects. After screening for a Chinese minor allele frequency above 0.05, a total of twelve SNPs (rs4793294, rs4793295, rs8075353, rs9896668, rs4432291, rs1558535, rs11657109, rs17780195, rs9906859, rs1023570, rs11077614 and rs56342858) from the LINC00511 gene were identified based on the Haploview software. The information for these twelve SNPs is shown in Table S1 (www.nutroncol.com/). All twelve SNPs were typed using the SNPscan method (Shanghai Tianhao Biotechnology Co., LTD) with GeneMapper software.

Data Analysis

Student's t-test and the χ^2 test were used to compare quantitative and qualitative variables between the case and control groups, respectively. After adjusting for demographic factors (age, age at menarche, menopausal status, breast-feeding, family history of cancer in first degree relatives, the number of pregnancies and the parity), an unconditional logistic regression was applied to explore the independent risk factors for breast cancer among the twelve SNPs of LINC00511 in four genotypic models. A stratified analysis and the SHesis online software were applied to further evaluate the association between SNPs of LINC00511 and breast cancer susceptibility. Further, MDR (Multifactor Dimensionality Reduction) software was applied to evaluate the interactive role of genetic and reproductive factors. The SPSS 21.0 statistical software package (Shanghai, Co., LTD) was used to perform all statistical analyses, and a two-sided value of $P < 0.05$ was deemed a sign of statistical significance.

Results

Basic Characteristics of Subjects

A total of 1009 subjects (504 breast cancer patients and 505 healthy controls, frequency matched by age) were enrolled in this study (details are shown in Table 1). Breast cancer patients tended to have gone through menarche at a later age (breast cancer patients: 14.21 ± 1.70 vs healthy controls: 13.97 ± 1.75 , $P = 0.030$). As the number of pregnancies increased, the women were more likely to develop breast cancer (3 pregnancies, OR: 1.871 95% CI: 1.236-2.831; ≥ 4 pregnancies, OR: 3.129 95% CI: 2.017-4.726). Moreover, compared with women who gave birth two or fewer times, the women who had more children had a higher risk of breast cancer (2 times, OR: 5.847 95% CI: 4.274-7.998; 3 times, OR: 4.705 95% CI: 3.099-7.143; ≥ 4 times, OR: 3.994 95% CI: 2.361-6.757). As expected, a family history of cancer in a first degree relative was also a risk factor for breast cancer (OR: 1.869, 95% CI: 1.116-3.130). However, breastfeeding acted as a protective factor for breast cancer (OR: 0.724, 95% CI: 0.535-0.980). No other statistically significant differences were found between the case and control groups.

The Association Between LINC00511 SNPs and Breast Cancer Susceptibility

The relationship between the 12 SNPs and breast cancer was analyzed, and the results are shown in Table 2 and Table S2 (www.nutroncol.com/). After adjusting for the current age, age at menarche, menopausal status, number of pregnancies, parity, breast-feeding and family history of cancer in a first degree relative, three SNPs of LINC00511 remained significantly associated with breast cancer susceptibility. In a codominant model, the TT genotype of rs11657109 reduced the risk of breast cancer (OR: 0.454, 95%CI: 0.212-0.970). In addition, codominant (AG, OR: 0.723, 95%CI: 0.539-0.970; GG, OR: 0.398, 95%CI: 0.184-0.860), dominant (OR: 0.681, 95%CI: 0.513-0.905) and recessive (OR: 0.442, 95%CI: 0.206-0.947) models showed a protective role for the rs17780195 G allele. The mutation of rs9906859 may also lead to a reduction in breast cancer susceptibility, as indicated by codominant (CT, OR: 0.710, 95% CI: 0.535-0.943; CC, OR: 0.536, 95% CI: 0.302-0.951), dominant (OR: 0.682, 95% CI: 0.520-0.894) and over-dominant models (OR: 0.754, 95% CI: 0.571-0.995).

Stratified Analysis of the Relationship Between Breast Cancer Susceptibility and LINC00511 SNPs

After further stratifying patients by reproductive factors (current age, age at menarche, menopausal status, number of pregnancies, parity, breast feeding history and family history of cancer in a first-degree relative), the association between three SNPs (rs11657109, rs17780195 and rs9906859) and breast cancer was still present [Table 3 and Table S3 (www.nutroncol.com/)]. The AT+TT genotype of rs11657109

significantly decreased the risk of breast cancer by 33% among patients age < 50 (OR:0.670, 95%CI:0.464-0.969), while it played a completely different role in the subgroup of patients who underwent menopause when younger than 50 (OR:1.996, 95%CI:1.035-3.849). Apparently, the protective role of the rs17780195 AG+GG genotype and rs9906859 CT+CC genotype was only present among the following subgroups: current age < 50 (OR: 0.567, 95% CI: 0.389-0.826; OR: 0.564, 95%CI: 0.394-0.806, respectively), age at menarche $\geq$ 13 (OR: 0.662, 95% CI: 0.486-0.902; OR: 0.688, 95%CI: 0.512-0.925, respectively), pre-menopausal (OR: 0.619, 95% CI: 0.424-0.903; OR: 0.612, 95%CI: 0.426-0.878, respectively), number of pregnancies $\geq$ 3 (OR:

0.597, 95% CI: 0.410-0.869; OR: 0.631, 95%CI: 0.438-0.910, respectively), number of pregnancies < 1 (rs9906859 CT+CC, OR: 0.630, 95% CI: 0.421-0.942), number of pregnancies $\geq$ 1 (rs17780195 AG+GG, OR: 0.630, 95% CI: 0.421-0.942), with a history of breast-feeding (OR: 0.690, 95% CI: 0.503-0.947; OR: 0.701, 95%CI: 0.517-0.951, respectively), and no family history of cancer in first degree relatives (OR: 0.683, 95% CI: 0.508-0.918; OR: 0.695, 95%CI: 0.525-0.922, respectively). Of note, the risk of breast cancer was increased by the rs17780195 AG+GG genotype and rs9906859 CT+CC genotype among patients who underwent menopause under 50 (OR: 2.085, 95% CI: 1.074-4.048; OR: 2.222, 95%CI: 1.168-4.225, respectively).

Table 1 The baseline characteristics of 504 breast cancer patients and 505 cancer-free controls

Variables	Case (%) n=504	Control (%) n=505	<i>P</i> ^b	OR (95%CI)
Age (Mean $\pm$ SD)	48.00 $\pm$ 9.85	48.15 $\pm$ 9.61	0.806 ^a	
Age at menarche (Mean $\pm$ SD)	14.21 $\pm$ 1.70	13.97 $\pm$ 1.75	0.030 ^a	
Age at menopause (Mean $\pm$ SD)	48.60 $\pm$ 3.90	48.72 $\pm$ 3.70	0.760 ^a	
Menopausal status				
Pre-menopausal	320 (63.5)	294 (58.2)		1
Post-menopausal	184 (36.5)	211 (41.8)	0.086	0.801 (0.622-1.032)
No. of pregnancies				
< 1	53 (10.5)	94 (18.6)		1
2	129 (25.6)	177 (35.0)	0.215	1.293 (0.861-1.940)
3	135 (26.8)	128 (25.3)	0.003	1.871 (1.236-2.831)
$\geq$ 4	187 (37.1)	106 (21.0)	< 0.001	3.129 (2.071-4.726)
Parity (no.)				
< 1	156 (31.0)	354 (70.1)		1
2	219 (43.5)	85 (16.8)	< 0.001	5.847 (4.274-7.998)
3	85 (16.9)	41 (8.1)	< 0.001	4.705 (3.099-7.143)
$\geq$ 4	44 (8.7)	25 (5.0)	< 0.001	3.994 (2.361-6.757)
Breast-feeding				
No	121 (24.0)	94 (18.6)		1
Yes	383 (76.0)	411 (81.4)	0.037	0.724 (0.535-0.980)
Family history				
No	461 (91.5)	481 (95.2)		1
Yes	43 (8.5)	24 (4.8)	0.017	1.869 (1.116-3.130)
ER expression				
Negative	149 (30.3)			
Positive	342 (69.7)			
PR expression				
Negative	191 (39.1)			
Positive	298 (60.9)			
HER-2 expression				
Negative	138 (29.6)			
Positive	329 (70.4)			

^aStudent's t test.

^bTwo-sided χ^2 test, *P* < 0.05 was considered to be statistically significant

Moreover, the AG+GG genotype of rs56342858 led to an increase in breast cancer susceptibility in women who underwent menopause below 50 (OR: 2.243, 95%CI: 1.154-4.357).

The Associations between LINC00511 SNPs and the ER, PR and HER-2 Status of Breast Cancer Patients

The estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) are well-known drivers of breast cancer growth and progression. As shown in Table 4, LINC00511 SNPs were significantly associated with the HER-2 receptor phenotype. The presence of AG (OR: 0.555, 95%CI: 0.354-0.872) and AG+ GG (OR: 0.533, 95%CI: 0.344-0.826) in rs17780195 were associated with HER-2 status. There was also a significant association between rs9906859 and the HER-2 status (CT: OR: 0.603, 95%CI: 0.388-0.939; CC: OR: 0.293,

95%CI: 0.117-0.729; CT+CC: OR: 0.550, 95%CI: 0.360-0.839). The rs1558535 SNP was also strongly correlated with the HER-2 status (AT: OR: 0.599, 95%CI: 0.372-0.965; TT: OR: 0.186, 95%CI: 0.051-0.675; AT + TT: OR: 0.536, 95%CI: 0.340-0.845). Additionally, the mutant homozygote (OR: 0.308, 95%CI: 0.108-0.879) and mutants (OR: 0.619, 95%CI: 0.402-0.953) of rs4432291 are related to the HER-2 status.

Haplotype Analysis of Twelve SNPs in LINC00511

The combined effects of the twelve selected SNPs (rs4793294, rs4793295, rs8075353, rs9896668, rs4432291, rs1558535, rs11657109, rs17780195, rs9906859, rs1023570, rs11077614 and rs56342858) were examined by haplotype analysis. As shown in Table 5, the haplotype Grs₄₇₉₃₂₉₄Grs₄₇₉₃₂₉₅Ar_{s8075353}Cr_{s9896668}Ar_{s4432291}Ar_{s1558535}Ar_{s11657109}Ar_{s17780195}Tr_{s9906859}

Table 2 The association between three SNPs and breast cancer susceptibility

SNP	Genetic model	Genotype	Case (%)	Control (%)	<i>P</i> ^a	Adjusted OR (95%CI)	<i>P</i> ^b
rs11657109	Codominant	AA	337 (51.4)	319 (48.6)	0.702	1	
		AT	154 (48.4)	164 (51.6)		0.840 (0.630,1.119)	0.233
		TT	13 (37.1)	22 (62.9)		0.454 (0.212,0.970)	0.041
	Dominant	AA	337 (51.4)	319 (48.6)		1	
		AT+TT	167 (47.3)	186 (52.7)		0.792 (0.600,1.045)	0.100
	Recessive	AA+AT	491 (50.4)	483 (49.6)		1	
		TT	13 (37.1)	22 (62.9)		0.481 (0.226,1.021)	0.057
	Over-Dominant	AA+TT	350 (50.7)	341 (49.3)		1	
		AT	154 (48.4)	164 (51.6)		0.873 (0.657,1.160)	0.349
rs17780195	Codominant	AA	352 (52.5)	319 (47.5)	0.782	1	
		AG	139 (46.6)	159 (53.4)		0.723 (0.539,0.970)	0.030
		GG	13 (35.1)	24 (64.9)		0.398 (0.184,0.860)	0.019
	Dominant	AA	352 (52.5)	319 (47.5)		1	
		AG+GG	152 (45.4)	183 (54.6)		0.681 (0.513,0.905)	0.008
	Recessive	AA+AG	491 (50.7)	478 (49.3)		1	
		GG	13 (35.1)	24 (64.9)		0.442 (0.206,0.947)	0.036
	Over-Dominant	AA+GG	365 (51.6)	343 (48.4)		1	
		AG	139 (46.6)	159 (53.4)		0.757 (0.566,1.1012)	0.061
rs9906859	Codominant	TT	303 (53.3)	266 (46.7)	0.698	1	
		CT	167 (46.6)	191 (53.4)		0.710 (0.535,0.943)	0.018
		CC	26 (41.3)	37 (58.7)		0.536 (0.302,0.951)	0.033
	Dominant	TT	303 (53.3)	266 (46.7)		1	
		CT+CC	193 (45.8)	228 (54.2)		0.682 (0.520,0.894)	0.006
	Recessive	TT+CT	470 (50.7)	457 (49.3)		1	
		CC	26 (41.3)	37 (58.7)		0.612 (0.349,1.074)	0.087
	Over-Dominant	TT+CC	329 (52.1)	303 (47.9)		1	
		CT	167 (46.6)	191 (53.4)		0.754 (0.571,0.995)	0.046

^a*P* value of Hardy-Weinberg equilibrium in controls;

^b*P* value of logistic regression analysis adjusted for current age, age at menarche, menopausal status, number of pregnancies, parity, breast-feeding status, and family history of cancer in a first-degree relative

Grs₁₀₂₃₅₇₀Grs₁₁₀₇₇₆₁₄Ars₅₆₃₄₂₈₅₈ had the highest frequency of all haplotypes among both cases and controls (25.1% and 24.0%, respectively). There was an increase in the risk of breast cancer in haplotypes Trs₄₇₉₃₂₉₄Grs₄₇₉₃₂₉₅Grs₈₀₇₅₃₅₃ Crs₉₈₉₆₆₆₈Ars₄₄₃₂₂₉₁Ars₁₅₅₈₅₃₅Ars₁₁₆₅₇₁₀₉Ars₁₇₇₈₀₁₉₅ Trs₉₉₀₆₈₅₉ Grs₁₀₂₃₅₇₀Ars₁₁₀₇₇₆₁₄Ars₅₆₃₄₂₈₅₈ (OR: 1.252, 95%CI: 1.000-1.569).

Interaction between LINC00511 SNPs and Reproductive Factors

Multifactor Dimensionality Reduction was used to evaluate the interaction between LINC00511 SNPs and reproductive factors (Table 6). There were three models generated based on the twelve LINC00511 SNPs and various reproductive factors. The best model incorporated rs9906859, breastfeeding and age, which indicated that there is an interaction between LINC00511 and several reproductive factors (OR: 5.318, 95%CI: 2.214-12.774).

The False Positive Report Probability (FPRP)

We performed a false positive report probability analysis

for the present findings. As shown in Table 7, the results are reliable because the prior probability is less than 0.5. It was noted that rs11657109, rs17780195 and rs9906859 in MIR2052HG could still reduce the risk of breast cancer. In addition, the relationship between the rs4432291 AG+GG genotype, rs1558535 AT+TT genotype and HER-2 status was still noteworthy.

Discussion

To the best of our knowledge, this is the first study to explore the association between LINC00511 SNPs and breast cancer risk. Three SNPs (rs11657109, rs17780195 and rs9906859) of LINC00511 were detected as protective factors that reduced the risk of breast cancer. Genotype TT of rs11657109 significantly decreased the risk of breast cancer. Moreover, the protective role of three SNPs was still present after patients were stratified by several reproductive factors. Conversely, the mutant of rs56342858 only showed a positive correlation with breast cancer in the subgroup of patients younger than 50. The findings also indicated that rs4432291, rs1558535, rs17780195

Table 3 Stratification analysis of the relationship between four SNPs and breast cancer susceptibility.

	rs11657109 (AT+TT/AA) OR (95%CI) P		rs17780195 (AG+GG/AA) OR (95%CI) P		rs9906859 (CT+CC/TT) OR (95%CI) P		rs56342858 (AG+GG/AA) OR (95%CI) P	
Age								
< 50	0.670 (0.464,0.969)	0.033	0.567 (0.389,0.826)	0.003	0.564 (0.394,0.806)	0.002	0.746 (0.522,1.066)	0.108
≥ 50	0.961 (0.614,1.502)	0.860	0.831 (0.524,1.316)	0.429	0.826 (0.531,1.285)	0.396	1.009 (0.647,1.575)	0.968
Age at menarche								
< 13	0.729 (0.358,1.481)	0.382	0.809 (0.390,1.676)	0.568	0.682 (0.343,1.355)	0.274	0.865 (0.432,1.734)	0.683
≥ 13	0.808 (0.596,1.094)	0.168	0.662 (0.486,0.902)	0.009	0.688 (0.512,0.925)	0.013	0.840 (0.623,1.133)	0.254
Menopausal status								
Pre-menopausal	0.740 (0.511,1.071)	0.110	0.619 (0.424,0.903)	0.013	0.612 (0.426,0.878)	0.008	0.811 (0.566,1.163)	0.255
Post-menopausal	0.841 (0.542,1.306)	0.442	0.795 (0.508,1.246)	0.318	0.779 (0.507,1.198)	0.255	0.873 (0.564,1.351)	0.543
Age at menopause								
< 50	1.996 (1.035,3.849)	0.039	2.085 (1.074,4.048)	0.030	2.222 (1.168,4.225)	0.015	2.243 (1.154,4.357)	0.017
≥ 50	0.747 (0.399,1.398)	0.362	0.844 (0.442,1.611)	0.608	0.829 (0.445,1.544)	0.555	0.633 (0.339,1.182)	0.151
No. of pregnancies								
< 3	0.852 (0.556,1.305)	0.461	0.789 (0.507,1.227)	0.292	0.759 (0.501,1.151)	0.195	0.909 (0.599,1.380)	0.656
≥ 3	0.782 (0.537,1.137)	0.198	0.597 (0.410,0.869)	0.007	0.631 (0.438,0.910)	0.014	0.817 (0.564,1.185)	0.287
Parity (no.)								
< 1	0.819 (0.544,1.234)	0.339	0.665 (0.434,1.021)	0.062	0.630 (0.421,0.942)	0.025	0.901 (0.606,1.341)	0.898
≥ 1	0.766 (0.506,1.159)	0.207	0.661 (0.437,1.001)	0.050	0.698 (0.465,1.048)	0.083	0.810 (0.535,1.226)	0.320
Breast-feeding								
No	0.680 (0.362,1.277)	0.231	0.592 (0.306,1.143)	0.118	0.558 (0.302,1.032)	0.063	0.790 (0.428,1.459)	0.451
Yes	0.798 (0.584,1.092)	0.158	0.690 (0.503,0.947)	0.022	0.701 (0.517,0.951)	0.022	0.831 (0.611,1.131)	0.240
Family history ^a								
No	0.816 (0.611,1.089)	0.167	0.683 (0.508,0.918)	0.011	0.695 (0.525,0.922)	0.011	0.865 (0.651,1.149)	0.316
Yes	0.412 (0.133,1.273)	0.123	0.649 (0.205,2.054)	0.463	0.402 (0.129,1.252)	0.116	0.412 (0.133,1.273)	0.123

^aFamily history: family history of cancer in a first-degree relative

and rs9906859 were associated with the HER-2 status. Interestingly, the Trs₄₇₉₃₂₉₄Grs₄₇₉₃₂₉₅Grs₈₀₇₅₃₅₃Crs₉₈₉₆₆₆₈Ars₄₄₃₂₂₉₁Ars₁₅₅₈₅₃₅Ars₁₁₆₅₇₁₀₉Ars₁₇₇₈₀₁₉₅Trs₉₉₀₆₈₅₉Grs₁₀₂₃₅₇₀Ars₁₁₀₇₇₆₁₄Ars₅₆₃₄₂₈₅₈ haplotype increased the possibility of developing breast cancer (OR: 1.252, 95%CI: 1.000-1.569). Moreover, the interaction of rs9906859, breastfeeding and age older than 50 increased the breast cancer risk by 4.318-

fold (OR: 5.318, 95%CI: 2.214-12.774).

Single nucleotide polymorphisms (SNPs), a common genetic polymorphism, are defined as mutations of a single nucleotide, and comprise both intron and exon SNPs [19]. Recently, a genome-wide association study (GWAS) reported that there was an association between SNPs and a variety of cancers, such as hepatocellular carcinoma, gastric

Table 4 The associations between LINC00511 SNPs and the ER, PR and HER-2 status of breast cancer patients

Genotype	ER		P	OR (95%CI)	PR		P	OR (95%CI)	HER-2		P	OR (95%CI)
	nega- tive (n = 149)	posi- tive (n = 342)			nega- tive (n = 190)	posi- tive (n = 298)			nega- tive (n = 136)	posi- tive (n = 328)		
rs4432291												
AA	96	232		1	133	193		1	83	226		1
AG	45	101	0.497	0.860 (0.557,1.328)	52	94	0.367	1.210 (0.800,1.832)	45	93	0.086	0.674 (0.429,1.058)
GG	7	9	0.183	0.495 (0.176,1.392)	5	11	0.467	1.501 (0.503,4.475)	8	8	0.028	0.308 (0.108,0.879)
AG+GG	52	110	0.325	0.811 (0.534,1.231)	57	105	0.301	1.236 (0.828,1.845)	53	101	0.029	0.619 (0.402,0.953)
rs1558535												
AA	103	258		1	143	216		1	90	251		1
AT	41	76	0.089	0.674 (0.428,1.061)	43	74	0.628	1.115 (0.717,1.734)	38	72	0.035	0.599 (0.372,0.965)
TT	4	7	0.499	0.645 (0.181,2.302)	4	7	0.910	1.075 (0.304,3.797)	7	4	0.011	0.186 (0.051,0.675)
AT+TT	45	83	0.075	0.671 (0.432,1.042)	47	81	0.626	1.112 (0.726,1.703)	45	76	0.007	0.536 (0.340,0.845)
rs11657109												
AA	103	227		1	133	196		1	85	225		1
AT	45	105	0.980	1.006 (0.656,1.541)	57	93	0.810	1.051 (0.702,1.573)	48	96	0.099	0.692 (0.446,1.072)
TT	1	10	0.194	3.979 (0.494,32.041)	1	9	0.087	6.210 (0.767,50.268)	3	7	0.679	0.742 (0.180,3.051)
AT+TT	46	342	0.751	1.070 (0.703,1.631)	58	102	0.526	1.137 (0.764,1.692)	51	103	0.096	0.694 (0.452,1.067)
rs17780195												
AA	103	243		1	138	207		1	84	242		1
AG	42	92	0.579	0.883 (0.568,1.372)	50	83	0.766	1.066 (0.700,1.622)	47	80	0.011	0.555 (0.354,0.872)
GG	4	7	0.479	0.633 (0.178,2.248)	3	8	0.467	1.655 (0.425,6.440)	5	6	0.082	0.327 (0.093,1.154)
AG+GG	46	99	0.491	0.860 (0.561,1.320)	53	91	0.649	1.100 (0.730,1.656)	52	86	0.005	0.533 (0.344,0.826)
rs9906859												
TT	91	206		1	123	173		1	70	209		1
CT	49	114	0.897	0.937 (0.637,1.486)	58	105	0.318	1.228 (0.821,1.835)	52	104	0.025	0.603 (0.388,0.939)
CC	7	16	0.825	0.900 (0.352,2.296)	6	16	0.248	1.779 (0.670,4.725)	11	11	0.008	0.293 (0.117,0.729)
CT+CC	56	130	0.857	0.963 (0.641,1.447)	64	121	0.213	1.280 (0.868,1.885)	63	115	0.006	0.550 (0.360,0.839)

Table 5 The results of a haplotype analysis of twelve SNPs in LINC00511

Haplotype ^a	Cases (%)	Controls (%)	χ^2	Number upright	OR (95%CI)
G G A C A A A A T G G A	247.26 (0.251)	236.59 (0.240)	0.060	0.807	1.027 (0.828,1.275)
G G A C A A T G C G G G	38.12 (0.039)	46.91 (0.048)	1.218	0.270	0.781 (0.503,1.212)
G G A T G A T A C A G G	26.02 (0.026)	34.87 (0.035)	1.589	0.207	0.718 (0.427,1.205)
G G G C A A A A T A G A	187.76 (0.190)	196.00 (0.199)	0.605	0.437	0.912 (0.724,1.150)
T A A T G T T G C G G G	40.95 (0.042)	45.74 (0.046)	0.427	0.514	0.865 (0.561,1.336)
T G G C A A A A T G A A	230.19 (0.233)	190.61 (0.194)	3.835	0.050	1.252 (1.000,1.569)

^aSNP sequence: rs4793294, rs4793295, rs8075353, rs9896668, rs4432291, rs1558535, rs11657109, rs17780195, rs9906859, rs1023570, rs11077614 and rs56342585

Table 6 Interactions between Linc00511 SNPs and reproductive factors

	Testing balance accuracy	Cross-validation consistency	χ^2	P	OR (95%CI)
Breastfeeding	0.662	10/10	9.722	0.0018	4.448 (1.675,11.811)
Breastfeeding, Family history	0.658	8/10	6.857	0.0088	3.299 (1.322,8.231)
rs9906859, Breastfeeding, Age	0.673	10/10	14.924	0.0001	5.318 (2.214,12.774)

Table 7 Analysis of false positive report probability

Genotype		Stratified factors	OR (95%CI)	P	Prior probability			
					0.25	0.10	0.01	
rs11657109	TT/AA	All subjects	0.454 (0.212,0.970)	0.041	0.437	0.699	0.996	
	AT+TT/AA	Age <50	0.670 (0.464,0.969)	0.033	0.164	0.371	0.866	
		Age at menopause <50	1.996 (1.035,3.849)	0.039	0.373	0.641	0.952	
rs17780195	AG/AA	All subjects	0.723 (0.539,0.970)	0.030	0.108	0.266	0.799	
	GG/AA	All subjects	0.398 (0.184,0.860)	0.019	0.377	0.645	0.952	
	AG+GG/AA	All subjects	0.681 (0.513,0.905)	0.008	0.042	0.115	0.589	
	GG/AA+AG	All subjects	0.442 (0.206,0.947)	0.036	0.425	0.689	0.961	
	AG+GG/AA	Age <50	0.567 (0.389,0.826)	0.003	0.045	0.123	0.607	
		Age at menarche ≥13	0.662 (0.486,0.902)	0.009	0.053	0.143	0.648	
		Pre-menopausal	0.619 (0.424,0.903)	0.013	0.099	0.247	0.783	
		Age at menopause <50	2.085 (1.074,4.048)	0.030	0.352	0.620	0.947	
		No. of pregnancies ≥3	0.597 (0.410,0.869)	0.007	0.070	0.184	0.713	
		Parity ≥1	0.661 (0.437,1.001)	0.050	0.239	0.485	0.912	
		Breast-feeding	0.690 (0.503,0.947)	0.022	0.100	0.250	0.785	
		No family history ^a	0.683 (0.508,0.918)	0.011	0.058	0.155	0.669	
rs9906859	AG/AA	HER-2 status	0.555 (0.354,0.872)	0.011	0.130	0.310	0.832	
	AG+GG/AA	HER-2 status	0.533 (0.344,0.826)	0.005	0.085	0.217	0.753	
	CT/TT	All subjects	0.710 (0.535,0.943)	0.018	0.075	0.195	0.727	
	CC/TT	All subjects	0.536 (0.302,0.951)	0.033	0.303	0.566	0.935	
	CT+CC/TT	All subjects	0.682 (0.520,0.894)	0.006	0.029	0.082	0.494	
	CT/TT+CC	All subjects	0.754 (0.571,0.995)	0.046	0.146	0.339	0.849	
	CT+CC/TT	Age <50	0.564 (0.394,0.806)	0.002	0.027	0.077	0.479	
		Age at menarche ≥13	0.688 (0.512,0.925)	0.013	0.064	0.170	0.693	
		Pre-menopausal	0.612 (0.426,0.878)	0.008	0.067	0.177	0.703	
		Age at menopause <50	2.222 (1.168,4.225)	0.015	0.281	0.540	0.928	
		No. of pregnancies ≥3	0.631 (0.438,0.910)	0.014	0.097	0.243	0.779	
		Parity <1	0.630 (0.421,0.942)	0.025	0.157	0.359	0.860	
rs56342858		Breast-feeding	0.701 (0.517,0.951)	0.022	0.097	0.244	0.780	
		No family history ^a	0.695 (0.525,0.922)	0.011	0.054	0.146	0.652	
	CT/TT	HER-2 status	0.603 (0.388,0.939)	0.025	0.187	0.408	0.884	
	CC/TT	HER-2 status	0.293 (0.117,0.729)	0.008	0.392	0.660	0.955	
	CT+CC/TT	HER-2 status	0.550 (0.360,0.839)	0.006	0.082	0.211	0.746	
	AG+GG/AA	Age at menopause <50	2.243 (1.154,4.357)	0.017	0.304	0.567	0.935	
	rs4432291	GG/AA	HER-2 status	0.308 (0.108,0.879)	0.028	0.528	0.770	0.974
	AG+GG/AA	HER-2 status	0.619 (0.402,0.953)	0.029	0.193	0.418	0.888	
	rs1558535	AT/AA	HER-2 status	0.599 (0.372,0.965)	0.035	0.242	0.490	0.913
	TT/AA	HER-2 status	0.186 (0.051,0.675)	0.011	0.548	0.784	0.976	
	/AA	HER-2 status	0.536 (0.340,0.845)	0.007	0.111	0.273	0.805	

^afamily history of cancer in a first degree relative

cancer and colorectal cancer [20-22]. Several breast cancer-related SNPs have also been reported, most of which are located in noncoding sequences. Peng et al. reported that the MALAT1 SNP was important in breast cancer [13]. Li et al. revealed the effects of HOTAIR on the risk of breast cancer [23]. In the present study, we discovered that the mutant LINC00511 SNPs (rs11657109, rs17780195 and rs9906859) decreased breast cancer susceptibility.

LINC0051, which is considered to be an oncogene, is highly expressed in cancer tissues and promotes the invasion and metastasis of multiple cancers, including breast cancer [15,24,25]. Lu G et al. reported that LINC00511 regulated E2F1 protein expression and ultimately affected breast cancer proliferation through competitively binding to miR-185-3p [15]. An increasing number of studies has revealed that mutant variants can affect the expression and secondary structure of lncRNAs [26-28]. These alterations of the secondary structures of lncRNAs would affect the status of the binding site(s) for microRNAs, which would alter the interaction between microRNAs and mRNAs [29,30]. In this study, we discovered that there was association between three SNPs of LINC00511 and breast cancer susceptibility. Based on the evidence described in this manuscript, the reduction of breast cancer may be related to the influence of SNPs on the secondary structure and expression of LINC00511, either individually or in combination. Further studies are warranted to clarify the molecular biological mechanism underlying the observed relationships.

Breast cancer has been attributed to a variety of factors. Multiple reproductive factors have been reported as risk factors for breast cancer, such as age, menopausal status, family history of cancer in a first degree relative and a large number of pregnancies[31-33], while breast-feeding has been shown to decrease the risk of breast cancer [34, 35]. Claus EB et al. was among the first to report the important roles of genes in breast cancer [36]. However, the interactions between genes and reproductive factors has rarely been reported in breast cancer. In this study, we discovered that the interaction among rs9906859, breastfeeding and age increased the risk of breast cancer by 4.318-fold. It is well known that HER-2 expression is associated with the prognosis of breast cancer [37]. In this study, there was an association found between LINC00511 SNPs (rs4432291, rs1558535, rs17780195 and rs9906859) and the HER-2 status, confirming that LINC00511 SNPs are related to breast cancer progression.

There are several strengths associated with the present study. First, a relatively large number of subjects were included in the study, and the research was applicable for a common population. Second, only new breast cancer patients were included, which avoided Neyman bias. Third, confounding bias was minimized by frequency matching. Fourth, 10% of the samples were selected to check the results of the genotyping by sequencing. However, there were also a few limitations to this study that should be kept

in mind. First, all of the subjects were Han Chinese, so it's unclear whether the findings are generalizable for other ethnic groups. Second, there were missing data for the ER, PR, and HER-2 status for some patients, decreasing the statistical efficiency. Third, this study was just a preliminary exploration of the association between LINC00511 SNPs and breast cancer susceptibility. Further research is warranted to explain the molecular mechanism underlying how LINC00511 SNPs affect the susceptibility to breast cancer.

Conclusion

In brief, LINC00511 SNPs (rs11657109, rs17780195 and rs9906859) play protective roles against breast cancer. LINC00511 SNPs (rs4432291, rs1558535, rs17780195 and rs9906859) are associated with the HER-2 status. The interaction of rs9906859, breastfeeding and age increases the breast cancer risk by 4.318-fold.

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Conflict of Interest

All authors declare that they have no conflicts of interest.

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