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New Breast Cancer Risk Variant Discovered at 10q25 in East Asian Women

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Abstract

Background—Recently, 41 new genetic susceptibility loci for breast cancer risk were identified in a genome-wide association study conducted in European descendants. Most of these risk variants have not been directly replicated in Asian populations.

Methods—We evaluated nine of those non-replication loci in East Asians in order to identify new risk variants for breast cancer in these regions. First, we analyzed single nucleotide polymorphisms (SNPs) in these regions using data from two GWAS conducted among Chinese and Korean women, including 5,083 cases and 4,376 controls (Stage 1). In each region we selected a SNP showing the strongest association with breast cancer risk for replication in an independent set of 7,294 cases and 9,404 controls of East Asian descents (Stage 2). Logistic regression models were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI) as a measure of the association of breast cancer risk and genetic variants.

Results—Two SNPs were replicated in Stage 2 at $P < 0.05$: rs1419026 at 6q14 (per allele OR = 1.07, 95% CI: 1.03-1.12, $P = 3.0\times10^{-4}$) and rs941827 at 10q25 (OR = 0.92, 95% CI: 0.89-0.96, $P = 5.3\times10^{-5}$). The association with rs941827 remained highly statistically significant after adjusting for the risk variant identified initially in women of European ancestry (OR = 0.88, 95% CI: 0.82-0.97, $P = 5.3\times10^{-5}$).

Conclusion—We identified a new breast cancer risk variant at 10q25 in East Asian women.

Impact—Results from this study improve the understanding of the genetic basis for breast cancer.

Keywords

breast cancer; genetic susceptibility; GWAS replication; single nucleotide polymorphism

Genetic factors play a significant role in the etiology of breast cancer (1-4). To date, genome-wide association studies (GWAS) have identified approximately 67 genetic susceptibility risk loci for breast cancer (5-19). With a few exceptions (9, 13, 14, 16, 20), most susceptibility loci were initially identified in GWAS conducted in European-ancestry populations. Most, if not all, of the initially reported risk variants, in the form of single nucleotide polymorphisms (SNPs) (termed as index SNPs in subsequent text), are tagging SNPs. These SNPs were identified likely through their linkage disequilibrium (LD) with disease variants. Because LD patterns differ across populations of different ancestries, some findings from GWAS conducted in European descendants cannot be directly extrapolated to other populations (20-27). We recently evaluated all breast cancer risk variants identified to date and found that approximately half of the risk variants identified initially in European descendents cannot be directly replicated in East Asians (28). In the present study, we investigated nine regions where the index SNP has not been replicated in Asian samples in an attempt to identify other breast cancer risk variants for East Asian women.

Methods

Study populations

This study was conducted as part of the Asia Breast Cancer Consortium (ABCC), which has been described elsewhere (9, 13, 14, 18, 22, 28). Briefly, samples analyzed in this study were from eight epidemiological studies in the ABCC (Table 1). Samples were from 13,642 Chinese women, 11,713 Korean women and 802 Japanese women. Chinese participants were selected from four studies: the Shanghai Breast Cancer Study (SBCS), the Shanghai

Breast Cancer Survival Study (SBCSS), the Shanghai Endometrial Cancer Study (SECS, controls only), and the Shanghai Women's Health Study (SWHS)] (9, 29, 30). Korean participants came from four studies: the Seoul Breast Cancer Study (SeBCS) (20), Korea National Cancer Center (Korea-NCC), Korea Genome Epidemiology Study (KoGES) (31), and Korean Hereditary Breast Cancer (KOHBRA) (32). Japanese samples were from the Japan Nagano Breast Cancer Study (33). In total, 12,377 cases and 13,780 controls were analyzed in the present study.

Genotyping and quality-control

Stage 1 testing was conducted using existing data from two GWAS, wherein 5,285 Chinese women and 4,777 Korean women were genotyped primarily using the Affymetrix Genome-wide Human SNP Array 6.0. Genotyping protocols have been described elsewhere (9, 18, 20). From the Chinese GWAS, we included one negative control and at least three positive quality-control (QC) samples from the Coriell Cell Repositories in each of the 96-well plates for genotyping with Affymetrix SNP Array 6.0 chips. A total of 273 positive QC samples were successfully genotyped; the average concordance rate was 99.9% with a median value of 100%. Genetically identical and unexpected duplicate samples were excluded, as they were close relatives with a pair-wise proportion of identify-by-descent (IBD) estimate greater than 0.25. All samples with a call rate < 95% were excluded. SNPs were excluded if: 1) minor allele frequency (MAF) < 1%; 2) call rate < 95%; or 3) genotyping concordance rate < 95% in QC samples. The final dataset included 2,918 cases and 2,324 controls for 690,947 markers. For the Korean GWAS, the Affymetrix SNP Array 6.0 was used (20). A total of 30 QC samples were successfully genotyped; the average concordance rate was 99.8%. SNPs were excluded if: 1) genotype call rate < 95%; 2) MAF < 1% in either cases or controls; 3) evidence for deviation from Hardy-Weinberg equilibrium (HWE) at *P*-value < 10^{-6}; or 4) poor genotyping cluster plot in either cases or controls. After QC filtering, the final dataset included 2,165 cases and 2,052 controls for 555,525 markers. All samples from both studies were genetically confirmed to be females.

We used the program MACH 1.0 (34) to impute genotypes for autosomal SNPs in HapMap Phase II release 22 for samples from the Chinese and Korean GWAS. Only SNPs with imputation quality score RSQR ≥ 0.3 were included in subsequent analyses. Dosage data for imputed SNPs in samples from each of the Stage 1 studies were analyzed using the program mach2dat (34).

We genotyped nine selected SNPs in Stage 2 using the iPLEX MassARRAY platform (Sequenom, San Diego, CA, USA). PCR primers and allelic-specific extension primers were designed with the MassARRAY Assay Design 4.0 software, and alleles of each SNP were detected through matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry on the MassARRAY Analyzer 4 system (Sequenom, San Diego, CA, USA). In each 96-well plate, five QC samples were used in the Sequenom assay, including one negative control (water), two blinded duplicates, and two samples from the HapMap project. Mean concordance rate was 99.7% for the blind duplicates and 98.9% for the HapMap samples.

Statistical analyses

PLINK version 1.06 was used to analyze the genome-wide data obtained in Stage 1 (35). Population structure was investigated by analyzing 690,947 SNPs that passed QC in Chinese women (2,918 cases and 2,324 controls) and 555,525 SNPs that passed QC in Korean women (2,165 cases and 2,052 controls), showing an estimated inflation factor λ of 1.042 for Chinese (18) and 1.043 for Koreans (20). Therefore, population substructure, if present, should not substantially affect the results of this study. Logistic regression was employed to

estimate breast cancer risk under a log-additive model and adjusted for age and study site, when appropriate odds ratios (ORs) associated with each SNP and 95% confidence intervals (CIs) were estimated for cancer risk. Conditional analyses were performed by adjusting the index SNP in each locus to evaluate possible independent association of breast cancer with the SNP under study. All analyses were conducted using SAS version 9.3 (SAS Institute In., Cary, NC, USA) unless noted otherwise.

Results

Table 2 presents the associations of nine index SNPs with breast cancer risk from the Chinese and Korean GWAS (Stage 1). Results from the original GWAS of European-ancestry populations are shown, also. None of these index SNPs were associated with breast cancer risk at $P < 0.05$ in our study. To search for other possible variants in these regions which could be associated with breast cancer risk, we selected a SNP from each of these regions for further evaluation. In each region, we selected a SNP that showed the most significant association with breast cancer risk and is located within +/- 500kb of the index SNP of that region (Table 3).

Stage 1 and 2 results for the nine selected SNPs are presented in Table 3. SNPs rs1419026 at 6q14 and rs941827 at 10q25 showed an association with breast cancer risk at $P < 0.05$ in the same direction in both stages. In the combined analysis of 12,377 breast cancer cases and 13,780 control women, per allele ORs were 1.07 (95% CI: 1.03-1.12, $P = 3.0\times10^{-4}$) and 0.92 (95% CI: 0.89-0.96, $P = 5.3\times10^{-5}$) for rs1419026 and rs941827, respectively. The association of rs1419026 with breast cancer risk was, in general, consistent across participating studies and heterogeneity test was not statistically significant ($P = 0.675$). The association of breast cancer risk with rs941827 was substantially stronger in the Nagano study (OR = 0.72, 95%CI = 0.58 – 0.89, $P = 0.002$) than other seven studies combined (OR = 0.93, 95%CI = 0.89 – 0.97, $P = 3.8\times10^{-4}$) (P for heterogeneity, 0.027). After excluding the Nagano study, the heterogeneity test was no longer statistically significant ($P = 0.103$).

Conditional analyses for rs1419026 and rs941827 were performed by adjusting the index SNP in each of these loci. These analyses were conducted using Stage 1 samples with data available for both new SNPs and index SNPs. The association with rs941827 at 10q25 remained statistically significant after adjusting for index SNP rs7904519 (OR = 0.88, 95% CI: 0.82-0.93, $P = 5.3\times10^{-5}$) (data now shown in tables). However, the significant association with rs1419026 disappeared after adjusting for its index SNP rs17529111 (OR = 1.05, 95% CI: 0.96-1.15, $P = 0.293$). SNPs rs1419026 and rs941827 were associated with both ER+ and ER-cancer (Table 4).

Nominally significant associations were also observed for two other SNPs (rs821287 and rs10278902) in Stage 2. However, the direction of the association for these two SNPs was inconsistent in Stages 1 and 2, and thus these two SNPs were considered not being replicated in this study.

Discussion

In this large study conducted in East Asian women, we identified a new genetic risk variant for breast cancer at 10q25, a breast cancer susceptibility locus identified recently in a GWAS of European descendants (19). We also found a SNP (rs1419026) at 6q14 that showed a stronger association with breast cancer risk in East Asians than the index SNP (rs17529111) initially identified in this locus in a GWAS conducted among European descendants. Our study has expanded the list of breast cancer risk variants identified for East

Asian women and provides data that might be useful in fine-mapping GWAS-identified regions to identify causal variants for this common malignancy.

The index SNP rs7904519 at 10q25 was not replicated in our study. The risk allele frequency is very low in East Asian women (0.045) compared with European descendants (0.405). In the present study, we found a significant association of breast cancer risk with SNP rs941827, with an effective allele frequency of 0.26 in East Asian women and 0.29 in Europeans. These two SNPs are not correlated ($r^2 < 0.03$ in either CEU or CHB+JPT samples). The index SNP (rs7904519) is located in intron 3 of the *TCF7L2* gene (NM_030756). The SNP identified in our study (rs941827), is located in intron 7 of the vesicle transport through interaction with t-SNAREs homolog 1A (yeast) (*VTI1A*) gene (NM_145206), approximately 215 kb upstream of rs7904519. The *VT11A* gene encodes a soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) that mediates the transport of vesicles between the Golgi apparatus and the plasma membrane (36, 37). The potential role of the VTI1A protein in breast carcinogenesis remains unknown. Intriguingly, SNPs rs941827 and rs7904519 are included in a ~420-540-kb region that has been found to be deleted in some breast and colorectal cancer samples (38, 39). This deletion causes a *VTI1A-TCF7L2* fusion, which may affect the regulatory function of the TCF/β-Catenin complex on the Wnt signaling (40). Further studies are needed to clarify the mechanism of the association of *VTI1A* variants and breast cancer risk identified in this study.

In our study, some imputed SNPs could not be investigated properly because of their low imputation quality in Stage 1. Some of the index SNPs evaluated in Stage 1 showed an association in the same direction as reported previously in the European-ancestry study, although the association was not statistically significant perhaps due to a small sample size. In addition, we selected only one SNP per locus for Stage 2 replication because of budget constraints. It is possible that additional risk variants may be located in some of these regions and can be further investigated in the future. Nevertheless, using data from East Asian women, we identified one new genetic risk variant at 10q25 for breast cancer. We also identified a risk variant at 6q14 that showed a stronger association with breast cancer in East Asians than the index SNP initially discovered in this region in a GWAS conducted in European descendants. These results are new and should be helpful for future studies to understand the genetic basis for breast cancer.

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Table 1

Summary of selected characteristics of participants by studies

Study	No. of Cases	No. of Controls	Population ethnicity	Study design[a]	Mean age (year)[b]	Menopause (%)[c]	ER+ (%)[d]
SBCGS1[e] (GWAS)	2918	2324	Chinese	Population-based	52/50[f]	43/42	65
SBCGS2[e] (Stage 2)	1613	1800	Chinese	Population-based	53/53	50/55[f]	62
SBCGS3[e] (Stage 3)	2601	2386	Chinese	Population-based	54/55[f]	50/53	65
SeBCS1 (GWAS)	2165	2052	Korean	Hospital-based	48/51[f]	36/55[f]	63
SeBCS2 (Stage 2)	777	1104	Korean	Hospital-based	48/48	36/37	63
KOHBRA/KoGES	1397	3209	Korean	Hospital-based with community controls	40/50[f]	23/NA	63
Korea-NCC	505	504	Korean	Hospital-based	49/49	50/45	65
Nagano	401	401	Japanese	Hospital-based	54/54	55/65[f]	75
Total	12,377	13,780					

Abbreviations: SBCGS, Shanghai Breast Cancer Genetic Study; SeBCS, Seoul Breast Cancer Study; KOHBRA/KoGES, Korean Hereditary Breast Cancer/Genome/Epidemiology Study; Korea-NCC, Korea National Cancer Center Study; Nagano, Japan Nagano Breast Cancer Study; NA, not available.

[a] Case-control study.

[b] Mean age of cases/controls with available data.

[c] Proportion of postmenopausal status of cases/controls with available data.

[d] Among cases with ER data.

[e] Including cases and controls from four studies conducted in Shanghai.

[f] Significant at $\alpha = 0.01$ level.

Table 2

Associations of index SNPs in nine recently-reported breast-cancer susceptibility loci

				Asian GWAS (5,083 cases and 4,376 controls)			European		
SNP[a]	Chr./gene[b]	Position (bp)[c]	Alleles[d]	EAF[e]	OR (95% CI)	P_{trend}	EAF[f]	OR (95% CI)[f]	P_{trend} [f]
rs2016394	2q31/*DLX2*	172681217	G/A	0.19	0.98 (0.90-1.08)	0.727	0.48	0.95 (0.93-0.97)	1.2×10^{-8}
rs204247	6p23/*RANBP9*	13830502	G/A	0.39	0.97 (0.92-1.03)	0.373	0.43	1.05 (1.03-1.07)	8.4×10^{-9}
rs17529111	6q14/*FAM46A*	82185105	C/T	0.20	1.07 (0.99-1.15)	0.094	0.22	1.06 (1.04-1.09)	4.3×10^{-9}
rs720475	7q35/*ARHGEF5*	143705862	A/G	0.02	1.07 (0.89-1.29)	0.455	0.25	0.94(0.92-0.96)	7.0×10^{-11}
rs11780156	8q24/*MYC*	129263823	T/C	0.22	1.00 (0.93-1.07)	0.908	0.16	1.07 (1.04-1.10)	3.4×10^{-11}
rs11814448	10p12/*DNAJC1*	22355849	C/A	0.01	1.31 (0.84-2.02)	0.230	0.02	1.26 (1.18-1.35)	9.3×10^{-16}
rs7904519	10q25/*TCF7L2*	114763917	G/A	0.04	1.01 (0.88-1.17)	0.844	0.46	1.06 (1.04-1.08)	3.1×10^{-8}
rs12575663	11q13/*OVOL1*	65331111	A/G	0.17	1.01 (0.93-1.09)	0.865	0.47	0.95 (0.93-0.96)	8.6×10^{-12}
rs6001930	22q13/*MKL1*	39206180	C/T	0.28	1.05 (0.99-1.12)	0.124	0.11	1.12(1.09-1.16)	8.8×10^{-19}

Abbreviations: Chr., chromosome; EAF, effect allele frequency; OR, odds ratio; CI, confidence interval.

[a] rs12575663 in complete LD with index SNP rs3903072 in CEU,CHB and JPN samples (r^2=1.0, based on LD data from HapMap release27)

[b] The closest gene.

[c] Location based on NCBI Human Genome Build 36.3.

[d] Effect/reference alleles based on NCBI Human Genome Build 36.3, dbSNP b126 forward strand.

[e] Effect allele frequency in controls of Asian samples.

[f] Summary results from the original studies in European descendents (EAF, OR and 95% CI from iCOGS; *P* from combined GWAS+iCOGS).

Table 3

Associations of breast cancer risk with SNPs selected for this study

									Stage 1 (5,083/4,376)		Stage 2 (7,294/9,404)		Combined (12,377/13,780)	
Tested SNP[a]	**Chr./gene**[b]	**Position (bp)**[c]	**Alleles**[d]	**EAF**[e]	**Index SNP**	**CEU (r^2)**[f]	**CHB (r^2)**[f]	**Imputed**	**OR (95% CI)**[g]	**P_{trend}**[g]	**OR (95% CI)**[g]	**P_{trend}**[g]	**OR (95% CI)**[g]	**P_{trend}**[g]
rs788166	2q31/*DLX2*	172623735	C/G	0.62	rs2016394	0.01	0.06	Yes	1.09 (1.02-1.15)	0.006	1.01 (0.97-1.06)	0.605	1.04 (1.00-1.08)	0.037
rs821287	6p23/*RANBP9*	13464145	G/A	0.68	rs204247	0.01	0.05	Yes	0.86 (0.77-0.95)	0.003	1.07 (1.02-1.12)	0.005	1.03 (0.99-1.08)	0.164
rs1419026	6q14/*FAM46A*	82145898	T/C	0.29	rs17529111	0.29	0.56	Yes	1.07 (1.00-1.13)	0.048	1.08 (1.02-1.13)	**0.003**	1.07 (1.03-1.12)	**3.0×10^{-4}**
rs10278902	7q35/*ARHGEF5*	143320582	G/A	0.59	rs720475	0	0	Yes	0.94 (0.88-1.00)	0.034	1.06 (1.01-1.11)	0.014	1.01 (0.98-1.05)	0.434
rs2608036	8q24/*MYC*	129194161	G/A	0.82	rs11780156	0.07	0.05	No	1.10 (1.02-1.19)	0.014	1.04 (0.98-1.10)	0.192	1.06 (1.01-1.11)	0.011
rs16921849	10p12/*DNAJC1*	21873162	G/A	0.34	rs11814448	0.01	0.01	Yes	1.07 (1.00-1.14)	0.036	0.98 (0.93-1.02)	0.342	1.01 (0.97-1.05)	0.621
rs941827	10q25/*TCF7L2*	114548877	C/T	0.29	rs7904519	0.01	0.02	No	0.88 (0.82-0.93)	5.0×10^{-5}	0.95 (0.90-1.00)	**0.049**	0.92 (0.89-0.96)	**5.3×10^{-5}**
rs500161	11q13/*OVOL1*	65452014	T/C	0.51	rs12575663	0.56	0.11	Yes	1.05 (0.99-1.12)	0.084	0.99 (0.95-1.04)	0.761	1.01 (0.98-1.05)	0.425
rs138019	22q13/*MKL1*	38941574	G/A	0.92	rs6001930	0.02	0.03	Yes	0.86 (0.77-0.97)	0.009	1.04 (0.96-1.14)	0.334	0.98 (0.91-1.04)	0.464

Abbreviations: Chr., chromosome; EAF, effect allele frequency; OR, odds ratio; CI, confidence interval; ABCC, Asian Breast Cancer Consortium.

[a] One SNP was selected in each locus for the study.

[b] The closest gene to corresponding index SNP in each region.

[c] Location based on NCBI Human Genome Build 36.3.

[d] Effect/reference alleles were defined based on NCBI Human Genome Build 36.3, dbSNP 126 forward strand.

[e] Effect allele frequency in controls of Stage 2 studies.

[f] Based on HapMap genotype data release 27, dbSNP building 126.

[g] Adjusted for age and study site.

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Table 4

Associations of rs1419026 and rs941827 with breast cancer risk, stratified by estrogen receptor (ER) status

	ER positive			ER negative		
SNP (locus)	**Cases/Controls**	**OR (95% CI)[a]**	**P_{trend} [a]**	**Cases/Controls**	**OR (95% CI)[a]**	**P_{trend} [a]**
rs1419026 (6q14)	6,864/13,570	1.06 (1.01-1.11)	**0.018**	3,801/13,570	1.10 (1.04-1.17)	**5.2×10^{-4}**
rs941827 (10q25)	6,851/13,561	0.92 (0.87-0.96)	**4.2×10^{-4}**	3,790/13,561	0.91 (0.86-0.97)	**0.002**

Abbreviations: OR, odds ratio; CI, confidence interval.

[a]Adjusted for age and study site.