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Fine-scale mapping of 8q24 locus identifies multiple independent risk variants for breast cancer

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What's new?

Previous genome-wide association studies identified rs13281615 and rs11780156 on 8q24 as breast cancer susceptibility loci. The authors performed a fine-mapping study including 55,540 breast cancer cases and 51,168 controls within the Breast Cancer Association Consortium and identified three additional, represented by rs35961416, rs7815245, and rs2033101, respectively. *In silico* analysis indicated two putatively functional variants rs7815245 and rs1121948.

Abstract

Previous genome-wide association studies among women of European ancestry identified two independent breast cancer susceptibility loci represented by single nucleotide polymorphisms (SNPs) rs13281615 and rs11780156 at 8q24. We conducted a fine-mapping study across 2.06 Mb (chr8:127,561,724 -129,624,067, hg19) in 55,540 breast cancer cases and 51,168 controls within the Breast Cancer Association Consortium. We found three additional independent association signals in women of European ancestry, represented by rs35961416 (OR = 0.95, 95% CI = 0.93-0.97, conditional $P = 5.8 \times 10^{-6}$), rs7815245 (OR = 0.94, 95% CI = 0.91-0.96, conditional $P = 1.1 \times 10^{-6}$), and rs2033101 (OR = 1.05, 95% CI = 1.02-1.07, conditional $P = 1.1 \times 10^{-4}$). Integrative analysis using functional genomic data from the Roadmap Epigenomics, the Encyclopedia of DNA Elements project, the Cancer Genome Atlas, and other public resources implied that SNPs rs7815245 in Signal 3, and rs1121948 in Signal 5 (in linkage disequilibrium with rs11780156, $r^2 = 0.77$), were putatively functional variants for two of the five independent association signals. Our results highlight multiple 8q24 variants associated with breast cancer susceptibility in women of European ancestry.

Introduction

Breast cancer is one of the most common malignancies among women worldwide.[1] Genome-wide association studies (GWASs) have identified approximately 100 loci associated with breast cancer.[2] Multiple independent variants on 8q24 have been shown to confer susceptibility for multiple types of cancer, including breast,[3,4] prostate, colorectal, bladder, ovarian, renal cell, glioma, chronic lymphocytic leukemia, and Hodgkin's lymphoma,[5] (also see Supplementary Figure S1). Although most of these loci are located in a "gene desert" region, several hundred kilobases (kb) telomeric to several genes including *FAM84B*, *POU5F1B*, *MYC*, and the long non-coding gene *PVT1*. A growing number of studies have shown that the 8q24 locus may harbor long-range regulatory elements involved in regulating expression of the *MYC* [6] or *PVT1* genes.[7]

In most GWAS, only the single nucleotide polymorphism (SNP) showing the strongest statistical association at each locus (hereinafter referred to as the index SNP) is reported. Those index SNPs themselves are usually not the causal variants but are in linkage disequilibrium (LD) with the functional variants. In addition to the common variants identified by GWAS, low-frequency variants in susceptible loci may also be associated with disease risk.[8] Furthermore, in each locus, there may exist allelic heterogeneity and multiple independent variants that may be associated with complex diseases.[8] Some of the missing heritability for disease may be derived from the incomplete coverage of genetic variants and poor representation of the full spectrum of causal variants on commercial genotyping arrays.[9,10] Therefore, it is necessary to conduct fine-scale mapping studies to investigate comprehensively all genetic variants in the LD blocks where a GWAS index SNP is located.

We conducted a fine-mapping study of the 8q24 region using data from 106,708 individuals within the Breast Cancer Association Consortium (BCAC). We systematically evaluated the associations with breast cancer risk of the SNPs across 2.06 Mb in this chromosome region. We aimed to identify additional independent association signals and potentially functional variants that may be responsible for the observed associations of variants in this locus with breast cancer risk.

Materials and Methods

Ethics statement

All studies were approved by the relevant institutional review committee and informed consent was obtained from all participants.

Subjects

Epidemiological and genotype data were obtained from 50 breast cancer case-control studies participating in the BCAC.[4] The sample set for the current project included 48,155 cases and 43,612 controls of European ancestry from 39 studies, 6,269 cases and 6,624 controls of Asian ancestry from 9 studies, and 1,116 cases and 932 controls of African ancestry from 2 studies. The estrogen receptor (ER) status of the primary tumor was available for 35,824 cases of European ancestry; 28,038 (78%) cases were ER+ and 7,786 (22%) were ER-.

SNP selection and genotyping

Fine-mapping SNPs were selected for inclusion on the custom Illumina iSelect array (iCOGS),[4,11–13] with the following criteria: 1) Defining the interval to include all SNPs with $r^2 >$ 0.1 with the index SNPs rs13281615 and rs11780156 based on HapMap 2 CEU, which identified a region of 2.06 Mb (base positions 127,561,724 -129,624,067; NCBI build 37 assembly); 2) Identifying all SNPs in the interval using the 1000 Genomes Project CEU (April 2010), and HapMap 3; 3) Selecting high-quality SNPs: only variants with the minor allele called at least twice in the 1000 Genomes Project and an Illumina designability score > 0.8 were included; 4) Selecting all SNPs with $r^2 > 0.1$ with the index SNPs rs13281615 and rs11780156 from the CEU data set of the 1000 Genomes Project or HapMap 3; 5) Selecting tagging SNPs at $r^2 > 0.9$ to capture the remaining SNPs that are not in LD with the index SNPs ($r^2 < 0.1$). Genotyping of the iCOGS array and details of the genotyping calling and quality control has been described elsewhere.[4,11,12] In order to improve SNP density and imputation quality, we conducted one-step imputation (without phasing) using the program IMPUTE2 (see URLs) with the March 2012 release of the 1000 Genomes Project as reference. Genotypes were successfully imputed for 10,593 variants in samples of European ancestry, 9,218 variants in samples of Asian ancestry, and 17,964 variants in samples of African ancestry, all with imputation-$r^2 > 0.3$. After excluding SNPs with minor allele frequency (MAF) < 0.02, the final genotype data in this project included 6,631 SNPs in samples of European ancestry, 6,459 SNPs in samples of Asian ancestry, and 10,830 SNPs in samples of African ancestry.

Statistical analysis

The per-allele odds ratio (OR) and 95% confidence interval (CI) for each SNP was estimated for breast cancer risk using a log-additive logistic model with covariates of study site and principal components (PC; eight PCs with one additional principal component from the LMBC study in Europeans, two PCs in Asians and two in African Americans). Per-allele ORs and CIs were estimated separately for each population for overall disease, for ER+ and for ER- breast cancer. To identify potential independent susceptibility variant(s), stepwise forward logistic regression analyses were employed with or without the index SNPs rs13281615 and rs11780156 forced in the model. SNPs with a P value $< 10^{-4}$ from the single variant analysis were included in this analysis.[11] To identify potentially functional variant candidate(s), we computed a likelihood ratio for each SNP relative to the representative SNP in each signal and excluded SNPs with a likelihood ratio < 0.01. Because no SNPs showed $P < 1\times10^{-4}$ in Asian or African ancestry data, such analyses were performed only on data from subjects of European ancestry. We used the haplo.stats package in R for haplotype analyses for the SNPs that are independently associated with breast cancer risk in women of European ancestry, with study sites and principal components as covariates. The familial relative risk (FRR) was estimated with the formula $\ln(\lambda)/\ln(\lambda_o)$, where λ is the FRR to offspring of an affected individual due to a single genetic locus or assumed multiplicatively interacting loci and λ_o is the overall FRR, which was assumed to be 1.8 for breast cancer.[14] All analyses were conducted using R version 3.0.1.

Functional annotation

We annotated a total of 245 breast cancer risk associated variants ($P<10^{-4}$ from univariate analysis) for potential functional significance using data from the Encyclopedia of DNA Elements (ENCODE), the Roadmap Epigenomics Mapping Consortium, and The Cancer

Genome Atlas (TCGA) (see URLs). For each variant, we investigated whether it is mapped to transcriptional elements primarily associated with enhancers (H3K4me1) or promoters (H3K4me3), in any of nine cell lines: normal human mammary epithelial cell line (HMEC), GM12878, H1-hESC, K562, HepG2, HSMM, HUVEC, NHEK, and NHLF. The epigenetic landscape of histone markers H3K4Me1, H3K4Me3, and H3K27Ac was also examined through layered histone tracks on seven ENCODE cell lines, including GM12878, H1-hESC, K562, HSMM, HUVEC, NHEK, and NHLF from the UCSC Genome Browser (see URLs). DNase I hypersensitive and transcription factor (TF) ChIP-Seq datasets were investigated in all available ENCODE cell lines, including HMEC and the breast cancer cell lines T-47D and MCF-7. Publicly available tools RegulomeDB[15] and HaploReg v4.1[16] were also used to evaluate potential functional variants.

For regions lacking ChIP-seq peaks data, we collected raw ChIP-seq data for the estrogen receptor-α (ESR1) and forkhead box protein A1 (FOXA1) in MCF-7, TAMR and ZR751 breast cancer cell lines (Supplementary Table S1) from the study by Hurtado *et al.* [17] The raw ChIP-seq data in .FASTQ format from different lanes in the same experiment were first merged and mapped to the human reference genome (hg19) using the Bowtie2 program[18] with the default setting. Aligned data were processed and converted into Binary Sequence Alignment/Map format (BAM) files using the SAMtools program.[19] After removing duplicated reads, we used the MACS14 (version 1.4.2) algorithm[20] to identify peaks with 50 bp resolution using the matched DNA input data as the control. The peaks were ranked by the number of uniquely aligned reads and only the top 5% of peaks were selected for motif discovery. The summits of the top 5% peaks were extended by 100 bp on either side. Similar methodological strategy has been used elsewhere.[21,22] Motifs between 5 and 30 bp in length were identified on both strands. We

employed the MEME 4.9.1 toolkit[23] to search DNA motifs and enrichment significance for ESR1 and FOXA1.

Expression quantitative trait (eQTL) analysis

eQTL analysis was performed followings the method described previously.[24] Briefly, RNA-Seq V2 data (level 3) of 1,006 breast cancer tumor tissues were downloaded from the TCGA data portal (see URLs). DNA methylation data measured by the Illumina HumanMethylation450 BeadChip and genotype data from the Affymetrix SNP 6.0 array were also retrieved from TCGA level 3 data. Genotype data of the flanking 2 Mb region of the index SNPs on 8q24 were extracted and then imputed to the 1000 Genomes Project data with Minimac (see URLs). Only common SNPs (MAF > 0.05) with high imputation quality ($r^2 > 0.3$) were included in the present study. For the interrogated 2 Mb region, copy number variation (CNV) data spanning the 8q24 genes *FAM84B*, *POU5F1B*, *MYC,* and *PVT1* from TCGA tumor tissue samples were collected from the CbioPortal (see URLs).

We used the TCGA breast cancer data described above to perform *cis*-eQTL analyses in tumor tissues. Several steps were taken to reduce the batch and other technical effects on gene expressions following the approach described by Pickrell et al.[25] First, the RNA-Seq by Expectation-Maximization value of each gene was log2 transformed and genes with a median expression level of 0 across tissues were removed. We then performed the principal component correction on gene expression to remove potential batch effects. A linear regression of expression values on the first five principal components was constructed and the residuals were used to replace the expression values of each gene among tissues. To make the data more closely conform to the linear model for the eQTL analysis, we further transformed the gene expression

levels to fit quantiles of N(0,1) distribution based on the ranks of the expression values to their respective quantiles. Finally, to further adjust for the potential effects of methylation and CNV on the expression of each gene in tumor tissues, we constructed residual linear regression models to detect eQTLs according to the approach used by Li et al.[26]

Results

Associations with breast cancer risk among women of European ancestry

We first conducted univariate analysis for 2,391 genotyped and 4,240 well-imputed SNPs in samples from women of European ancestry. A total of 359 SNPs were associated with breast cancer risk with a statistical significance of $P < 10^{-4}$ (Figure 1 and Supplementary Table S2). Confirming previous GWAS results, the index SNPs rs13281615 (Signal 2 in Table 1) and rs11780156 (Signal 5 in Table 1) showed significant associations with ORs of 1.11 (95% CI = 1.08-1.13, $P = 2.0 \times 10^{-24}$) and 1.07 (95% CI = 1.05-1.10, $P = 4.1 \times 10^{-8}$), respectively (Table 1, univariate analysis). We then conducted forward stepwise regression analysis for each of the 359 SNPs to identify potential independent association signals. When two index SNPs rs13281615 and rs11780156 were forced into the model, we found two additional independent association signals at statistical significance of $P < 1 \times 10^{-4}$ and a third one with suggestive evidence ($P = 1.1 \times 10^{-4}$) (Table 1 and Supplementary Figure S2). The first independent signal (Signal 1 in Table 1), represented by rs35961416 (chr8:128213561:I) with an insertion of base A, showed a P value of 5.8×10^{-6} after adjustment for other four signals (conditional OR = 0.95, 95% CI = 0.93-0.97). The second independent signal (Signal 3) represented by rs7815245 (conditional OR = 0.94, 95% CI = 0.91-0.96, $P = 1.1 \times 10^{-6}$, Table 1), was in moderate LD with the index SNP

rs13281615 in Signal 2 ($r^2 = 0.48$) but not with the second index SNP rs11780156 in Signal 5 ($r^2 < 0.01$). The third suggestive independent variant (Signal 4, rs2033101), not in LD with either of the two index SNPs, showed a conditional *P* value of 1.1×10^{-4} (OR = 1.05, 95% CI = 1.02-1.07, Table 1). We also performed forward stepwise regression analysis without the two index SNPs forced into the model. Five similar independent breast cancer risk associated SNPs were selected: Signal 1 (rs35961416) (conditional $P = 3.2 \times 10^{-6}$) and the suggestive Signal 4 (rs2033101) (conditional $P = 1.4 \times 10^{-4}$) remained the same; Signal 2 (rs13281615) was tagged by the highly correlated SNP rs10110330 ($r^2 = 0.97$, conditional OR = 1.06, 95% CI = 1.04-1.09, $P = 9.5 \times 10^{-6}$), Signal 3 (rs7815245) tagged by the most significant SNP rs17465052 ($r^2 = 0.93$, conditional OR = 0.94, 95% CI = 0.91-0.97, $P = 3.2 \times 10^{-6}$), and Signal 5 (rs11780156) tagged by c8_pos129263191 (rs67397162, $r^2 = 1$, conditional OR = 1.07, 95% CI = 1.05-1.10, $P = 1.1 \times 10^{-7}$). These results consistently showed four independent risk association signals and another suggestive one (Supplementary Figure S2). No significant evidence of between-study heterogeneity was observed for any of these independently risk-associated SNPs (data not shown).

Stratified by ER status, all five independent signals showed significant associations for ER+ breast cancer; however, with the exception of rs11780156 showing a *P* value of 0.012 (signal 5), no significant associations were observed for ER- breast cancer (Table 2).

Haplotype analyses were performed using data from the five independent risk signals (Table 3). In women of European ancestry, a total of 16 haplotypes with frequency of > 1% were observed. Compared to the reference haplotype, which carries the alleles associated with a reduced risk in all five SNPs, most haplotypes were associated with increased breast cancer risk. Haplotype 5, which carries the risk-associated alleles of the signals 1-3, showed the most

significant association ($P = 3.4 \times 10^{-11}$ for overall breast cancer) while Haplotype 1, which carries the risk-associated alleles of all signals except for Signal 4, was associated with the highest estimated OR (OR = 1.27, 95% CI = 1.15-1.39 for overall breast cancer) (Table 3). As shown in Table 3, similar haplotype associations were observed for ER+ but not for ER- breast cancer.

Association with breast cancer risk in women of Asian or African ancestry

Of the five independently risk-associated variants identified in women of European ancestry, only rs35961416 (Signal 1) showed a nominal association in African-American women at $P < 0.05$ ($P = 0.04$, Table 4). Based on univariate analyses of all SNPs on 8q24 that passed QC, SNP rs76382129 showed a P value of 8.3×10^{-4} in women of Asian ancestry and five SNPs showed P values of between 9.6×10^{-4} and 1.6×10^{-4} in women of African ancestry (Supplementary Table S3). Another 16 SNPs showed breast cancer risk association with P values between 0.01 and 0.001 in either population and in the same direction across the two populations (Table 4).

Functional annotation

For each of the five independent signals identified among women of European ancestry, we excluded SNPs with $r^2 \leq 0.2$ with the representative SNP in each signal region and then calculated the likelihood of all risk-associated variants to select potentially functional variant candidates. Setting a likelihood ratio threshold of > 0.01 relative to the representative/index SNP in each signal region, we did not identify any functional variant candidates for rs35961416

(Signal 1) and rs2033101 (Signal 4) whereas we identified 154 functional variant candidates for Signal 2, 170 variants for Signal 3 (143 variants overlap with those for Signal 2), and 62 variants for Signal 5, respectively (Supplementary Tables S4-S6). Thus, a total of 245 unique SNPs including the five representative SNPs in five signal regions were further evaluated for their potentially functional significance.

Our integrative functional annotation from ENCODE, Roadmap Epigenomics, the RegulomeDB[15], the HaploReg databases[16], and other public data identified the representative SNP rs7815245 in Signal 3 and SNP rs1121948 (in LD with rs11780156) in Signal 5 as most likely functional variant candidates underlying respective independent association signals (Figure 2). Based on the Roadmap Epigenomics data, SNP rs7815245 in Signal 3 is mapped to a conserved enhancer region with a genomic evolutionary rate profiling (GERP) score of 5.04 among eight tissues including breast variant human mammary epithelial cells (vHMEC) and breast myoepithelial primary cells. It is in a DNase I hypersensitive region in eight tissues including vHMEC. It is also predicted to change the transcription factor TCF12 binding motif. This SNP is also located in the binding regions of two critical nuclear hormone responsible receptors, estrogen receptor-α (ESR1), and forkhead box protein A1 (FOXA1) (Supplementary Figure S3). ChIP-seq data from different breast cancer cell lines and technical replicates showed consistent results (Supplementary Figure S3A). DNA binding motif analysis further confirmed that SNP rs7815245 is located in the ESR1 DNA binding motif ($P = 1.5 \times 10^{-3}$) and is very close to the FOXA1 DNA binding motif ($P = 5.2 \times 10^{-3}$) (Supplementary Figure S3B). In addition, the breast cancer risk-associated T allele was correlated with decreased expression of the *POU5F1B* gene ($P = 0.04$, Supplementary Table S7).

SNP rs1121948, which is in strong LD with the index SNP rs11780156 (r^2=0.77) in Signal 5, resides in the binding motifs of the TFs GATA-binding protein 3 (GATA3) and MYC-associated factor X (MAX) in the breast cancer cell line MCF-7. HaploReg data shows that this SNP resides in promoter regions of lung and muscle tissues, in strong enhancer regions of 14 tissues including HSMM and NHLF cells, and in DNase I hypersensitive sites of four tissues. Two active epigenetic markers (H3K4Me1 and H3K27Ac) were enriched in the interval containing rs1121948 in seven ENCODE cell lines (Figure 2C). We examined the effect of the associations of the 62 SNPs from the likelihood analysis for Signal 5 and expression of genes within 1 Mb of the index SNP rs11780156. We found that the risk-associated G allele of rs1121948 was weakly associated with decreased expression of the *PVT1* gene (*P*=0.037, Supplementary Table S7).

Discussion

In this study, we conducted a fine-mapping investigation at the breast cancer susceptibility locus on 8q24. Among women of European ancestry, we identified four independent association signals represented by rs35961416, rs13281615, rs7815245 and rs11780156, respectively, and another suggestive one tagged by rs2033101. This discovery increases the proportion of familial risk of breast cancer explained by variation on 8q24 from 0.25% (due to the GWAS index SNPs rs13281615 in Signal 2 and rs11780156 in Signal 5) to 0.55%.

SNP rs7815245 (Signal 3) showed a more significant association than the previously GWAS-identified index SNPs rs13281615 (Signal 2) and rs11780156 (Signal 5). This SNP is located in an enhancer region among eight tissues including breast variant HMEC and

myoepithelial cells. TF occupancy data showed that SNP rs7815245 falls within the DNA binding motifs for ESR1 and FOXA1, two critical DNA binding proteins for the development of several hormone-dependent cancers including breast cancer. Breast cancer susceptibility variants rs4784227 on 16q12.1 and rs2981578 on 10q26 have also been reported to modulate the affinity for these two transcription factors.[11,27] In addition, FOXA1 has shown a critical role in estrogen-ESR1 activity and endocrine response in breast cancer cells.[17,28,29] These results imply that the association between SNP rs7815245 at Signal 3 and breast cancer risk might be mediated by their functional effects through these two transcription factors. The risk allele T of rs7815245 down-regulated expression of its downstream gene *POU5F1B*, which encodes a weak transcriptional activator highly similar to the POU class 5 homeobox 1 transcription factor and is overexpressed in prostate cancer.[30] However, further functional studies are needed to clarify the biological mechanism of this SNP in breast cancer susceptibility.

The most attractive candidate gene for cancer risk variants in the gene-desert 8q24 region is the proto-oncogene *MYC*, because it plays a vital role in tumorigenesis and metastasis of several types of cancer including breast cancer.[31–33] As a key transcription factor, MYC forms heterodimers with MAX, and then regulates transcription of genes involved in cell growth, and proliferation.[31] Aberrant MYC signaling can promote cell transformation and tumor progression.[32,33] Although most of the GWAS-identified SNPs on 8q24 for multiple types of cancers[5,34] are not mapped to the *MYC* genic region, they may cis-regulate nearby genes including *MYC* and its 53-kb downstream non-coding gene *PVT1*.[5] For example, cancer risk-associated variants may regulate *MYC* expression by forming a large chromatin loop with the *MYC* locus.[6,26,35] This hypothesis has been partially supported by the fact that trait-associated loci are frequently found to be *cis*-eQTL.[26,36,37] Our e-QTL analysis of the TCGA breast cancer tumor

tissues showed a trend that rs1121948 in Signal 5 might affect *MYC* or *PVT1* expression levels (Supplementary Table 7), consistent with a co-expression pattern.[38] However, the risk-increased alleles are associated with down-regulated gene expression of *MYC* or *PVT1*. This is inconsistent with overexpression of these two genes commonly observed in breast cancer tumors,[39–42] leaving challenges to link the risk alleles and the possible candidate gene(s) in malignancy.

Of the five independent association signals observed among women of European ancestry, only rs35961416 showed a significant association in women of African ancestry. This could be due to small effect size, different allele frequency, or allelic heterogeneity by race. Differences in GWAS findings across populations have commonly been observed for breast cancer and many other complex traits.[43–45] Taking the GWAS index SNP rs13281615 as an example, the risk allele frequency in women of European ancestry was 0.40.[46] Under an additive inheritance mode to detect the same per-allele effect (OR = 1.08) at $P = 0.05$, our Asian sample with 6,269 breast cancer cases and 6,624 controls (risk allele frequency of 0.53) and African American sample with 1,116 breast cancer cases and 932 controls (risk allele frequency of 0.44) has a power of 0.09% and 0.1%, respectively.

In addition to a smaller sample size for women of Asian or African ancestry, there are several other limitations in this study. First, no functional laboratory experiments were conducted for any of the putative functional SNPs implicated in our study, preventing us from drawing a more definitive conclusion regarding the functionality of these variants. For example, our *in silico* analyses suggest that rs1121948 is located in binding sites of GATA3 and MAX, which may regulate *MYC* expression, but such potential interaction needs to be demonstrated experimentally.[47–50] Second, we limited our investigation to variants with a MAF > 0.02, and

thus it is possible that some rare variants in these loci may also contribute to the risk of breast cancer.

In conclusion, our fine mapping study identified two additional and another suggestive independent association signals on 8q24 among women of European ancestry, which together with two previous reported GWAS index signals plain approximately 0.55% of excess familial risk of breast cancer. In addition, our functional analyses revealed two putatively functional variants that can be further investigated experimentally. Our study provides additional evidence of the importance of common independent variants on 8q24 in breast cancer susceptibility.

URLs. 1000 Genomes, http://browser.1000genomes.org; BCAC, http://apps.ccge.medschl.cam.ac.uk/consortia/bcac/; CbioPortal, http://www.cbioportal.org/public-portal/; ENCODE, http://genome.ucsc.edu/ENCODE/; HaploReg v4.1, http://www.broadinstitute.org/mammals/haploreg/haploreg.php; HapMap project, http://hapmap.ncbi.nlm.nih.gov/; iCOGs, http://ccge.medschl.cam.ac.uk/research/consortia/icogs/; IMPUTE v.2.2, https://mathgen.stats.ox.ac.uk/impute/impute_v2.html; LocusZoom, http://csg.sph.umich.edu/locuszoom/; Minimac, http://genome.sph.umich.edu/wiki/Minimac; R version 3.0.1, http://www.r-project.org/; RegulomeDB, http://regulome.stanford.edu/; UCSC Genome Browser, http://genome.ucsc.edu; TCGA, http://cancergenome.nih.gov/.

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FIGURE LEGENDS

Figure 1. Manhattan plot of overall breast cancer risk association in Europeans at the 8q24 locus. SNPs are plotted based on their chromosomal positions (hg19) and -$\log_{10}$ *P*-values for univariate association. The regions spanning five independent association signals (representative SNP for each signal are shown in Table 1) and their highly correlated SNPs are indicated by dashed rectangles.

Figure 2. Functional annotation of the independent signal regions. (**A**) Chromatin states across the 45.6 kb region harboring two associated signals rs13281615 and rs7815245. The top 3 tracks show enrichment of transcription regulatory histone markers H3K4me1, H3K4me3 and H3K27ac from seven cell lines in ENCODE. The next 9 tracks are the chromatin state annotation by ChromHMM derived from 9 cell types. ChromHMM color coding is as follows: orange, strong enhancer; yellow, weak enhancer; light green, weak transcribed; light gray, low signal. The next 5 tracks show the designated histone modifications in the HMEC cell line. The last two tracks show the open chromatin enrichment from DNase clusters and evolutionary conservation measurement by PhastCons from 100 vertebrates. (B) LD structure of the region harboring the index SNP rs13281615 and the independent signal rs7815245 in European samples. (C) Chromatin states across the 58.9 kb region harboring the second index SNP rs11780156 and the potential underlying functional SNP rs1121948. The contents of the tracks are the same as described in (A). (D) LD structure of the 58.9 kb region wherein SNPs rs11780156 and rs1121948 lie, marked with red arrows.

Table 1. Identification of five independent association signals for overall breast cancer risk among women of European ancestry: a collaborative study of 48,155 breast cases and 43,612 controls.

Signal	SNP	Base position (hg 19)	Alleles[a]	MAF	Imputation r^2	LD[b] (r^2)	Univariate Analysis		Conditional Analysis	
							per-allele OR (95% CI)[c]	*P*[c]	Adjusted per-allele OR (95% CI)[d]	Adjusted *P*[d]
Signal 1	rs35961416	128213561	**A**/-	0.44	0.75	-	0.95(0.93-0.97)	$1.3x10^{-5}$	0.95(0.93-0.97)	$5.8x10^{-6}$
Signal 2	rs13281615[e]	128355618	**G**/A	0.40	0.97	-	1.11(1.08-1.13)	$2.0x10^{-24}$	1.06(1.03-1.09)	$6.6x10^{-6}$
Signal 3	rs7815245	128383597	**T**/C	0.42	1	0.48	0.90(0.88-0.92)	$1.3x10^{-27}$	0.94(0.91-0.96)	$1.1x10^{-6}$
Signal 4	rs2033101	128964222	**T**/C	0.19	0.95	-	1.05(1.03-1.08)	$5.2x10^{-5}$	1.05(1.02-1.07)	$1.1x10^{-4}$
Signal 5	rs11780156[e]	129194641	**T**/C	0.16	1	-	1.07(1.05-1.10)	$4.1x10^{-8}$	1.07(1.04-1.10)	$1.7x10^{-7}$
	rs1121948	129165056	**G**/A	0.20	1	0.77	1.07(1.04-1.09)	$2.0x10^{-7}$	-	-

Abbreviations: LD, linkage disequilibrium; OR, odds ratio; CI, confidence interval; MAF, minor (effect) allele frequency.

[a] Minor/major alleles; effect alleles are shown in bold.

[b] r^2 for linkage disequilibrium with index SNP rs13281615 (0.48) and rs11780156 (0.77),respectively; "-" indicates $r^2<0.01$ with any index SNPs.

[c] Adjusted for age, study site and principal components.

[d] Adjusted for the other four signals, age, study site and principle components.

[e] Independent index SNPs rs13281615 and rs11780156 from previously reported genome-wide association studies.

Table 2. Association of the five independent signals with breast cancer risk by ER status among women of European ancestry.

SNP	ER+ cases (n=28,038)		ER- cases (n=7,786)		*P* for heterogeneity test[b]
	Adjusted per-allele OR (95% CI)[a]	Adjusted *P*[a]	Adjusted per-allele OR (95% CI)[a]	Adjusted *P*[a]	
rs35961416	0.93(0.91-0.96)	$4.8x10^{-7}$	0.97(0.93-1.01)	0.138	0.217
rs13281615	1.08(1.04-1.11)	$3.1x10^{-6}$	1.00(0.95-1.05)	0.971	0.032
rs7815245	0.94(0.91-0.97)	$1.6x10^{-4}$	0.96(0.91-1.01)	0.104	0.276
rs2033101	1.06(1.03-1.09)	$1.3x10^{-4}$	1.04(0.99-1.08)	0.140	0.307
rs11780156	1.08(1.05-1.11)	$6.6x10^{-7}$	1.06(1.01-1.12)	0.012	0.118

Abbreviations: ER, estrogen receptor; OR, odds ratio; CI, confidence interval.

[a] Adjusted for other four independent signal, age, study site and principle components.

[b] Heterogeneity test between ER-positive and ER-negative disease.

Table 3. Haplotype analyses of the two independent signals in relation to breast cancer risk among women of European ancestry.

						All cases (n=48,155)			ER+ cases (n=28,038)			ER- cases (n=7,786)		
	SNP 1[a]	SNP 2[a]	SNP 3[a]	SNP 4[a]	SNP 5[a]	Frequency[b]	per-allele OR (95% CI)[c]	*P*[c]	Frequency[b]	per-allele OR (95% CI)[c]	*P*[c]	Frequency[b]	per-allele OR (95% CI)[c]	*P*[c]
Haplotypes	**A**/-	**G**/A	**T**/C	**T**/C	**T**/C									
Baseline	A	A	T	C	C	0.125	Reference (1.00)	-	0.127	Reference (1.00)	-	0.130	Reference (1.00)	-
Haplo.1	-	G	C	C	T	0.029	1.27(1.15-1.39)	1.1×10^{-6}	0.028	1.30(1.17-1.46)	2.9×10^{-6}	0.028	1.22(1.03-1.46)	0.024
Haplo.2	-	A	C	C	T	0.017	1.24(1.11-1.40)	2.1×10^{-4}	0.016	1.29(1.12-1.48)	2.9×10^{-4}	0.016	1.19(0.96-1.48)	0.115
Haplo.3	-	G	C	T	C	0.033	1.23(1.13-1.35)	3.2×10^{-6}	0.033	1.28(1.15-1.42)	3.0×10^{-6}	0.032	1.10(0.93-1.30)	0.276
Haplo.4	A	G	C	T	C	0.031	1.22(1.12-1.33)	1.2×10^{-5}	0.031	1.21(1.09-1.35)	3.6×10^{-4}	0.030	1.08(0.91-1.28)	0.370
Haplo.5	-	G	C	C	C	0.140	1.17(1.12-1.22)	3.4×10^{-11}	0.139	1.20(1.13-1.26)	1.1×10^{-10}	0.136	1.06(0.97-1.15)	0.220
Haplo.6	A	G	C	C	C	0.131	1.13(1.07-1.19)	2.2×10^{-5}	0.131	1.13(1.06-1.21)	2.1×10^{-4}	0.130	1.04(0.94-1.16)	0.470
Haplo.7	-	A	T	C	T	0.029	1.13(1.03-1.23)	0.117	0.028	1.12(1.01-1.25)	0.038	0.029	1.04(0.87-1.24)	0.654
Haplo.8	A	G	C	C	T	0.024	1.11(1.01-1.23)	0.036	0.024	1.06(0.94-1.20)	0.339	0.024	1.03(0.85-1.25)	0.758
Haplo.9	-	A	C	C	C	0.089	1.11(1.05-1.17)	2.3×10^{-4}	0.090	1.12(1.05-1.19)	5.7×10^{-4}	0.089	1.02(0.92-1.13)	0.688
Haplo.10	-	A	T	T	C	0.037	1.11(1.02-1.20)	0.011	0.037	1.13(1.03-1.24)	9.5×10^{-3}	0.037	1.05(0.90-1.22)	0.529
Haplo.11	-	A	C	T	C	0.020	1.09(0.98-1.21)	0.121	0.020	1.04(0.92-1.18)	0.510	0.021	1.27(1.05-1.53)	0.013
Haplo.12	A	A	C	C	C	0.034	1.05(0.97-1.15)	0.229	0.033	1.01(0.91-1.12)	0.877	0.035	1.09(0.93-1.28)	0.300
Haplo.13	A	A	T	C	T	0.023	1.04(0.92-1.16)	0.548	0.023	1.05(0.91-1.20)	0.494	0.023	1.11(0.90-1.37)	0.318
Haplo.14	-	A	T	C	C	0.148	1.02(0.97-1.08)	0.445	0.149	1.03(0.96-1.09)	0.447	0.153	1.03(0.92-1.14)	0.618
Haplo.15	A	A	T	T	C	0.029	0.97(0.88-1.08)	0.596	0.030	0.97(0.86-1.10)	0.654	0.030	0.96(0.80-1.16)	0.697
Haplo.rare	*	*	*	*	*	0.060	1.20(1.13-1.28)	7.0×10^{-9}	0.060	1.26(1.17-1.35)	6.1×10^{-10}	0.058	1.09(0.96-1.22)	0.183

Abbreviations: ER, estrogen receptor; OR, odds ratio; CI, confidence interval.

[a] SNPs1-5 represent signals rs35961416, rs13281615, rs7815245, rs2033101, and rs11780156, respectively; effect alleles are shown in bold.

[b] Haplotype frequency.

[c] Adjusted for age, study site, and principal components.

Table 4. Association of top SNPs identified in women of European and non-European ancestry with breast cancer risk among women of Asian (6,269 cases and 6,624 controls) and African ancestry (1,116 cases and 932 controls).

Top SNPs	Alleles[a]	Univariate Analysis (Asian)			Univariate Analysis (African)		
		EAF	OR(95% CI)[b]	*P*[b]	EAF	OR(95% CI)[b]	*P*[b]
Identified in women of European ancestry							
rs35961416	**A**/-	0.10	1.01(0.91-1.13)	0.804	0.39	0.85(0.73-0.99)	0.040
rs13281615	**G**/A	0.53	1.02(0.97-1.08)	0.357	0.44	1.02(0.90-1.16)	0.721
rs7815245[c]	**T**/C	0.17	0.96(0.89-1.02)	0.202	0.36	0.99(0.87-1.13)	0.908
rs2033101	**T**/C	0.33	1.00(0.95-1.05)	0.957	0.09	0.85(0.67-1.07)	0.174
rs11780156	**T**/C	0.20	0.99(0.93-1.06)	0.842	0.04	0.97(0.70-1.34)	0.838
Identified in women of non-European ancestry							
rs16901629	**G**/A	0.14	1.12(1.03-1.22)	6.6×10^{-3}	0.38	1.07(0.92-1.24)	0.407
rs974451	**A**/G	0.23	0.91(0.85-0.96)	1.4×10^{-3}	0.56	0.99(0.88-1.13)	0.915
rs7014860	**C**/A	0.24	1.14(1.03-1.25)	9.8×10^{-3}	0.25	1.01(0.83-1.24)	0.896
rs979200	**C**/T	0.45	1.07(1.02-1.13)	8.2×10^{-3}	0.67	1.09(0.95-1.24)	0.230
rs16901857	**G**/A	0.24	1.08(1.02-1.15)	6.6×10^{-3}	0.08	1.02(0.82-1.28)	0.841
rs75127456	A/C	0.10	0.89(0.81-0.97)	8.9×10^{-3}	0.07	0.92(0.71-1.19)	0.524
rs56005245	**C**/T	0.26	1.09(1.03-1.16)	2.5×10^{-3}	0.37	1.02(0.89-1.16)	0.780
chr8:128272219:I	**A**/AG	0.04	1.32(1.10-1.59)	2.9×10^{-3}	0.12	1.04(0.83-1.32)	0.715
rs28392817	**T**/G	0.17	1.10(1.03-1.18)	7.1×10^{-3}	0.78	1.1(0.94-1.28)	0.237
rs4733807	**A**/G	0.12	0.89(0.82-0.96)	3.6×10^{-3}	0.16	0.99(0.83-1.18)	0.907
rs55971392	**G**/A	0.10	0.88(0.8-0.96)	4.5×10^{-3}	0.04	0.88(0.61-1.27)	0.501
rs35686742	**C**/T	0.09	0.87(0.79-0.96)	4.4×10^{-3}	0.03	0.91(0.62-1.32)	0.619
rs6988558	**G**/C	0.44	0.98(0.93-1.04)	0.476	0.49	0.83(0.73-0.96)	9.6×10^{-3}
rs73356177	**A**/G	0.05	1.05(0.93-1.19)	0.426	0.10	1.36(1.11-1.67)	2.8×10^{-3}
rs1516964	**C**/T	0.04	0.88(0.76-1.01)	0.072	0.09	0.67(0.51-0.89)	6.1×10^{-3}
rs56142222	**G**/A	0.03	1.08(0.92-1.25)	0.351	0.22	1.22(1.05-1.42)	9.8×10^{-3}

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

[a] Effect/reference allele; effect alleles are shown in bold.

[b] Adjusted for study site and two principal components for each population.

[c] Except for r^2 of 0.23 and 0.43 for linkage disequilibrium between rs7815245 and the index SNP rs13281615 in Asians and African American, all other SNPs are not in LD with either of the index SNPs rs13281615 or rs11780156 in non-European populations ($r^2 < 0.02$).

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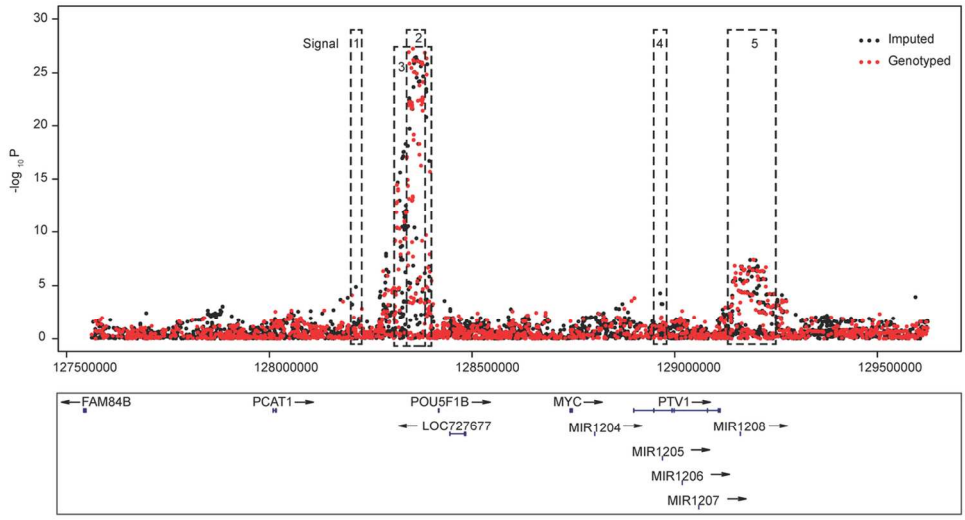

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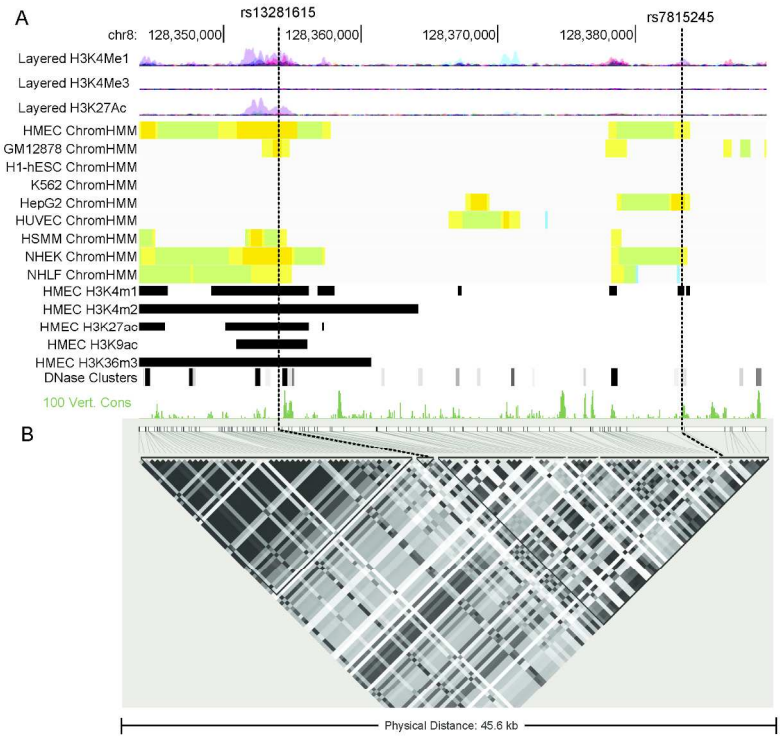

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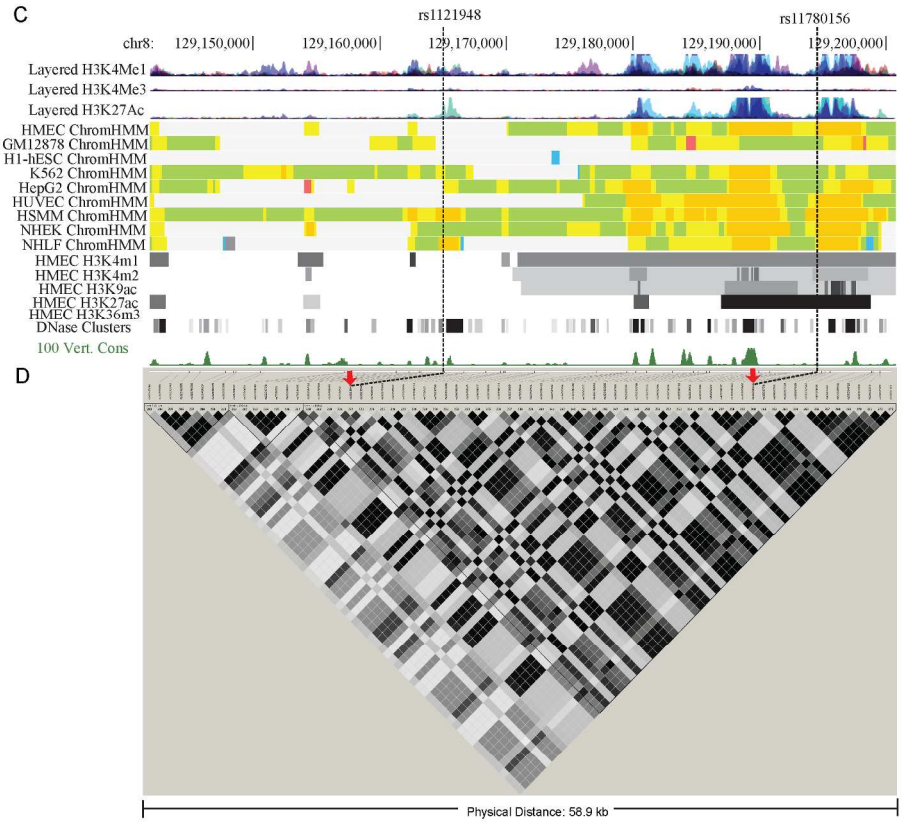

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