Association Study Confirmed Three Breast Cancer-Specific Molecular Subtype-Associated Susceptibility Loci in Chinese Han Women

YIHUI XU,a,b,† MENGYUN CHEN,c,† CHENCHELIU,a,b XIAOWEI ZHANG,a WEI LI,a HUADONG CHENG,a JUN ZHU,c MINGJUN ZHANG,a ZHENDONG CHEN,a BO ZHANG,a,b

aDepartment of Oncology, No. 2 Hospital, Anhui Medical University, Hefei, Anhui, China; bSchool of Life Sciences, Anhui Medical University, Hefei, Anhui, China; cInstitute of Dermatology and Department of Dermatology the first Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China

†Contributed equally.

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Key Words. Breast cancer • Single nucleotide polymorphisms • Subtypes • Genome-wide association studies

ABSTRACT

Background. Breast cancer is a heterogeneous and polygenic disease that can be divided into different molecular subtypes based on histological and genomic features. To date, numerous susceptibility loci of breast cancer have been discovered by genome-wide association studies and may expand the genetic features. However, few loci have been further studied according to molecular subtypes.

Materials and Methods. We genotyped 23 recently discovered single nucleotide polymorphisms using the Sequenom iPLEX platform in a female Chinese cohort of 3,036 breast cancer patients (2,935 samples matched molecular subtypes) and 3,036 healthy controls.

Results. Through a stratification analysis, 5q11.2/MAP3K1 (rs16886034, rs16886364, rs16886397, rs1017226, rs16886448) and 7q32.3/LINC-PINT (rs4593472) were associated with Luminal A, and 10q26.1/FGFR2 (rs35054928) was associated with Luminal B.

Conclusion. In our study, breast cancer-specific molecular subtype-associated susceptibility loci were confirmed in Chinese Han women, which contributes to a better genetic understanding of breast cancer in different molecular subtypes. The Oncologist 2017;22:890–894

Implications for Practice: To date, genome-wide association studies have identified more than 90 susceptibility loci associated with breast cancer. However, few loci have been further studied according to molecular subtype. The results of this study are that breast cancer-specific molecular subtype-associated susceptibility loci were confirmed in Chinese Han women, which contributes to a better genetic understanding of breast cancer in different molecular subtypes.

INTRODUCTION

Breast cancer is one of the most common malignancies in females. GLOBOCAN data from 2012 show that in China, morbidity and mortality associated with breast cancer have increased rapidly [1]. Some studies have shown that genetic predisposition as a pathogenic factor, together with hereditary factors, plays an important role in such heterogeneous disease [2]. Molecular subtypes are well accepted based on genomic and histological features. Breast cancer can be basically divided into four subtypes (Luminal A, Luminal B, human epidermal growth receptor 2 [HER2]-amplified, and basal-like) [3]. These subtypes are significantly different in biological features, which implicate treatment and prognostic evaluation [4]. Although molecular subtypes have been routinely used in clinical work, especially for matching the appropriate medicine to a patient [5], the comprehensive genetic understanding of different molecular subtypes is still not clear. To date, genome-wide association studies (GWAS) have identified more than 90 susceptibility loci associated with breast cancer [6], most of which expand the genetic features and contribute to pathogenic study. However, few loci have been further studied according to molecular subtype [7, 8]. In our previous study, several specific molecular subtype-associated loci were confirmed; for example, 3p24.1/TGFBR2 (rs12493607) was associated with HER2-amplified breast cancer, and 16q12.2/FTO (rs11075995) was associated with basal-like breast cancer [9, 10]. Some novel susceptibility loci in Europeans have been identified in recent years [11–14]. The susceptibility of these loci in non-European populations is still unknown and is of great interest [15]. We have validated these loci and confirmed three loci in Chinese Han women: 5q11.2, 5q14.3, and
10q26.1 [16]. Furthermore, we also studied these loci according to molecular subtype using a stratification analysis.

**MATERIALS AND METHODS**

**Subjects**

A total of 3,036 patients suffering from breast cancer (2,935 samples matched molecular subtypes) and 3,036 healthy controls (female only) were recruited through collaborations with Hospital No. 1 and Hospital No. 2, Anhui Medical University, in the province of Anhui. The basic breast cancer molecular characteristics are shown in Table 1. The estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 status were evaluated by examining the breast tissue by biopsy or cytology and immunohistochemical analysis. The diagnosis of each case was confirmed by at least two oncologists. All of the Chinese controls were clinically confirmed to be free of breast cancer, other neoplastic diseases, systemic disorders, or a family history of neoplastic diseases (including first-, second-, and third-degree relatives). Uniform criteria were used for the recruitment of patients and controls. The same questionnaire was used to collect clinical and demographic information from each participant. After written informed consent was obtained, peripheral blood was collected from each participant. The study was approved by the Institutional Ethical Committee of each hospital and was conducted in accordance with the Declaration of Helsinki.

**Single Nucleotide Polymorphism Selection**

We choose 23 single nucleotide polymorphisms (SNPs) that passed the quality control test in our previous study [16].

**Stratification Analysis**

For stratification analysis, an association study was performed between selected SNPs and different cohorts in molecular subtypes.

**Statistical Analysis**

The association between the SNPs and breast cancer susceptibility was assessed using logistic regression, adjusting for age. The strength of association was estimated by calculating the odds ratio (OR) with a 95% confidence interval (CI). The Hardy-Weinberg equilibrium was assessed using the chi-square test. All of the statistical analyses were performed using SPSS 13.0 (IBM, Armonk, NY, https://www.ibm.com) and Plink 1.07 software. Conservatively accounting for the multiple comparisons by Bonferroni correction, the threshold for statistical significance was $p < 2.17 \times 10^{-3}$ (.05/23).

**RESULTS**

Through a stratification analysis, 5q11.2/MAP3K1 (rs16886034, $p = 1.06 \times 10^{-3}$, OR = 1.31; rs16886364, $p = 5.87 \times 10^{-4}$, OR = 1.31; rs16886397, $p = 2.73 \times 10^{-4}$, OR = 1.33; rs1017226, $p = 3.75 \times 10^{-4}$, OR = 1.32; rs16886448, $p = 1.93 \times 10^{-4}$, OR = 1.34) and 7q32.3/LINC-PINT (rs4593472, $p = 1.10 \times 10^{-3}$, OR = 0.78) were associated with Luminal A, and 10q26.1/FGFR2 (rs35054928, $p = 2.01 \times 10^{-5}$, OR = 1.27) was associated with Luminal B (Table 2).

**DISCUSSION**

In our further association study, we confirmed some loci related to specific molecular subtypes in Chinese Han women.

### Table 1. The basic breast cancer characteristics

| Characteristics               | Sample |
|-------------------------------|--------|
| Cases                         |        |
| Sample size                   | 3,036  |
| Mean age (years) at onset      | 52.6 ± 10.6 |
| Mean age (years)               | 51.9 ± 11.2 |
| Familial history of breast cancer |        |
| Familial (%)                  | 7.87%  |
| Sporadic (%)                  | 92.13% |
| Controls                      |        |
| Sample size                   | 3,036  |
| Mean age (years)              | 47.4 ± 9.8 |

*2,935 samples matched molecular subtypes.

5q11.2/MAP3K1 was first confirmed as a susceptibility gene for Chinese Han women, specifically in Luminal A breast cancer. 7q32.3/LINC-PINT was first confirmed as a susceptibility loci/gene for Luminal A breast cancer. 10q26.1/FGFR2 was previously confirmed as a susceptibility gene for Luminal B breast cancer [17, 18].

rs16886034, rs16886364, rs16886397, rs1017226, and rs16886448 are in the mitogen-activated protein kinase kinase 1 (MAP3K1) gene, which is located on chromosome 5q11.2 and encodes a serine/threonine kinase that is involved in the mitogen-activated protein kinase (MAPK) signaling pathway and is responsible for the transcriptional regulation of important cancer genes, including c-Myc, c-Elk1, c-Jun, and c-Fos [19, 20]. MAPK signal transduction is a critical pathway for cellular regulation and can be stimulated by a wide variety of exposures, including estrogen, in a variety of cell types [21]. The MAP3K1 gene has been identified in many GWAS of breast cancer [22–25], and a number of studies have investigated the relationship between MAP3K1 and breast cancer subtypes; the results were inconsistent in different breast cancer subtypes. MAP3K1 expression is upregulated in the Luminal A subtype and downregulated in the Luminal B, HER2-amplified, and basal-like subtypes [26, 27]. A somatic mutation study of breast-invasive carcinoma in the context of mRNA expression subtypes revealed that MAP3K1 alterations were enriched in the Luminal A subtype [28].

rs4593472 was in LINC-PINT on Chromosome 7q32.3. LINC-PINT is a p53-induced long intergenic non-protein-coding RNA located in a 375 kb region between MKL1 and KLF14. KLF14 is a member of the Kruppel-like family of transcription factors, which are tumor suppressors [29]. Michailidou reported that this SNP was associated with ER-positive breast cancer [30].

The SNP rs35054928 is located in the intronic region of the fibroblast growth factor receptor 2 (FGFR2) gene. FGFR2 encodes fibroblast growth factor receptor type 2, which is a receptor tyrosine kinase that plays a critical role in the growth signaling pathway and is involved in the growth and differentiation of...
Table 2. Breast cancer-specific molecular subtype-associated susceptibility loci in Chinese Han women

| CHR | SNP      | Allele<sup>a</sup> | p (overall) | MAF<sup>b</sup> | Controls | OR (95% CI) | p   |
|------|----------|--------------------|-------------|-----------------|----------|-------------|-----|
| 1    | rs2774307| A/G               | 5.45 × 10⁻¹| 0.1143          | 0.1197   | 0.95 (0.81–1.12)| 5.29 × 10⁻¹ |
| 1    | rs2290854| A/G               | 7.55 × 10⁻¹| 0.328           | 0.3252   | 1.01 (0.91–1.13)| 8.18 × 10⁻¹ |
| 2    | rs4442975| G/T               | 8.39 × 10⁻¹| 0.1104          | 0.1106   | 1.00 (0.85–1.18)| 9.85 × 10⁻¹ |
| 3    | rs6796502| A/G               | 4.62 × 10⁻²| 0.1526          | 0.16     | 0.95 (0.82–1.09)| 4.45 × 10⁻¹ |
| 5    | rs16886034| C/T            | 2.00 × 10⁻³| 0.1191          | 0.09326  | 1.31 (1.12–1.55)| 1.06 × 10⁻³ |
| 5    | rs16886113| G/T            | 1.24 × 10⁻³| 0.1357          | 0.1117   | 1.25 (1.07–1.46)| 4.85 × 10⁻³ |
| 5    | rs16886181| C/T            | 5.29 × 10⁻⁶| 0.3571          | 0.3174   | 1.20 (1.07–1.33)| 1.33 × 10⁻³ |
| 5    | rs16886364| G/A            | 9.20 × 10⁻⁴| 0.1362          | 0.1074   | 1.31 (1.12–1.53)| 5.87 × 10⁻⁴ |
| 5    | rs16886937| G/A            | 1.17 × 10⁻³| 0.1365          | 0.1061   | 1.33 (1.14–1.56)| 2.73 × 10⁻⁴ |
| 5    | rs1017226| C/T             | 5.24 × 10⁻⁶| 0.1363          | 0.1066   | 1.32 (1.13–1.55)| 3.75 × 10⁻⁴ |
| 5    | rs2229882| T/C             | 5.14 × 10⁻⁴| 0.0694          | 0.05112  | 1.38 (1.12–1.71)| 2.42 × 10⁻³ |
| 5    | rs16886448| G/C            | 1.62 × 10⁻³| 0.1351          | 0.1042   | 1.34 (1.15–1.57)| 1.93 × 10⁻⁴ |
| 5    | rs7726354| T/C             | 2.91 × 10⁻³| 0.06947         | 0.05268  | 1.34 (1.09–1.66)| 5.78 × 10⁻³ |
| 5    | rs421379| T/C              | 2.83 × 10⁻¹| 0.07128         | 0.03879  | 1.90 (1.53–2.37)| 4.95 × 10⁻¹ |
| 7    | rs4593472| T/C              | 4.82 × 10⁻³| 0.1263          | 0.157    | 0.78 (0.67–0.90)| 1.10 × 10⁻³ |
| 8    | rs13267382| G/A           | 3.81 × 10⁻¹| 0.4452          | 0.4402   | 1.02 (0.92–1.13)| 7.01 × 10⁻¹ |
| 8    | rs13365225| G/A           | 3.05 × 10⁻¹| 0.3471          | 0.3286   | 1.09 (0.97–1.21)| 1.36 × 10⁻¹ |
| 9    | rs10816625| G/A           | 4.95 × 10⁻¹| 0.49           | 0.4868   | 1.01 (0.91–1.12)| 8.08 × 10⁻¹ |
| 9    | rs676526| C/T             | 5.86 × 10⁻¹| 0.04216         | 0.0419   | 1.01 (0.78–1.30)| 9.62 × 10⁻¹ |
| 10   | rs35054928| C/DEL         | 7.73 × 10⁻⁶| 0.4709          | 0.4361   | 1.15 (1.04–1.28)| 7.94 × 10⁻³ |
| 11   | rs1047739| T/C            | 1.91 × 10⁻¹| 0.04694         | 0.04936  | 0.95 (0.74–1.21)| 6.70 × 10⁻¹ |
| 17   | rs745570| G/A            | 9.13 × 10⁻¹| 0.366           | 0.3939   | 0.89 (0.80–0.99)| 2.98 × 10⁻² |
| 17   | rs3785982| T/C            | 2.36 × 10⁻²| 0.1907          | 0.1867   | 1.03 (0.90–1.17)| 6.93 × 10⁻¹ |

<sup>a</sup>Minor allele/Major allele.

<sup>b</sup>Minor allele frequency.

Abbreviations: CHR, chromosome; CI, confidence interval; MAF, major allele frequency; OR, odds ratio; SNP, single nucleotide polymorphisms.
cells in various tissues among many tumors [31, 32]. Intron 2 of FGF2R contains putative transcription factor binding sites, increases Oct-1/Runx2 and C/EBPβ transcription factor binding, which increases FGF2R expression [33], and causes poor overall survival and disease-free survival [34, 35]. The association between the FGF2R gene and breast cancer appears to be stronger for ER-positive and PR-positive tumors than for ER-negative or PR-negative tumors, which suggests a sex hormone-dependent role of the FGF2R gene in breast cancer [36–38]. FGG2R was associated with Luminal B, as reported by O’Brien et al. [17] and Liang et al. [18], similar to that observed in our study.

Luminal A and Luminal B breast cancers are also ER-positive breast cancers. Luminal tumors represent around two thirds of all breast cancers. Luminal breast cancer is a highly heterogeneous disease comprising different histologies, gene expression profiles, and mutational patterns, with very varied clinical courses and responses to systemic treatment [39, 40]. Due to the heterogeneity of breast cancer, it is necessary to define suitable patient cohorts and predictive biomarkers for a personalized therapy with a high therapeutic index [41]. Some next-generation sequencing studies show Luminal A tumors frequently exhibit abrogation of stress-induced apoptotic kinase c-Jun NH2-terminal kinase (JNK) signaling and loss-of-function mutations in the MAP3K1 genes; this abrogation has been associated with resistance to chemotherapy compared with patients with normal JNK signaling [42]. That could explain why Luminal A tumors are not sensitive to chemotherapy [43, 44]. Fibroblast growth factor receptor (FGFR) signaling through FGFR ligand-dependent or -independent activation has been implicated in oncogenesis, angiogenesis, and treatment resistance in various tumor types [45]. Approaches to targeting FGFR in various tumor types include tyrosine kinase inhibitors (TKIs), monoclonal FGFR antibodies, and FGFR-trapping molecules, with TKIs being more clinically advanced. A phase II clinical trial assessing dovitinib, a nonselective FGFR TKI, showed activity in subclonal FGFR antibodies, and FGF-trapping molecules, with TKIs associated with resistance to chemotherapy compared with patients with normal JNK signaling [42]. That could explain why Luminal A tumors are not sensitive to chemotherapy [43, 44].

CONCLUSION

In summary, we confirmed that 5q11.2/MAP3K1 and 7q32.3/LINC-PINT were associated with Luminal A, and 10q26.1/FGR2 was associated with Luminal B. In our study, breast cancer–specific molecular subtype-associated susceptibility loci were confirmed in Chinese Han women, which contributes to a better genetic understanding of breast cancer in different molecular subtypes. These specific molecular subtype-associated loci are potentially meaningful for guiding clinical evaluation and therapy.

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AUTHOR CONTRIBUTIONS

Conception/Design: Bo Zhang

Provision of study material or patients: Yihui Xu, Mengyun Chen, Chenchen Liu

Collection and/or assembly of data: Xiaowei Zhang, Wei Li, Huaidong Cheng, Jun Zhu, Mingjun Zhang, Zhendong Chen

Data analysis and interpretation: Yihui Xu, Mengyun Chen, Chenchen Liu

Manuscript writing: Yihui Xu, Mengyun Chen

Final approval of manuscript: Bo Zhang

DISCLOSURES

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