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ORIGINAL ARTICLE

A common variant SNP rs1937810 in the *MPP7* gene contributes to the susceptibility of breast cancer in the Chinese Han population

Rong Li[1] | **Wenpei Zhang**[2] | **Bohui Shi**[3] | **Li Ma**[4] | **Fanliu Jiang**[2] | **Xiaochen Wang**[2] | **Jieqiong Li**[5]

[1]Department of Radiotherapy, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[2]Key Laboratory of National Health Commission for Forensic Sciences, Xi'an Jiaotong University Health Science Center, Xi'an, China

[3]Department of Breast Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[4]Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[5]Department of Nursing, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Correspondence
Jieqiong Li, Department of Nursing, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China.
Email: jieqlinur@163.com

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Abstract

Background: Breast cancer (BC) is common cancer caused by environmental factors and genetic ones. Previous evidence has linked gene MAGUK P55 Scaffold Protein 7 (*MPP7*) to BC, despite that there has been no research evaluating the relationship between *MPP7* genetic polymorphisms and BC susceptibility. We aimed to investigate the potential association of the MPP7 gene with the susceptibility to BC in Han Chinese individuals.

Methods: In total, 1390 patients with BC and 2480 controls were enrolled. For genotyping, 20 tag SNPs were chosen. The serum levels of protein MPP7 were measured in all subjects using an enzyme-linked immunosorbent assay. Genetic association analysis was performed in both genotypic and allelic modes, and the relationship between BC patients' clinical features and genotypes of relevant SNPs was examined. The functional implications of significant markers were also evaluated.

Results: After adjusting for Bonferroni correction, SNP rs1937810 was found to be significantly associated with the risk of BC ($p = 1.19 \times 10^{-4}$). The odds ratio of CC genotypes in BC patients was 49% higher than in controls (1.49 [1.23–1.81]). Serum MPP7 protein levels were significantly higher in BC patients than in controls ($p < 0.001$). The protein level of the CC genotype was the highest, and that of the CT and TT genotypes decreased in turn (both $p < 0.001$).

Conclusions: Our results linked SNP rs1937810 to the susceptibility of BC and the clinical features of BC patients. This SNP is also proved to be significantly related to the serum level of protein MPP7 in both BC patients and controls.

KEYWORDS
breast cancer, case–control study, genetic polymorphism, MPP7 gene

Rong Li and Wenpei Zhang contributed equally to the work.

1 | INTRODUCTION

Early breast cancer (BC) mortality has decreased by nearly 40% during the last four decades because of advances in prevention, early detection, and treatment (Kirkham et al., 2019). However, it is still the most common and diagnosed malignancy in women worldwide. In 2018, more than 2 million new cases were identified and 627,000 of them died (Bray et al., 2018). Multiple stages of BC tumorigenesis are influenced by both environmental and genetic factors (Vogelstein & Kinzler, 1997). It has been shown that the heritability of this disease is ~30% (Lichtenstein et al., 2000). Illustrating genetic differences between patients and controls can uncover the genetic determinants of disease, which is of great significance for studies, drug therapy, and patient outcomes. In the past few years, many genes have been identified and were closely linked to the prevalence and prognosis of BC, such as BRCA, (Reiner et al., 2013; Weitzel et al., 2013) HER2 (Capelan et al., 2013), and TP5 (Jackson et al., 2012). Therefore, drugs like Trastuzumab (Herceptin), Pertuzumab (Perjeta), and tamoxifen were then developed and used clinically, which greatly improved the survival rate of some patients. However, BC has great heterogeneity among patients (Mayer et al., 2014) and the exact pathogenesis is still unclear.

Cell polarity refers to morphological and molecular asymmetries (Campanale et al., 2017) which provide the structural foundation for cell adhesion and communication (Butler & Wallingford, 2017). Previous studies have indicated that tumor occurrence and metastasis are inextricably linked to cell polarity (Andersen et al., 2015; Bazzoun et al., 2013; Vaira et al., 2012) and failure in epithelial cell polarity contributes to tumorigenesis (Liu et al., 2014). Membrane-associated guanylate kinases (MAGUKs) play important roles in the development and physiology of numerous tissues (Funke et al., 2005) and cell adhesion, tight junction, and polarity (Liu et al., 2014). Among the MAGUKs protein family, MAGUK p55 subfamily member 7 (MPP7) along with Discs Large 1 (DLG1) and Lin7 forms a tripartite complex that regulates cell junctions (Bohl et al., 2007). The same findings also indicated that MPP7 could target the lateral surface of epithelial cells by interacting with the polarity protein hDlg1 (Stucke et al., 2007). Furthermore, in pancreatic ductal adenocarcinoma, MPP7 was identified and linked to the activation of YAP1 (a transcriptional coactivator in the Hippo pathway), promoting autophagy (New et al., 2019). Recent studies have shown that compared to normal samples, *MPP7* expression was found to be extremely elevated in breast tumor tissues (Liao et al., 2021). *MPP7* overexpression can promote migration and invasion, whereas MPP7 silencing inhibits migration and invasion in BC cells (Liao et al., 2021). Moreover, MPP7 expression showed an increase in metastatic tumors, and tumor stages were positively associated with *MPP7* expression (Liao et al., 2021). More importantly, in patients with BC, high *MPP7* expression was significantly associated with poor disease-free survival (Liao et al., 2021). All these findings suggest that *MPP7* is closely related to BC. However, whether polymorphisms of the *MPP7* gene are associated with susceptibility to BC raises our interest.

The goal of this study was to conduct a large-sample genetic association study in Chinese Han people to investigate the potential link between genetic polymorphisms in gene *MPP7* and susceptibility to BC.

2 | MATERIALS AND METHODS

2.1 | Study participants

In total, 1390 patients diagnosed with BC and 2480 controls were enrolled in the First Affiliated Hospital of Xi'an Jiaotong University, the Second Affiliated Hospital of Xi'an Jiaotong University, Shaanxi Provincial Cancer Hospital, and Ankang City Central Hospital. Before blood samples were collected, all BC patients had been diagnosed for the first time and had not received any relevant treatment. Diagnostic criteria were based on histopathological examination. The World Health Organization Classification of Tumors was used to determine the clinical stage of BC (WHO 2012). Related clinical indicators included tumor node metastasis (TNM) stages (I–IV) and the histopronostic Scarff–Bloom–Richardson (SBR) grade (I–III). Based on the immunohistochemical results of estrogen receptor (ER), progesterone receptor (PR), and HER2, BC was divided into four subtypes: luminal A (ER+ and/or PR+/HER2−), luminal B (ER+ and/or PR+/HER2+), HER2-overexpressing (ER−/PR−/HER2+), and triple-negative (ER−/PR−/HER2−). Monoclonal rabbit anti-human ER clone antibody (SP1) and monoclonal mouse anti-human PR clone antibody (PgR636) were used to detect the expression of ER and PR, respectively. Those individuals with a history of other cancers or with severe systemic disease were excluded. The healthy controls showed no obvious physical symptoms or discomfort. All study participants included in this study were unrelated individuals from Han ethnic group. In addition, the demographic data of all subjects and relevant clinical information of BC patients were obtained through the special clinical information questionnaire and electronic medical records for this study, and the relevant information used in this study was summarized in Table 1. All participants signed informed consent forms. The Medical Ethics Committee of our hospital approved this study.

TABLE 1 Characteristics of study participants.

Demographic and clinical variables	Patients ($N=1390$)	Controls ($N=2480$)	t statistics/χ^2	p values
Age, years	54.3 ± 6.6	54.4 ± 7.5	−0.30	0.76
Body mass index, kg/m^2	23.7 ± 1.2	23.4 ± 1.4	7.08	***<0.01***
Serum level of MPP7, ng/mL	4.9 ± 0.7	2.3 ± 0.3	134.43	***<0.001***
Family history (%)				
Yes	146 (11)	234 (9)		
No	1244 (89)	2246 (91)	1.03	0.31
Smoking (%)				
Yes	107 (8)	122 (5)		
No	1283 (92)	2358 (95)	11.86	***<0.01***
Tumor location (%)				
Right	727 (52)	–		
Left	632 (45)	–		
Bilateral	31 (3)	–	–	–
PR status (%)				
Positive	1005 (72)	–		
Negative	385 (28)	–	–	–
ER status (%)				
Positive	1031 (74)	–		
Negative	359 (26)	–	–	–
Ki67 status (%)				
High	964 (69)	–		
Low	426 (31)	–	–	–
HER2-overexpressing (%)				
Positive	439 (32)	–		
Negative	951 (68)	–	–	–
Tumor subtype				
Luminal A	226 (16)	–		
Luminal B	805 (58)	–		
HER2-overexpressing	121 (9)	–		
Triple-negative	238 (17)	–	–	–
SBR grade				
Grade I	365 (26)	–		
Grade II	824 (59)	–		
Grade III	201(15)	–	–	–
TNM stage (%)				
I–II	713 (52)	–		
III–IV	677 (48)	–	–	–

Note: Continuous variables are presented as mean ± standard deviation. Significant results are indicated in bold italics.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; SBR, Scarff–Bloom–Richardson; TNM, tumor, node, metastasis staging system.

2.2 | Candidate SNP selection and genotyping

SNP candidates were chosen using 1000 genome CHB data as a reference. SNPs located within *MPP7* were focused. First, 527 SNPs with a minor allele frequency (MAF) of 0.1 were extracted from the reference data. Then, using $r^2=0.5$ criteria, 20 tag SNPs were chosen for genotyping (Table S1). The chosen SNPs are all found in the intronic regions of the gene *MPP7*.

Participants in the study had peripheral blood samples drawn. A commercial DNA extraction kit (Axygen Scientific Inc.) was used to extract genomic DNA samples. For SNP genotyping, the Sequenom MassARRAY platform was used, and the manufacturer's instructions were followed. The genotype call data was then released for further analysis. During the genotyping experiments, technicians were not informed of the sample labels to avoid potential bias.

2.3 | Serum level of MPP7 protein measurements

MPP7 protein levels in serum were examined by enzyme-linked immunosorbent assay kits from eBioscience. The experiments were carried out in accordance with the protocols provided by the manufacturers. The supernatant samples were processed again by phosphate-buffered saline before a 30-min incubation at 37°C with the enzyme-labeled reagent. After stopping the reaction with the appropriate solutions, the absorbance of the solutions was measured with a microplate reader set to 450 nm.

2.4 | Statistical analyses

To detect the potential genotyping errors, Hardy–Weinberg equilibrium (HWE) tests were conducted. Distributions of genotypes and alleles were described and compared between BC patients and controls for each genotyped SNP and the statistical significance was evaluated using chi-squared tests. To address the issue of multiple comparisons, Bonferroni corrections were used. Linkage disequilibrium (LD) patterns were measured and illustrated using the genetic software Haploview v4.2 (Barrett et al., 2005). LD blocks were formed using an algorithm suggested by Gabriel et al. (2002). To supplement the results of single marker-based association analyses, haplotype-based association analyses were also performed. In addition to the association analyses performed between BC patients and controls, the relationship between BC patients' clinical features and genotypes of relevant SNPs was also examined. The serum levels of MPP7 were compared among different genotypes of relevant SNPs in BC patients and controls. Since these data do not follow a normal distribution (Shapiro–Wilk test $p<0.01$ in both patients and control groups), we have opted to perform a Kruskal–Wallis one-way analysis of variance to examine the statistical significance. The genetic association analyses software Plink v1.9 was utilized for general genetic association analyses and HWE tests (Purcell et al., 2007). The statistical language R was used for general statistical computing. The functional implications of significant markers were investigated using the GTEx database (GTEx Consortium, 2015) and RegulomeDB (Dong & Boyle, 2019).

3 | RESULTS

3.1 | Clinical and demographic features of the participants

Significant differences were identified for body mass index ($t=-7.08$, $p<0.01$) and smoking status ($\chi^2=7.08$, $p<0.01$) between BC patients and healthy controls. The two groups had no significant differences in age ($t=-0.30$, $p=0.76$) or family history ($\chi^2=1.03$, $p=0.31$). MPP7 serum levels were discovered to be considerably higher in the cases than in the controls (Table 1). Among those 1390 BC patients, 727 (52%) had a tumor location on the right side. In total, 1005 (72%) and 1031 (74%) BC patients showed positive for progesterone receptor and estrogen receptor tests, respectively. In addition, 964 (69%) study participants with BC showed high levels of Ki-67 protein. The TNM staging system classified 713 (52%) and 677 (48%) BC patients as I–II and III–IV, respectively. A total of 439 BC patients (32%) were positive for HER2 overexpression. The tumor subtype classified 226 (16%), 805 (58%), 121 (9%), and 238 (17%) BC patients as Luminal A, Luminal B, HER2+, and Triple-negative, respectively. In addition, based on the SBR grade, a total of 365 (26%), 824 (59%), and 201 (15%) BC patients have been classified as grade I, II, and III, respectively.

3.2 | Genetic and allelic association between SNP rs1937810 and BC risk

In control samples, all 20 genotyped SNPs were found in HWE (Table S1). Only SNP rs1937810 was found to be significantly associated with the risk of BC after Bonferroni correction among the 20 genotyped tag SNPs (Table S2). The distributions of both genotypes ($\chi^2=18.07$, $p=1.19\times10^{-4}$) and alleles ($\chi^2=13.75$, $p=2.09\times10^{-4}$) for SNP rs1937810 were different in BC patients and controls (Table 2). From allelic analyses, allele C was related to the increased risk of BC. The odds ratio of having C alleles in BC patients was about 20% higher compared with controls (OR [95% CI] = 1.19 [1.09–1.31]). The odds ratio of CC genotypes in BC patients was 49% higher than in controls (1.49 [1.23–1.81]). The RegulomeDB score of SNP rs1937810 was 6 which indicated that it has a very limited functional consequence. Furthermore, based on GTEx data, human breast mammary tissue samples did

not show any correlation between the SNP rs1937810 and *MPP7* mRNA expression levels (Figure S1). LD plot was presented in Figure 1. Only one LD block (comprised of two SNPs: rs139574072 and rs1953324) was identified. Haplotype association analyses were conducted but no significant results were obtained (Table S3).

3.3 | Relationship between SNP rs1937810 and clinical features in BC patients

Genotypic distributions of SNP rs197810 were examined for several clinical features of the BC patients including tumor location, PR status, ER status, Ki-67 level, and TNM stage, HER2 overexpression pattern, tumor subtype, and SBR grade (Table 3). Among all these clinical variables, ER status and tumor subtype were identified to be significantly associated with genotypes of SNP rs197810 ($\chi^2=6.78$, $p=0.03$; $\chi^2=15.93$, $p=0.01$). We have identified a significantly lower proportion of ER-positive patients among BC patients with CC genotypes (68%) compared to those with CT (76%) or TT genotypes (75%). In other words, the allele C of SNP rs197810 was significantly associated with the increased proportion of ER-negative BC patients. Additionally, we have also observed significantly more triple-negative BC patients in patients with CC genotypes (24%) compared to those with CT (16%) or TT genotypes (15%).

3.4 | Relationship between MPP7 serum levels and genotypes of SNP rs1937810

Serum levels of MPP7 protein were distributed differently in BC patients with different genotypes of SNP rs1937810 (Table 4). The serum levels of MPP7 protein were, in general, higher in BC patients with genotype CC compared to those with genotype TT (Kruskal–Wallis $\chi^2=75.98$, $p<0.001$). The allele C was found to be related to the increased serum level of MPP7 protein in BC patients. A similar pattern was also observed in controls despite that the serum level of MPP7 protein was lower in controls (Kruskal–Wallis $\chi^2=292.12$, $p<0.001$). Results of the association between the serum level of MPP7 and genotypes of 20 selected SNPs in both BC cases and controls were summarized in Table S4.

4 | DISCUSSION

Gene *MPP7* has been reported to be a significant locus for multiple human complex traits and disorders including

TABLE 2 Genotypic and allelic associations between SNP rs1937810 and risk of breast cancer.

SNP	Genotypic analysis						Allelic analysis					
	Genotypes	Patients	Controls	χ^2	OR (95% CI)	*p* values	Alleles	Patients	Controls	χ^2	OR (95% CI)	*p* values
rs1937810	CC	280 (20)	370 (15)		1.49 (1.23–1.81)							
	CT	657 (47)	1217 (49)		1.06 (0.92–1.23)		C	1217 (44)	1957 (39)		1.19 (1.09–1.31)	
	TT	453 (33)	893 (36)	18.07	Ref	1.19×10^{-4}	T	1563 (56)	3003 (61)	13.75	Ref	2.09×10^{-4}

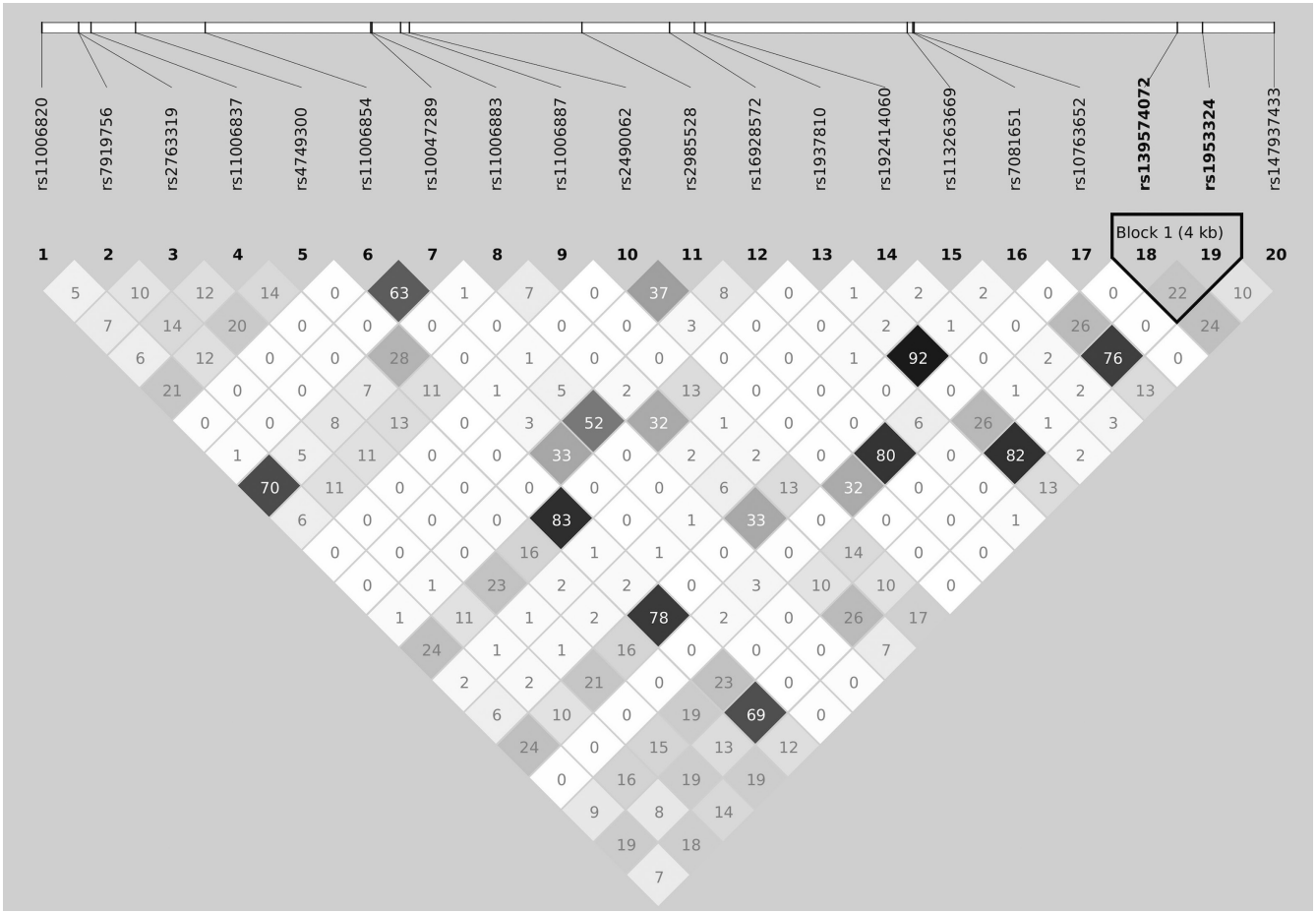

FIGURE 1 The linkage disequilibrium plot of the 20 genotyped SNPs. The values of r^2 are indicated in each cell and are also utilized as a color scheme.

bone mineral density (Pei et al., 2018), Achilles tendon injury (Kim et al., 2017), and adolescent idiopathic scoliosis (Liu et al., 2018). Although multiple lines of evidence have linked gene *MPP7* and human BC-related pathological features (Liao et al., 2021; Schrörs et al., 2020), no genetic associations have been reported between susceptibility to BC and genetic polymorphisms of gene *MPP7*. To the best of our knowledge, this study is the first to demonstrate a connection between *MPP7* genetic variations and the risk of BC in Han Chinese individuals. In addition, we have also identified increased serum levels of MPP7 protein in BC patients compared with controls. A recent study has reported the MPP7 protein as a novel biomarker of esophageal cancer using animal models (Li et al., 2022). Future animal model studies could provide further evidence for the role of MPP7 protein in BC and its underlying mechanisms.

The significant SNP discovered in the present research is an intronic DNA change, indicating that it could not have biological effects by altering the amino acid. Further bioinformatics mining showed that it might have very limited functional consequences based on big data of functional genomics. In this sense, the association signal itself might not be able to represent any direction of biological function. This significant hit, on the other hand, might be just a surrogate for some other underlying DNA changes that were not covered in the current study. This DNA change might be a single common genetic polymorphism or a set of rare or low-frequency DNA variants or a combination of both forms. Recently, multiple study reports have linked DNA variants of low MAF with the risk of BC (Li et al., 2018; Moyer et al., 2020). Considering the limitations of single-marker analysis in genetic association studies of complex diseases (Guan et al., 2020; Han et al., 2018; Wang et al., 2022), and the multi-molecular interaction effects involved in the molecular mechanisms of complex diseases (Guan et al., 2021; Shen et al., 2022), more studies including a sequencing technology-based study would be desired to systematically investigate the functional genomic architecture of *MPP7* and its role played in the etiology of BC in the future.

The serum levels of the protein MPP7 were found to be significantly higher in BC patients compared to

TABLE 3 Genetic association between clinical features of the patients and genotypes of rs1937810.

Clinical variables	Genotypes of rs1937810 CC (*N* = 280)	CT (*N* = 657)	TT (*N* = 453)	χ^2	*p* values
Tumor location (%)					
Right	144 (51)	345 (53)	238 (53)		
Left	128 (46)	296 (45)	208 (46)		
Bilateral	8 (3)	16 (2)	7 (1)	1.67	0.80
PR status (%)					
Positive	191 (68)	486 (74)	328 (72)		
Negative	89 (32)	171 (26)	125 (28)	3.25	0.20
ER status (%)					
Positive	191 (68)	501 (76)	339 (75)		
Negative	89 (32)	156 (24)	114 (25)	6.78	***0.03***
Ki67 status (%)					
High	201 (72)	455 (69)	308 (68)		
Low	79 (28)	202 (31)	145 (32)	1.18	0.55
HER2-overexpressing (%)					
Positive	84 (30)	203 (31)	152 (34)		
Negative	196 (70)	454 (69)	301 (66)	1.28	0.53
Tumor subtype					
Luminal A	35 (12)	109 (16)	82 (18)		
Luminal B	156 (56)	392 (60)	257 (57)		
HER2-overexpressing	22 (8)	52 (8)	47 (10)		
Triple-negative	67 (24)	104 (16)	67 (15)	15.93	***0.01***
TNM stage (%)					
I–II	133 (48)	348 (53)	232 (51)		
III–IV	147 (52)	309 (47)	221 (49)	2.35	0.31
SBR grade (%)					
I	62 (22)	173 (26)	130 (29)		
II	170 (61)	391 (60)	263 (58)		
III	48 (17)	93 (14)	60 (13)	4.95	0.29

Note: Significant results are indicated in bold italics.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; SBR, Scarff–Bloom–Richardson; TNM, tumor, node, metastasis staging system.

TABLE 4 Average MPP7 serum levels in groups with different rs1937810 genotypes.

Participant groups	Genotypes of rs1937810 CC	CT	TT	Kruskal–Wallis χ^2	*p* values
Patients (*N* = 1390)	5.1 ± 0.7	5.0 ± 0.7	4.8 ± 0.6	75.98	***<0.001***
Controls (*N* = 2480)	2.5 ± 0.3	2.3 ± 0.3	2.2 ± 0.3	292.12	***<0.001***

Note: Average MPP7 serum levels are presented as mean ± standard deviation. Significant results are indicated in bold italics.

controls in the current study. This result was in line with that of the research by Liao et al. (2021). They found that breast tumor tissues had much higher levels of MPP7 expression than normal ones. The current study's findings suggested that increased *MPP7* gene expression in breast tumors may affect MPP7 serum protein levels. In addition, the risk allele (the allele C) identified in the present study was also related to an increased level of serum MPP7 protein. The direction of its effect on the risk of BC is in accordance with its effect on the serum

level of MPP7 protein. Furthermore, our findings in the association between clinical features of BC patients and genotypes of targeted have suggested that the risk allele of rs1937810 was also associated with a lower proportion of ER-positive BC patients. These results were also in line with those of the study by Liao et al. They have reported that the high expression of *MPP7* was significantly related to the poor prognosis in patients of BC (Liao et al., 2021). In other words, the C allele would not only increase the susceptibility of BC but also predicted the worse prognosis of BC patients. The current work did not look into the implications of SNP rs1937810 on the expression of *MPP7*, although the serum levels of MPP7 were measured and examined. Bioinformatics data mining using GTEx database did not supplement this missing piece of evidence. It could be problematic to use this data because we lack information about the exact health status of the tissue donors. It is possible that they had underlying conditions that could have affected the gene expression. Therefore, in the future, in vivo and in vitro studies would be required to systematically determine the implications of the targeted SNPs on the expression of *MPP7*.

The gene of MPP7 might affect the susceptibility of BC through two signaling pathways. The first one is the PI3K/AKT signaling pathway (phosphatidylinositol 3-kinase/protein kinase B). This pathway is a signal transduction pathway related to cell growth, survival, and invasiveness. Several recent studies have linked it to BC (Miricescu et al., 2020; Zhang et al., 2019). According to a recent study, MPP7 increases AKT phosphorylation, which speeds up the migration of BC cells (Liao et al., 2021). Another biological pathway that might be affected by MPP7 is the epithelial–mesenchymal transition (EMT) progress. EMT is the process by which epithelial cells lose cell–cell adhesion and cell polarity while gaining invasive and migratory abilities to become mesenchymal stem cells. This process is proven to be a vital process in cancer metastasis. Interestingly, the DLG5 which is another member of MAGUKs has been shown to have a regulatory implication on the progression of EMT (Liu et al., 2017). A recent study has reported that the MPP7-regulated genes are mainly involved in the EMT progression (Liao et al., 2021). In this sense, our reported significant SNPs might affect the susceptibility of BC by affecting the expression level of *MPP7* and in turn regulating the EMT progression.

It is important to take into account the limitations of our study. Few gene association mapping studies have been performed to investigate the relationship between DNA variants of gene *MPP7* and susceptibility of BC. Therefore, replication studies, especially those based on other populations, are needed to confirm the results of the present work. The population stratification might confound the gene association mapping signals and might cause false-positive results. Nevertheless, since all participants were recruited from the same local hospital, the genetic heterogeneity could be partially controlled.

5 | CONCLUSIONS

The present study is a preliminary study focusing on the relationship between genetic polymorphisms of gene *MPP7* and BC susceptibility. The results of the current work linked SNP rs1937810 to the susceptibility of BC and the clinical features of BC patients. This SNP is also proved to be significantly related to the serum level of protein MPP7 in both BC patients and controls.

AUTHOR CONTRIBUTIONS

Jieqiong Li conceived and designed the study. Rong Li and Wenpei Zhang carried out candidate SNPs selection and statistical analyses. Rong Li, Bohui Shi, and Li Ma conducted the subject screening. Rong Li, Wenpei Zhang, Yilin Dai, and Xiaochen Wang contributed to the collection and preparation of DNA samples and conducted ELISA detection. Rong Li and Wenpei Zhang wrote the paper and prepared the figures. All authors reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no potential conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

All the data are contained in the article. The raw data used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All participants signed informed consent forms. The Medical Ethics Committee of our hospital approved this study.

ORCID

Jieqiong Li https://orcid.org/0000-0001-8496-8614

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SUPPORTING INFORMATION

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