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11q13 Is a Susceptibility Locus for Hormone Receptor Positive Breast Cancer


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ABSTRACT: A recent two-stage genome-wide association study (GWAS) identified five novel breast cancer susceptibility loci on chromosomes 9, 10, and 11. To provide more reliable estimates of the relative risk associated with these loci and investigate possible heterogeneity by subtype of breast cancer, we genotyped the variants rs2380205, rs1011970, rs704010, rs614367, and rs10995190 in 39 studies from the Breast Cancer Association Consortium (BCAC), involving 49,608 cases and 48,772 controls of predominantly European ancestry. Four of the variants showed clear evidence of association ($P \leq 3 \times 10^{-4}$) and weak evidence was observed for rs2380205 ($P = 0.06$). The strongest evidence was obtained for rs614367, located on 11q13 (per-allele odds ratio 1.21, $P = 4 \times 10^{-39}$). The association for rs614367 was specific to estrogen receptor (ER)-positive disease and strongest for ER plus progesterone receptor (PR)-positive breast cancer, whereas the associations for the other three loci did not differ by tumor subtype.


KEY WORDS: breast cancer susceptibility; polymorphisms; genome-wide association; risk factors; hormone receptor status; 11q13

Introduction

Recent genome-wide association studies (GWAS) have provided statistically robust evidence for the association of common genetic variants with breast cancer risk. In particular, variants in the gene regions of FGFR2, TOX3, MAP3K1, LSP1, SLC4A7, COX11, RAD51L1, and in chromosomal regions 8q24, 2q35, 5p12, 6q25, 1p11, and 9q21 (all MIM# 114480) were identified as susceptibility variants through GWAS [Ahmed et al., 2009; Antoniou et al., 2010; Broeks et al., 2011; Easton et al., 2007; Hunter et al., 2007; Milne et al., 2009; Stacey et al., 2007, 2008; Thomas et al., 2009]. Typically, the variants in these loci occur commonly within the general population, but they confer only modest increases in risk with odds ratios (ORs) ranging from 1.10 to 1.43 per allele. Together these variants explain approximately 5% of the familial risk for breast cancer. Despite these relatively small risk effects, the identification of new disease susceptibility loci using GWAS may contribute critically to our understanding of the mechanisms underlying breast cancer tumorigenesis. Furthermore, some loci are more strongly associated with specific tumor subtypes; for instance, the FGFR2 rs2981582 variant is more strongly associated with estrogen receptor (ER)-positive than ER-negative disease [Broeks et al., 2011; Milne et al., 2009; Turnbull et al., 2010; Yang et al., 2011].

A recent two-stage GWAS conducted by Turnbull et al. [Turnbull et al., 2010] involving 3,659 cases with family history of breast cancer and 4,897 controls in the first stage, and 12,576 cases and 12,223 controls in the second stage, identified five novel susceptibility loci. The loci are on 11q13, 9p21, 10p15, 10q21, and 9q22 and are, respectively, close to the cyclin D1 (CCND1; MIM# 114500) and fibroblast growth factor genes (FGF3; MIM# 610706, FGF4; MIM# 104980, FGF19; MIM# 603891), the cyclin-dependent kinase inhibitors CDKN2A (MIM# 6006719), and CDKN2B, (MIM# 600431), the zinc finger genes ZNF365 (MIM# 607818) and ZMIZ1 (MIM# 607159), and ANKR1D6 [Turnbull et al., 2010]. Although the evidence for these associations was very strong, additional analyses, involving a much larger number of well-characterized breast cancer patients, are needed to independently confirm these associations and assess whether their risks vary with respect to tumor subtype. The Breast Cancer Association Consortium (BCAC), through its global collaborative approach, has gathered more than 96,000 breast cancer cases and controls for independent replication analysis, thereby providing a unique resource for this type of study [Breast Cancer Association Consortium, 2006; Easton et al., 2007].

Materials and Methods

Study Population

Ethics Statement: Written informed consent was obtained from all study participants and the analyses were approved by the institutional review boards at each study center.

Thirty-nine case-control studies from BCAC, which were not included previously in Turnbull et al. [Turnbull et al., 2010], participated in this pooled analysis. Of these, 29 studies were conducted in Europe, 5 in North America, 3 in Asia, and 2 in Australia. All studies provided information on disease status and age at diagnosis for cases and self-reported race/ethnicity for all subjects. All but five studies (BIGGS, HUBCS, KARBAC, ORIGO) also provided age at interview for controls. Family history of breast cancer among first degree relatives was provided by 13 studies (ABCFS, BBCS, CE-CILE, CTS, ESTHER, GENICA, GESBC, KBCP, MARIE, MCBCS, SASBAC, SBCS, UGBCS). ER and PR status as well as histology of the tumor were available for a subset of cases. This histopathology information was generally abstracted from medical reports. A total of 44,662 cases and 45,502 controls of European descent and 4,076 cases and 2,573 controls of Asian descent were included in this analysis. The description of study designs and final sample sizes per study are provided in the Supp. Table S1.

Genotyping and Quality Control

The rs1011970, rs2380205, rs10995190, rs704010, and rs614367 genetic variants were genotyped by MassARRAY iPLEX Gold (Sequenom, San Diego, CA), TaqMan (Applied Biosystems, Foster City, CA), and Fluidigm technology (Fluidigm, South San Francisco, CA) (Supp. Table S1). The method used by each study is identified in Supp. Table S1. All studies included ≥2% duplicates and 93 CEPH DNAs (HAPMAPPT01, Coriell Institute for Medical Research, Camden, NJ). The average genotype completion rate per variant was 99% and all genotype completion rates per study were greater than 95% for each variant. We used a χ²-test (1df) to verify that the genotype distributions for each single nucleotide polymorphism (SNP) were consistent with those expected under Hardy–Weinberg equilibrium (HWE) within each study and separately among European and Asian control subjects. A Bonferroni
correction for multiple tests was applied for the HWE test and gave a P value of 0.0002 as the cutoff for statistical significance, based on approximately 200 independent tests carried out. There was no evidence of departure from HWE for any SNP except rs614367 in one study (PBCS), which was therefore excluded from the analysis for this variant.

### Statistical Analysis

We used unconditional logistic regression to estimate OR and 95% confidence interval (CI). OR per allele or P values for trend were calculated by assuming a log-additive model. Pooled ORs were calculated using individual-level data. Logistic regression models were adjusted for study by including study specific indicator variables. Restricting the analysis to studies for which age at interview of controls was available, additional adjustment for age made no substantial difference in the results. Europeans and Asians were analyzed separately. Subgroup analyses were performed for breast cancer defined by hormone receptor status (ER and PR) and histological subtypes (ductal, lobular, and other tumors) and by family history of breast cancer. For the analyses stratified by family history, we excluded studies with cases selected for family history of breast cancer (ABCS, CINO-BCS, HEBCS, KARBC, KConFab/AOCS, MBCSG, NC-BCFR; Supp. Table S1). Heterogeneity of OR across the studies or across the stratification groups was assessed using the Cochran Q test. All tests were two sided. All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

### Results

We analyzed SNPs rs1011970, rs2380205, rs10995190, rs704010, and rs614367 in 49,608 breast cancer cases and 48,772 controls from 39 studies participating in BCAC. Of these women, 93% were of European descent and 7% of Asian descent (Table 1). Four of the variants, rs1011970, rs10995190, rs704010, and rs614367, were associated with overall breast cancer risk in women of European descent (P < 1 × 10⁻⁶; Table 1, Fig. 1, and Supp. Fig. S1). Per-allele ORs for these variants were very similar to those observed in the initial study by Turnbull et al. (Table 1) [Turnbull et al., 2010]. We estimated a lower OR for homozygotes at rs1011970 (OR = 1.10 in our study vs. OR = 1.29 in Turnbull et al.) and rs10995190 (OR = 0.75 in our study vs. OR = 0.83). These differences, however, might be explained by the wide CIs around the risk estimates due to low minor allele frequencies (MAF = 0.16), respectively. Significant heterogeneity by study was only observed for the SNP rs1011970 (P heterogeneity = 0.01; Supp. Fig. 1). This heterogeneity was due to the BSUCH study in which the per-allele OR was opposite directed to the overall estimated effect. After removing BSUCH from the analysis, heterogeneity between studies was not significant (P heterogeneity = 0.25), but the association of rs1011970 with breast cancer risk was similar (OR 1.08, 95% CI 3 × 10⁻⁹ vs. OR 1.09, 95% CI 10⁻¹⁰, before and after exclusion of BSUCH, respectively). The SNP rs2380205 on 10p15 showed limited evidence for association with breast cancer risk (P = 0.06). The 95% CI limits for the per-allele OR (0.98, 95% CI 0.96–1.00) excluded the OR estimate of 0.94 previously reported by Turnbull et al. [Turnbull et al., 2010], indicating either that the original association was false positive, or that the effect size is substantially smaller than previously reported.

In women of Asian descent, none of the variants was significantly associated with breast cancer risk with the exception of a borderline association with rs704010 (Table 1). However, each of the variants exhibited much lower minor allele frequencies (MAF) in women of Asian descent (Table 1), and none of the estimated per-allele ORs differed significantly from those of European descent.

Next, subgroup analyses for breast cancer defined by hormone receptor status (ER and PR status), histopathological subtype (ductal, lobular, and other tumors), and family history of breast cancer were performed separately in women of European and Asian descent. In Europeans, SNP rs614367 was significantly associated with ER-positive (OR 1.26; 95% CI 1 × 10⁻⁶) but not with ER-negative breast cancer (OR 1.01; 95% CI 0.97–1.06) (Fig. 1). The association was stronger for ER-positive/PR-positive (OR 1.29; 95% CI 7 × 10⁻⁵) than for ER-negative/PR-negative tumors (OR 1.12; 95% CI 2 × 10⁻³; P heterogeneity = 10⁻⁶; Fig. 1). The per-allele OR for rs1011970 was also slightly higher for ER-negative than for ER-positive breast cancer (OR 1.13; 95% CI 2 × 10⁻³ vs. OR 1.07; 95% CI 1 × 10⁻²; Fig. 1), but this difference was not significant (P heterogeneity = 0.06). The per-allele ORs for rs2380205, rs704010, and rs10995190 did not differ by tumor receptor status (Fig. 1). There was no evidence for heterogeneity in the per-allele ORs by histopathological subtypes for any SNP. With respect to family history of breast cancer we observed that the OR of SNP rs10995190 was lower than in women without family history (OR 0.83; 95% CI 6 × 10⁻⁶), whereas it was greater than 1 in women with a family history of breast cancer (OR 1.05; 95% CI 0.45; P heterogeneity = 5 × 10⁻²; Fig. 1). No other SNP showed significant differences between women with and without family history of breast cancer (Fig. 1).

Subgroup analyses in women of Asian descent showed that the association with rs704010 was stronger for ER-negative/PR-negative breast cancer (OR 1.30; 95% CI 7 × 10⁻²; Fig. 2). No heterogeneity by
Figure 1. Forest plots of stratified analysis of the five variants in European women. Except for the OR for heterozygous and homozygous effect, OR and 95% CI were derived from the per-allele model. All models are adjusted for age and study. \(P\) for heterogeneity was derived from the Cochran \(Q\) test. Squares represent odds ratios; size of the square represents inverse of the variance of the log odds ratio; horizontal lines represent 95% confidence intervals.
Figure 2. Forest plots of stratified analysis of the five variants in Asian women. Except for the OR for homozygous and homogzygous effect, OR and 95% CI were derived from the per-allele model. All models are adjusted for age and study. P for heterogeneity was derived from the Cochran Q test. Squares represent odds ratios; size of the square represents inverse of the variance of the log odds ratio; horizontal lines represent 95% confidence intervals.
histopathological subtype was observed for any SNP. We did not perform analyses stratified by family history of breast cancer because the number of subjects was too small among Asian women.

To examine potential associations between the breast-cancer-risk-associated SNPs and gene expression we screened the publicly available Expression Quantitative Trait Locus (eQTL) database GENEVAR (www.sanger.ac.uk/resources/software/genevar). No associations with gene expression were observed.

**Discussion**

This is the largest association study in breast cancer to date and it provides independent and strong evidence for rs1011970, rs10995190, rs704010, and rs614367 being breast cancer susceptibility loci. These variants are located within the footprint of plausible candidate genes: CDKN2A/2B (rs1011970), ZMIZ1 (rs704010), ZNF365 (rs10995190), and CCND1 (rs614367) consistent with the critical role of cell cycle control, gene regulation, and cell proliferation pathways in breast tumorigenesis. Each of these genes and one of the SNPs have been reported to be linked with other diseases or phenotypes. In particular, GWAS studies identified several SNPs in 9p21 near CDKN2 that have been associated with cutaneous nevi/melanoma [Falchi et al., 2009], glioma [Shete et al., 2009; Wrensch et al., 2009], type 2 diabetes [Zeggini et al., 2007] and coronary artery disease [Harismendy et al., 2011]. One SNP in the 3′ untranslated region of CDKN2A has been linked with pancreatic cancer [Chen et al., 2007]. All 9p21 SNPs differ from the breast cancer risk SNP rs1011970 described herein, yet this SNP is in linkage disequilibrium with the glioma SNP rs4977756 (r2 = 0.137; D′ = 1.0). Interestingly, the 9p21 interval is the second densest gene locus for predicted enhancers in the human genome and the one containing the most disease-associated variants indicating that this chromosomal region has important regulatory function [Harismendy et al., 2011]. The ZMIZ1 is known to be a recombination partner to form an ABL1 fusion gene in B-cell acute lymphoblastic leukaemia [Soler et al., 2008] and a nonsynonymous SNP of ZNF365 gene has been associated with Crohn’s disease [Haritunians et al., 2011]. Of note, the ZNF365 SNP rs10995190 now confirmed to be associated with breast cancer risk in this study has recently been associated with mammographic density which is considered one of the strongest risk factors for breast cancer [Lindstrom et al., 2011].

The strongest association with breast cancer was for SNP rs614367 in European women. The estimated OR (1.21 overall, and 1.29 for ER-positive/PR-positive breast cancer) is comparable to that reported for the FGR2 locus, the most strongly associated known common susceptibility variant for breast cancer. SNP rs614367 is located in an LD block of ~170kb on 1q13 that contains no known genes. This polymorphism lies ~130kb upstream of CCND1, encoding cyclin D1, which is known to be mutated, amplified or overexpressed in various cancers, including breast cancer [Dickson et al., 1995; Kim and Diehl, 2009]. Cyclin D1 together with cyclin-dependent kinases CDK4 and CDK6 mediate phosphorylation of the retinoblastoma protein (Rb) in the cell cycle G1 phase, leading to inactivation of pRb and commitment of mammalian cells to proceed to cell division in response to multiple signaling pathways, including tyrosine kinase and ER signaling [Lange and Yee, 2011]. If the association with rs614367 proves to be functionally related to CCND1, the stronger association of rs614367 with ER-positive disease would be consistent with the role of CCND1 as a mediator of estrogen-induced cell proliferation. There is evidence from cell line models that cyclin D1 expression together with inactivation of pRb are features of poor response to endocrine therapies [Lange and Yee, 2011]. However, it is not certain at this stage whether or not the association between rs614367 and breast cancer risk is mediated through CCND1. Whether 11q13 genetic variation affects the role of cyclin D1 as an oncogenic driver remains to be determined, as other plausible candidates, including FGFR4 and FGFR9 located at distances of 180kb and 270kb from rs614367, respectively, might also be involved.

The absence of any general breast cancer risk effects in women of Asian descent may be attributed to much lower MAFs of the SNPs tested in this present study and, therefore, lack of statistical power. Yet, the finding of an association of rs704010 with ER-negative/PR-negative breast cancer suggests a potential relevance in this ethnic group, but much larger sample sizes will be needed for the identification of SNP associations with breast cancer risk as well as patient and tumor characteristics.

In conclusion, we confirm the association of four new breast cancer susceptibility loci, provide precise estimates of the associated risks, and provide evidence of variation in the strength of associations by hormone receptor status. We are currently following up these findings through fine-mapping approaches to identify the causal SNPs and genes. This should in turn allow further studies on the impact of the risk causing variants on gene function, and hence explain the observed associations at the molecular level.

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