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Breast Cancer

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

Yihui Xu,[a,b,†] Mengyun Chen,[c,†] Chenchen Liu,[a,b] Xiaowei Zhang,[a] Wei Li,[a] Huaidong Cheng,[a] Jun Zhu,[c] Mingjun Zhang,[a] Zhendong Chen,[a] Bo Zhang[a,b]

[a]Department of Oncology, No. 2 Hospital, Anhui Medical University, Hefei, Anhui, China; [b]School of Life Sciences, Anhui Medical University, Hefei, Anhui, China; [c]Institute of Dermatology and Department of Dermatology the first Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China

[†]Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

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/genes 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

Correspondence: Bo Zhang, M.D., Ph.D., Department of Oncology, No. 2 Hospital, Anhui Medical University, Hefei, Anhui, China. Telephone: 86-551-62923252; e-mail: alvinbo@163.com Received October 26, 2016; accepted for publication January 5, 2017; published Online First on April 13, 2017. 1083-7159/2017/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2016-0423

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, $p = 2.01 \times 10^{-6}$, 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%
Four subtypes of breast cancer[a]	
Luminal A breast cancer	955 (33%)
Luminal B breast cancer	1,075 (37%)
HER-2 amplified breast cancer	328 (11%)
Basal-like breast cancer	577 (19%)
Controls	
Sample size	3,036
Mean age (years)	47.4 ± 9.8

[a]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 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 *MKLN1* 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

				Luminal A breast cancer (955 cases, 3,036 controls)				Luminal B breast cancer (1,075 cases, 3,036 controls)			
CHR	SNP	Allele[a]	*p* (overall)	MAF[b] Cases	Controls	OR (95% CI)	*p*	MAF[b] Cases	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}	0.1138	0.1197	0.94 (0.81–1.10)	4.73×10^{-1}
1	rs2290854	A/G	7.55×10^{-1}	0.328	0.3252	1.01 (0.91–1.13)	8.18×10^{-1}	0.3106	0.3252	0.94 (0.84–1.04)	2.16×10^{-1}
2	rs4442975	G/T	8.39×10^{-1}	0.1104	0.1106	1.00 (0.85–1.18)	9.85×10^{-1}	0.1222	0.1106	1.12 (0.96–1.31)	1.47×10^{-1}
3	rs6796502	A/G	4.62×10^{-2}	0.1526	0.16	0.95 (0.82–1.09)	4.45×10^{-1}	0.1381	0.16	0.84 (0.73–0.97)	1.64×10^{-2}
5	rs16886034	C/T	2.00×10^{-3}	0.1191	0.09326	1.31 (1.12–1.55)	1.06×10^{-3}	0.1127	0.09326	1.24 (1.05–1.45)	9.48×10^{-3}
5	rs16886113	G/T	1.24×10^{-3}	0.1357	0.1117	1.25 (1.07–1.46)	4.85×10^{-3}	0.1368	0.1117	1.26 (1.09–1.46)	2.19×10^{-3}
5	rs16886181	C/T	5.29×10^{-6}	0.3571	0.3174	1.20 (1.07–1.33)	1.33×10^{-3}	0.3699	0.3174	1.26 (1.14–1.40)	9.97×10^{-6}
5	rs16886364	G/A	9.20×10^{-4}	0.1362	0.1074	1.31 (1.12–1.53)	5.87×10^{-4}	0.1228	0.1074	1.16 (1.00–1.36)	5.23×10^{-2}
5	rs16886397	G/A	1.17×10^{-3}	0.1365	0.1061	1.33 (1.14–1.56)	2.73×10^{-4}	0.1199	0.1061	1.15 (0.98–1.34)	7.99×10^{-2}
5	rs1017226	C/T	5.24×10^{-4}	0.1363	0.1066	1.32 (1.13–1.55)	3.75×10^{-4}	0.1221	0.1066	1.17 (1.00–1.36)	5.02×10^{-2}
5	rs2229882	T/C	5.14×10^{-4}	0.0694	0.05112	1.38 (1.12–1.71)	2.42×10^{-3}	0.06876	0.05112	1.37 (1.12–1.68)	2.28×10^{-3}
5	rs16886448	G/C	1.62×10^{-3}	0.1351	0.1042	1.34 (1.15–1.57)	1.93×10^{-4}	0.1164	0.1042	1.13 (0.97–1.32)	1.20×10^{-1}
5	rs7726354	T/C	2.91×10^{-3}	0.06947	0.05268	1.34 (1.09–1.66)	5.78×10^{-3}	0.06489	0.05268	1.25 (1.02–1.53)	3.45×10^{-2}
5	rs421379	T/C	2.83×10^{-13}	0.07128	0.03879	1.90 (1.53–2.37)	4.95×10^{-1}	0.06981	0.03879	1.86 (1.50–2.30)	6.32×10^{-9}
7	rs4593472	T/C	4.82×10^{-3}	0.1263	0.157	0.78 (0.67–0.90)	1.10×10^{-3}	0.1465	0.157	0.92 (0.80–1.06)	2.47×10^{-1}
8	rs13267382	G/A	3.81×10^{-1}	0.4452	0.4402	1.02 (0.92–1.13)	7.01×10^{-1}	0.4495	0.4402	1.04 (0.94–1.15)	4.56×10^{-1}
8	rs13365225	G/A	3.05×10^{-1}	0.3471	0.3286	1.09 (0.97–1.21)	1.36×10^{-1}	0.3293	0.3286	1.00 (0.90–1.12)	9.53×10^{-1}
9	rs10816625	G/A	4.95×10^{-1}	0.49	0.4868	1.01 (0.91–1.12)	8.08×10^{-1}	0.5056	0.4868	1.08 (0.98–1.19)	1.36×10^{-1}
9	rs676256	C/T	5.86×10^{-1}	0.04216	0.0419	1.01 (0.78–1.30)	9.62×10^{-1}	0.04011	0.0419	0.96 (0.74–1.23)	7.24×10^{-1}
10	rs35054928	C/DEL	7.73×10^{-6}	0.4709	0.4361	1.15 (1.04–1.28)	7.94×10^{-3}	0.4958	0.4361	1.27 (1.15–1.40)	2.01×10^{-6}
11	rs1047739	T/C	1.91×10^{-1}	0.04694	0.04936	0.95 (0.74–1.21)	6.70×10^{-1}	0.05671	0.04936	1.16 (0.93–1.44)	1.88×10^{-1}
17	rs745570	G/A	9.13×10^{-1}	0.366	0.3939	0.89 (0.80–0.99)	2.98×10^{-2}	0.3748	0.3939	0.92 (0.83–1.02)	1.20×10^{-1}
17	rs3785982	T/C	2.36×10^{-2}	0.1907	0.1867	1.03 (0.90–1.17)	6.93×10^{-1}	0.1858	0.1867	0.99 (0.88–1.13)	9.34×10^{-1}

[a]Minor allele/Major allele.
[b]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 *FGFR2* contains putative transcription factor binding sites, increases Oct-1/Runx2 and C/EBPb transcription factor binding, which increases *FGFR2* expression [33], and causes poor overall survival and disease-free survival [34, 35]. The association between the *FGFR2* 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 *FGFR2* gene in breast cancer [36–38]. *FGFR2* 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 FGF 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 FGF-trapping molecules, with TKIs being more clinically advanced. A phase II clinical trial assessing dovitinib, a nonselective FGFR TKI, showed activity in the subgroup of patients with ER-positive/HER2-negative breast cancer [44, 46]. One type of Luminal B is ER-positive and/or PR positive, HER2-negative, with ki67 $\geq$14% [40]. The association between Luminal B subtype and *FGFR2* gene in Chinese Han implicate a potential drug indication of TKI in Chinese Luminal B breast cancer patients. However, it needs more clinical trial to confirm.

Conclusion

In summary, we confirmed that *5q11.2/MAP3K1* and *7q32.3/LINC-PINT* were associated with Luminal A, and *10q26.1/FGFR2* 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

The authors indicated no financial relationships.

References

1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

2. Lichtenstein P, Holm NV, Verkasalo PK et al. Environmental and heritable factors in the causation of cancer–Analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85.

3. Parker JS, Mullins M, Cheang MC et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009;27:1160–1167.

4. Gatza ML, Lucas JE, Barry WT et al. A pathway-based classification of human breast cancer. Proc Natl Acad Sci USA 2010;107:6994–6999.

5. Serrano-Gomez SJ, Sanabria-Salas MC, Hernández-Suarez G et al. High prevalence of luminal B breast cancer intrinsic subtype in Colombian women. Carcinogenesis 2016;37:669–676.

6. Haddad SA, Ruiz-Narváez EA, Haiman CA et al. An exome-wide analysis of low frequency and rare variants in relation to risk of breast cancer in African American women: The AMBER Consortium. Carcinogenesis 2016;37:870–878.

7. Palmer JR, Ruiz-Narvaez EA, Rotimi CN et al. Genetic susceptibility loci for subtypes of breast cancer in an African American population. Cancer Epidemiol Biomarkers Prev 2013;22:127–134.

8. Han W, Woo JH, Yu JH et al. Common genetic variants associated with breast cancer in Korean women and differential susceptibility according to intrinsic subtype. Cancer Epidemiol Biomarkers Prev 2011;20:793–798.

9. Zhang B, Li Y, Li L et al. Association study of susceptibility loci with specific breast cancer subtypes in Chinese women. Breast Cancer Res Treat 2014;146:503–514.

10. Zhang B, Li Y, Zheng X et al. A common variant in the SIAH2 locus is associated with estrogen receptor-positive breast cancer in the Chinese Han population. PLoS One 2013;8:e79365.

11. Ahsan H, Halpern J, Kibriya MG et al. A genome-wide association study of early-onset breast cancer identifies PFKM as a novel breast cancer gene and supports a common genetic spectrum for breast cancer at any age. Cancer Epidemiol Biomarkers Prev 2014;23:658–669.

12. Couch FJ, Wang X, McGuffog L et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet 2013;9:e1003212.

13. Fejerman L, Ahmadiyeh N, Hu D et al. Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25. Nat Commun 2014;5:5260.

14. French JD, Ghoussaini M, Edwards SL et al. Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. Am J Hum Genet 2013;92:489–503.

15. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature 2016;538:161–164.

16. Xu M, Xu Y, Chen M et al. Association study confirms two susceptibility loci for breast cancer in Chinese Han women. Breast Cancer Res Treat 2016;159:433–442.

17. O'Brien KM, Cole SR, Engel LS et al. Breast cancer subtypes and previously established genetic risk factors: A bayesian approach. Cancer Epidemiol Biomarkers Prev 2014;23:84–97.

18. Liang H, Yang X, Chen L et al. Heterogeneity of breast cancer associations with common genetic variants in FGFR2 according to the intrinsic subtypes in southern Han Chinese women. Biomed Res Int 2015;2015:626948.

19. Lu PH, Yang J, Li C et al. Association between mitogen-activated protein kinase kinase kinase 1 rs889312 polymorphism and breast cancer risk: Evidence from 59,977 subjects. Breast Cancer Res Treat 2011;126:663–670.

20. Klinge CM, Blankenship KA, Risinger KE et al. Resveratrol and estradiol rapidly activate MAPK signaling through estrogen receptors alpha and beta in endothelial cells. J Biol Chem 2005;280:7460–7468.

21. Watters JJ, Campbell JS, Cunningham MJ et al. Rapid membrane effects of steroids in neuroblastoma cells: Effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene transcription. Endocrinology 1997; 138:4030–4033.

22. Easton DF, Pooley KA, Dunning AM et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447: 1087–1093.

23. Turnbull C, Ahmed S, Morrison J et al. Genome-wide association study identifies five new breast cancer susceptibility loci. Nat Genet 2010;42:504–507.

24. Thomas G, Jacobs KB, Kraft P et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009;41:579–584.

25. Michailidou K, Hall P, Gonzalez-Neira A et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013;45: 353–361, 361e1–361e2.

26. Glubb DM, Maranian MJ, Michailidou K et al. Fine-scale mapping of the 5q11.2 breast cancer locus reveals at least three independent risk variants regulating MAP3K1. Am J Hum Genet 2015;96:5–20.

27. Nordgard SH, Johansen FE, Alnaes GI et al. Genes harbouring susceptibility SNPs are differentially expressed in the breast cancer subtypes. Breast Cancer Res 2007;9:113.

28. Cancer Genome Atlas Network, Koboldt DC, Fulton RS et al. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.

29. Small KS, Hedman AK, Grundberg E et al. Identification of an imprinted master trans regulator at the KLF14 locus related to multiple metabolic phenotypes. Nat Genet 2011;43:561–564.

30. Michailidou K, Beesley J, Lindstrom S et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 2015;47:373–380.

31. Cheng C, Hu W, Liu LP et al. Fibroblast growth factor receptor 2: A new potential therapeutic target for human cancer. Hum Pathol 2015;46:339–340.

32. Parsa S, Ramasamy SK, De Langhe S et al. Terminal end bud maintenance in mammary gland is dependent upon FGFR2b signaling. Dev Biol 2008; 317:121–131.

33. Meyer KB, Maia AT, O'Reilly M et al. Allele-specific up-regulation of FGFR2 increases susceptibility to breast cancer. PLoS Biol 2008;6:e108.

34. Sun S, Jiang Y, Zhang G et al. Increased expression of fibroblastic growth factor receptor 2 is correlated with poor prognosis in patients with breast cancer. J Surg Oncol 2012;105:773–779.

35. André F, Cortés J. Rationale for targeting fibroblast growth factor receptor signaling in breast cancer. Breast Cancer Res Treat 2015;150:1–8.

36. Garcia-Closas M, Hall P, Nevanlinna H et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet 2008;4:e1000054.

37. Stacey SN, Manolescu A, Sulem P et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2008;40:703–706.

38. Xu WH, Shu XO, Long J et al. Relation of FGFR2 genetic polymorphisms to the association between oral contraceptive use and the risk of breast cancer in Chinese women. Am J Epidemiol 2011;173:923–931.

39. Malvezzi M, Bertuccio P, Levi F et al. European cancer mortality predictions for the year 2013. Ann Oncol 2013;24:792–800.

40. Goldhirsch A, Wood WC, Coates AS et al. Strategies for subtypes–Dealing with the diversity of breast cancer: Highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011;22: 1736–1747.

41. Almstedt K, Schmidt M. Targeted therapies overcoming endocrine resistance in hormone receptor-positive breast cancer. Breast Care (Basel) 2015;10:168–172.

42. Stephens PJ, Tarpey PS, Davies H et al. The landscape of cancer genes and mutational processes in breast cancer. Nature 2012;486:400–404.

43. Small GW, Shi YY, Higgins LS et al. Mitogen-activated protein kinase phosphatase-1 is a mediator of breast cancer chemoresistance. Cancer Res 2007;67: 4459–4466.

44. Ignatiadis M, Sotiriou C. Luminal breast cancer: From biology to treatment. Nat Rev Clin Oncol 2013; 10:494–506.

45. Dieci MV, Arnedos M, Andre F et al. Fibroblast growth factor receptor inhibitors as a cancer treatment: From a biologic rationale to medical perspectives. Cancer Discov 2013;3:264–279.

46. Ades F, Zardavas D, Bozovic-Spasojevic I et al. Luminal B breast cancer: Molecular characterization, clinical management, and future perspectives. J Clin Oncol 2014;32:2794–2803.