Title: 9q31.2-rs865686 as a susceptibility locus for estrogen receptor-positive breast cancer: evidence from the Breast Cancer Association Consortium

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Abstract

Background: Our recent genome-wide association study identified a novel breast cancer susceptibility locus at 9q31.2 (rs865686).

Methods: To further investigate the rs865686 – breast cancer association, we conducted a replication study within the Breast Cancer Association Consortium, which comprises 37 case-control studies (48394 cases, 50836 controls).

Results: This replication study provides additional strong evidence of an inverse association between rs865686 and breast cancer risk (study-adjusted per G-allele odds ratio (OR) 0.90, 95% confidence interval (CI) 0.88, 0.91, P=2.01x10^{-29}) among women of European ancestry. There were ethnic differences in the estimated minor (G) allele frequency among controls (0.09, 0.30 and 0.38 amongst, respectively, Asians, Eastern Europeans and other Europeans; P for heterogeneity (P_{het})=1.3x10^{-143}), but no evidence of ethnic differences in per allele OR (P_{het}=0.43). rs865686 was associated with estrogen receptor-positive (ER+) disease (per G-allele OR 0.89, 95% CI 0.86, 0.91, P=3.13x10^{-22}) but less strongly, if at all, with ER-negative (ER-) disease (OR 0.98, 95% CI 0.94, 1.02, P=0.26) (P_{het}=1.16x10^{-6}), with no evidence of independent heterogeneity by progesterone receptor or human epidermal growth factor receptor-2 status. The strength of the breast cancer association decreased with increasing age at diagnosis, with case-only analysis showing a trend in the number of copies of the G allele with increasing age at diagnosis (P for linear trend=0.0095), but only among women with ER+ tumors.

Conclusions: This study is the first to demonstrate that rs865686 is a susceptibility marker for ER+ breast cancer.

Impact: The findings further support the view that genetic susceptibility varies according to tumor subtype.
Introduction

Several genome-wide association studies (GWAS) have examined, since 2007, the role of common genetic variation in breast cancer risk leading to the identification of more than 20 risk loci (1-10). We recently conducted a multi-stage GWAS, involving a total of 11781 cases and 12378 controls, which identified a novel breast cancer locus at 9q31.2 (rs865686) with an estimated per G-allele odds ratio (OR) of 0.89 (95% confidence interval (CI) 0.85, 0.92, P=1.75x10^{-10}) (11) (Figure 1). Although this result is statistically significant by the usual criteria, rs865686 lies over 600kb from the nearest gene and is not in linkage disequilibrium with any genomic elements that suggest a possible causal mechanism. Statistical replication of this association is therefore important to establish this region as a risk locus for breast cancer. To provide a more precise estimate of the magnitude of the rs865686 association with breast cancer risk, we conducted a replication study within the Breast Cancer Association Consortium (BCAC), a large international consortium comprising over 95000 breast cancer cases and controls, which has been used to confirm most other GWAS-identified breast cancer susceptibility loci (e.g. (12-14)). This large case-control series also provided an opportunity to investigate whether the strength of the SNP – breast cancer association varies by ethnicity, age at diagnosis or tumor subtype.

Materials and Methods

Study subjects

Thirty-seven BCAC case-control studies contributed to this analysis. A brief description of the participating studies is given in Supplementary Table 1. The large majority of women (98%) were of self-reported European descent; those who participated in studies conducted in Eastern European countries (HMBCS and HUBCS) and those in OFBCR who self-reported themselves as being Eastern European were further classified as Eastern Europeans. In all, 2% were of self-reported Asian ethnicity; the latter included all the
participants in the only study (ACP) conducted in Asia as well as Asians who participated in other studies (restricted to studies with at least 20 Asians). Women of other self-reported ethnicities were excluded because of small numbers. Data on morphology (invasive vs. in situ) and receptor status (estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2)), obtained mainly from clinical notes, were available for certain subsets of cases (Supplementary Table 2).

Each study was approved by the relevant institutional review boards/ethics committees. Written informed consent was obtained from each subject. Only anonymised data were made available to BCAC.

Genotyping
9q31.2-rs865686 was genotyped by MALDI-TOF MS (Sequenom®, San Diego, CA), TaqMan® (Applied Biosystems™, Foster City, CA) or Fluidigm® technologies (Fluidigm®, South San Francisco, CA) using standard protocols (Supplementary Table 3). Strict quality control criteria, as implemented by BCAC (15), were applied. Briefly, the genotyping concordance was verified by including at least 2% of samples in duplicate and a common set of 93 CEPH DNAs used by the HapMap Consortium (HAPMAPPT01, Coriell Institute for Medical Research, Cambden, NJ). All samples from any study with more than two discordant genotypes on the CEU plate were excluded. Overall SNP call rates were >97% for all studies (Supplementary Table 3). There was no evidence of departure from Hardy-Weinberg Equilibrium (HWE) among controls in any individual participating study (P>0.01 for all studies; Supplementary Table 3).

Statistical Methods
The SNP association with breast cancer risk was assessed by estimating per-allele ORs with 95% CI. Two European BCAC studies (BBCS and UKBGS) had contributed data to the original GWAS and were therefore analysed separately as the "discovery" (hypothesis-
generating) set; cases and controls of self-reported European ancestry from the remaining BCAC studies constituted the independent “replication” set (Figure 1).

In secondary analyses, data from the discovery and replication sets were combined in order to maximize power. There is a possibility of “winner’s curse” bias in this approach, which we assessed by comparing the primary SNP association in the combined data to the unbiased estimate in the replication set and also to the more accurate unbiased UMVCUE estimator proposed by Bowden and Dudbridge (16), which corrects for a “winner’s curse” effect in stage 1 of the GWAS. The 95% CI and P-value for the UMVCUE OR were calculated using the variance from 1000000 bootstrap samples. The 9q31.2-rs865686 SNP in stage 1 of the discovery GWAS had P=2.28×10^{-4} whereas all other SNPs from the GWAS had P>5×10^{-4} (11), hence the latter was taken as the P-value threshold within the UMVCUE calculations. We assumed that a lack of detectable selection bias in the primary SNP association with breast cancer would justify combining the discovery and replication sets in the secondary analyses.

Between-study heterogeneity in ORs was assessed using the Breslow-Day test. Pooled results were adjusted for study using Cochran-Mantel-Haenszel (CMH) tests. Dominant and recessive models were also considered and departure from log-additivity was tested. Heterogeneity in ORs between different ethnic groups was assessed by a Wald Test of the coefficients of the ethnicity covariates obtained from a logistic regression including interactions between odds ratio and ethnicity.

Per-allele ORs specific to each breast cancer subtype (as defined by ER, PR and HER2 status) were estimated taking all available controls as each reference outcome, adjusting for study. Heterogeneity in the OR by subtypes was tested using case-only logistic regression, with each binary receptor status as the predictor, allele (major/minor) as the response, and study as a covariate. This model was then extended to include all receptor statuses in a combined analysis of association and heterogeneity.
Heterogeneity in the OR by age at diagnosis (<40, 40-49, 50-59, 60-69, ≥70 years) was evaluated by conducting five separate case-control analyses amongst Europeans, taking all the controls as the reference outcome for each subgroup, with adjustment for study. In addition, a case-only allelic logistic regression, adjusted for study, was used to test for a linear trend between number of copies of the G allele and age at diagnosis.

In some studies, cases had been selected to have an increased genetic susceptibility in order to improve power. To assess whether there was heterogeneity in the OR by level of genetic enrichment of the cases, the combined OR estimate for the ten European studies (BBCS, CNIO-BCS, GC-HBOC, GC-HBOC, HEBCS, KARBAC, kConFab/AOCS, MBCSG, NC-BCFR, OFBCR and RBCS) that selected all, or a subset, of cases with increased genetic susceptibility (e.g. those with two independent primaries and/or with at least one affected first-degree relative) was compared to the combined OR estimate for the remaining 26 European studies of unselected cases, with adjustment for study within each group.

In addition, a quantitative “family-history” score was assigned to each individual woman reflecting her number of affected first-degree relatives and whether she was a unilateral or a bilateral/ipsilateral case (a value of 2 was added to the score for bilateral/ipsilateral cases) and included as a covariate within a logistic regression model, adjusting for study. A significant interaction between this score and the SNP effect provided a test of effect modification by family history.

To assess whether rs865686 is associated with age at menarche, independently of disease status, we used linear regression with age at menarche as response and genotype as predictor, with covariate adjustment for both case/control status and study.

All statistical tests were two-sided. All analyses were carried out using PLINK (17,18) and R (19).
Results

A total of 48394 breast cancer cases and 50836 controls from 37 BCAC case-control studies contributed to the analysis. Overall, 98% of the subjects were of self-reported European ancestry and 2% were of self-reported Asian ancestry. The mean (±SD) age at diagnosis for European cases was 55 (±14) years. The estimated minor (G) allele frequency (MAF) of rs865686 was significantly higher amongst European (MAF=0.38) than Asian controls (MAF=0.09) (P=1.11x10^{-114}). There was no clear evidence of sub-ethnic differences in the estimated MAF among Asians (0.12 for controls from the Indian subcontinent (N=99); 0.09 for controls from South East Asia (N=660); P=0.21) but, among Europeans, the estimated MAF was lower among controls from Eastern European populations (MAF=0.30) than among those from other European populations (MAF=0.38) (P=1.08x10^{-31}).

The replication set (comprising Europeans from all studies except BBCS and UKBGS) provided strong independent support for an association between rs865686 and overall breast cancer risk among women of European ancestry (Figure 1), with an estimated OR of 0.90 (95% CI 0.88, 0.92, P=1.23x10^{-25}) per G-allele, and no evidence of between-study heterogeneity (P_{het}=0.23). Genotype-specific ORs were 0.89 (95% CI 0.87, 0.92) for GT vs. TT and 0.81 (95% CI 0.78, 0.85) for GG vs. TT. None of the estimates departed from those expected under a log-additive model (P=0.34) with the OR being 0.87 (95% CI 0.85, 0.90) and 0.87 (95% CI 0.83, 0.90), respectively, for dominant (GG and GT vs. TT) and recessive (GG vs. GT and TT) models.

There was no evidence of heterogeneity in the per-allele OR between the discovery and the replication sets (P_{het}=0.16; Figure 1), with their combined data yielding a pooled per-allele OR of 0.90 (95% CI 0.88, 0.91, P=2.01x10^{-29}) for women of European descent. This pooled estimate is potentially biased by the “winner’s curse” effect, but in fact is almost identical to the unbiased UMVCUE estimator of Bowden and Dudbridge (16) (OR 0.8999, 95% CI 0.8823, 0.9178, P=1.07x10^{-25}) and the replication estimate (OR 0.8996, 95% CI
0.8819, 0.9176, P=1.23x10^{-25}). Therefore any selection bias in the discovery set is minimal, and in the following analyses we combined the data from all women of European ancestry.

There was no evidence of ethnic variation in the per-allele OR estimate (P_{het}=0.43), but the power of the study to detect this was low due to the relatively small sample size (N=1,882: 1,123 cases and 759 controls) and the low MAF (0.09) among Asians. The per-allele OR estimates were similar for non-Eastern Europeans (OR=0.90; 95% CI 0.88, 0.91) and Eastern Europeans (OR=0.92, 95% CI 0.84, 1.0), and the higher estimate for Asians had a wide CI (OR=1.02, 95% CI 0.80, 1.31), which overlapped the other two CIs.

Among women of European ancestry the allelic ORs were similar for invasive and in situ tumors (P_{het}=0.62), but differed according to receptor status (Figure 2). The SNP was more strongly associated with ER-positive (ER+) than ER-negative (ER-) tumors (P_{het}=1.16x10^{-6}) and with PR-positive (PR+) than PR-negative (PR-) tumors (P_{het}=5.14x10^{-5}).

There was no evidence, albeit based on a smaller sample size, of effect modification by HER2 status (P_{het}=0.64). Stratification according to the four different possible combinations of ER/PR status (Figure 2) showed that the rs865686 was strongly associated with ER+/PR+ and ER+/PR- disease (P=5.78x10^{-20} and P=8.21x10^{-5}, respectively) but not with ER-/PR+ or ER-/PR- disease (P=0.08 and P=0.94, respectively) (P_{het}=1.75x10^{-7}). When both ER and PR status were modelled jointly in a case-only analysis, only the association with ER status remained significant (P=0.0012 for ER, P=0.21 for PR), with no evidence of interaction between ER and PR status (P_{het}=0.27). Together these findings are consistent with the SNP being strongly associated with ER+ disease (per-allele OR: 0.89, 95% CI 0.86, 0.91, P=3.13x10^{-22}) but less strongly, if at all, with ER- disease (OR=0.98, 95% CI 0.94, 1.02, P=0.26; Figure 2). There was no evidence of heterogeneity in ORs by tumor histology, or receptor status, amongst women of Asian descent, but these analyses were based on a much smaller sample size than for women of European ancestry (data not shown).
In women of European ancestry, case-control analyses suggest a positive trend in the magnitude of the per-allele OR (i.e. ORs became closer to unity) with increasing age at diagnosis of breast cancer (Table 1). This result was confirmed by a case-only analysis, but only for ER+ tumors, which showed a significant trend (P=0.0095) in the number of copies of the G-allele with increasing age of onset of ER+ disease (Table 1), but did not detect any association amongst either all cases, or ER- cases (P=0.37 and P=0.35, respectively). Note that the estimated OR for cases diagnosed at age <40 years, albeit based on a small sample size, did not follow the overall trend with its magnitude being as high as the OR for the oldest age group (≥70 years). This may be due to chance or a truly different effect among very young cases.

There was no evidence among Europeans that the per-allele OR differed (P\textsubscript{het}=0.97) between the ten case-control studies based on “genetically-enriched” cases (combined per-allele OR 0.90, 95% CI 0.86, 0.94, P=1.48x10\textsuperscript{-6}) and the 26 studies based on unselected cases (combined per-allele OR 0.90, 95% CI 0.88, 0.92, P=2.38x10\textsuperscript{-24}). Analyses by family history score, which reflects number of affected first degree relatives and whether the woman had one (unilateral case) or two (ipsilateral and bilateral cases) independent primary tumors (see Methods section), gave similar results with no evidence that the SNP-associated effect was modified by this variable (P\textsubscript{het}=0.47). The OR for bilateral disease may be somewhat weaker than expected (20), but re-defining the family history score as simply the number of affected relatives, regardless of whether the woman was a unilateral or a bilateral/ipsilateral case, did not affect the findings (P\textsubscript{het}=0.45).

Two recent GWAS (21,22) reported associations between 9q31.2 SNPs (rs7861820, rs12684013, rs4452860, rs7028916 and rs2090409) and age at menarche, a factor known to affect breast cancer risk. These loci map more than 2 Mb from rs865686 and are not correlated with it (r\textsuperscript{2} < 0.01, D’ <0.09 in CEU HapMap phase 2). We found no evidence that rs865686 was associated with age at menarche (per allele difference in age at menarche: 0.0017 years, 95% CI -0.0169, 0.0203, P=0.86), within the BCAC subset of 58983 European
women (31522 cases and 27461 controls) with information available on age at menarche and rs865686 genotype.

Discussion

This combined analysis of data from a large international consortium confirms 9q31.2-rs865686 to be a breast cancer susceptibility locus in women of European ancestry, yielding a very precise estimate of the per-allele OR among European women (OR=0.90, 95% CI 0.88, 0.91). Replication studies have demonstrated that genetic susceptibility to breast cancer varies by expression levels of ER in breast tumors, with certain variants being associated with both ER+ and ER- disease whereas others are more strongly associated with ER+ or triple-negative (ER-,PR-,HER2-) disease (23). Our study is the first to show that the 9q31.2-rs865686 is associated with ER+ breast cancer but less so, if at all, with ER- disease. These results are not affected by the “winner’s curse” bias as data on receptor status were available only for studies in the replication set. Interestingly, a recent study of African-American women (24) found no evidence of heterogeneity by ER status (P_{het}=0.17), but with a significant association being observed among ER- (per-allele OR 0.87, 95% CI 0.78, 0.97) but not ER+ disease (OR=0.94, 95% CI 0.86, 1.03) (24). However, this other study had low power to detect differences by receptor status (n=1520 ER+ cases, 988 ER- cases and 2745 controls).

Our original GWAS (11) found no evidence of an association in the per-allele ORs with either age at menarche or age at diagnosis. The present study did not reveal any association of rs865686 with age at menarche or age at diagnosis overall amongst women of European ancestry, but it found a trend in the number of copies of the G allele with increasing age at diagnosis among ER+ breast cancer cases. No strong trends in risk with age at diagnosis for the other known common breast cancer SNPs have been reported despite the fact that the familial relative risk of breast cancer is much higher at younger ages, particularly in relatives of young cases (25).
Our study was well-powered to identify ethnic variations in MAF, with this being much lower among women of Asian descent (MAF=0.09) than among those of European ancestry (MAF=0.38), and among the latter lower among Eastern European (MAF=0.30) than among other European women (MAF=0.38). However, the magnitude of the per-allele OR for the breast cancer association was estimated less precisely in Eastern European and Asian women. The Asian sample was markedly under-powered for detecting an association between the SNP and breast cancer risk (only 15% power at P<0.05 as estimated by the Genetic Power Calculator (26) assuming the same OR as estimated in European women). Assuming a similar case-control ratio as in the present BCAC dataset ~11,000 Asian cases would be required to attain 80% power. The Eastern European sample had a greater power (approximately 70%), with only ~1,000 additional cases required to attain 80% power. Overall, these ethnic differences are consistent with those from the study of African-American women mentioned above (24) showing that they had a higher MAF (0.48) than European women but a similar per-allele OR (0.93, 95% CI 0.85, 0.99, P=0.034).

Further genetic and functional studies will be required to identify the causal variant (or variants) and the mechanisms underlying the 9q31.2-rs865686 association with breast cancer risk. This SNP maps to a 17 kb region of LD (109927817-109944558 bp) on 9q31.2 with no known genes. The nearest genes are Kruppel-like factor 4 (KLF4, 636 kb centrometric), RAD23B (799 kb centromeric) and actin-like 7A (ACTL7A, 736 kb telomeric). Interrogation of the Oncomine database (27) showed a decrease in KLF4 gene transcripts in breast cancers and a correlation between KLF4 expression and estrogen receptor-α (ERα) positivity. However, it remains to establish a causal link between these functional mechanisms and sequence variation at or near rs865686. To motivate such functional studies, indisputable epidemiological evidence is needed for association between rs865686 and breast cancer, which we now report in this study. With such evidence in place, this region now presents a strong example of a non-coding SNP whose causal mechanism on disease is unclear. Determination of the mechanism is a considerable challenge but will
eventually shed further light on breast cancer oncogenesis and, potentially, non-coding mechanisms in other complex diseases.

In conclusion, this large replication study found strong evidence for an association between the 9q31.2-rs865686 SNP and ER+ breast cancer amongst women of European ancestry. The findings are consistent with breast cancer being a biologically heterogeneous disease and highlight the need for subtype-specific studies to be conducted in different ethnic populations.
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Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
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Legends to Figures

Figure 1. Forest plot of the association of 9q31.2-rs865686 with breast cancer risk amongst women of European ancestry in the original genome-wide association study (GWAS), all stages combined [11], and replication within the Breast Cancer Association Consortium (BCAC) *

Abbreviations: Ca=no. cases; Co=no. controls; MAF=minor allele frequency; OR=odds ratio; 95% CI=95% confidence interval. Study abbreviations as in Supplementary Table 1.
* The discovery set (see Results) comprises data from two BCAC studies that had contributed data to the GWAS analysis (BBCS contributed data on 1,711 (out of the 1,978 subjects examined here) to stages 1 and 2 of the GWAS; UKBGS contributed data on 4,621 (out of the 4,661 subjects examined here) to stage 3 of the GWAS).

Figure 2. 9q31.2-rs865686 and breast cancer risk amongst women of European ancestry stratifying by ER, PR and HER2 receptor status*

Abbreviations: Ca=no. cases; Co=no. controls; OR=odds ratio; 95% CI=95% confidence interval
* P for heterogeneity (Phet) in the OR by ER status: 6.9x10^-4 amongst PR- tumors and 0.52 amongst PR+ tumors.
Phet in the OR by PR status: 0.13 amongst ER- cases and 0.52 amongst ER+ cases.

Table

Table 1. Association of 9q31.2-rs865686 and breast cancer risk amongst women of European ancestry, by ER status of the tumor and age at diagnosis

Abbreviations

BCAC=Breast Cancer Association Consortium; CI=Confidence Interval; CMH=Cochran-Mantel-Haenszel; ER=estrogen receptor; GWAS=genome-wide association study; HER2=human epidermal growth factor receptor-2; HWE=Hardy-Weinberg Equilibrium; MLE=maximum likelihood estimator; OR=odds ratio; PR=progesterone receptor; SNP=single nucleotide polymorphism; UMVCUE=Uniformly Minimum Variance Conditional Unbiased Estimator
Table 1. Association of 9q31.2-rs865686 and breast cancer risk amongst women of European ancestry, by ER status of the tumor and age at diagnosis

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NK=not known
* Study-adjusted odds ratio (OR) and 95% confidence interval (CI)
### Fig 1

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**European Pooled (P het = 0.16)**

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Cancer Epidemiology, Biomarkers & Prevention

9q31.2-rs865686 as a susceptibility locus for estrogen receptor-positive breast cancer: evidence from the Breast Cancer Association Consortium

Helen Warren, Frank Dudbridge, Olivia Fletcher, et al.

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