Ten variants associated with risk of estrogen receptor negative breast cancer

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Most common breast cancer susceptibility variants have been identified through genome-wide association studies (GWASs) of predominantly estrogen receptor (ER)-positive disease. We conducted a GWAS using 21,468 ER-negative cases and 100,594 controls combined with 18,908 *BRCA1* mutation carriers (9,414 with breast cancer), all of European origin. We identified independent associations at $P<5x10^{-8}$ with 10 variants at nine novel loci. At P<0.05, we replicated associations with 10 of 11 variants previously reported in ER-negative or *BRCA1* mutation carrier GWASs, and confirmed ER-negative disease associations for 105 susceptibility variants identified by other breast cancer GWASs. These 125 variants explain approximately 16% of the familial risk of this breast cancer subtype. There was high genetic correlation (0.72) between risk of ER-negative breast cancer and breast cancer risk for *BRCA1* carriers. These findings will lead to improved risk prediction and inform further fine-mapping and functional work to better understand the biological basis of ER-negative breast cancer.

GWASs have identified 107 single nucleotide polymorphisms (SNPs) that are independently associated with breast cancer risk[1-31]. Association studies focused on ER-negative disease, or *BRCA1* mutation carriers, who are more likely to develop ER-negative disease (70-80% of cases)[32], have identified 11 of these SNPs[2,8,11,18,28,29]. We aimed to discover additional ER-negative breast cancer susceptibility variants by performing a GWAS in women of European origin.

New genotyping data were generated for 9,655 ER-negative cases and 45,494 controls from 68 Breast Cancer Association Consortium (BCAC) studies and 15,566 *BRCA1* mutation carriers (7,784 with breast cancer) from 58 Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) studies (Supplementary Tables 1 and 2) using the Illumina OncoArray beadchip, a 570K SNP custom array with genome-wide coverage[33]. Imputation was used to derive estimated genotypes for ~21M SNPs, using the 1000 Genomes Project (Phase 3) as reference; ~11.5M of those with imputation $r^2>0.3$ and minor allele frequency (MAF)>0.005 were included in further analyses. For BCAC data, we estimated per-allele odds ratios (ORs) using logistic regression, adjusting for country and principal components. For CIMBA data, we estimated per-allele hazard ratios (HR) using a retrospective cohort analysis framework, modelling time to breast cancer and stratifying on country, Ashkenazi Jewish origin and birth cohort (see Online Methods). These analyses were also applied to an independent set of previously generated data from other genome-wide genotyping of additional European participants in 44 BCAC studies (11,813 ER-negative cases and 55,100 controls) and 54 CIMBA studies (3,342 *BRCA1* mutation carriers, 1,630 with breast cancer) (Supplementary Tables 1 and 2). Fixed-effects meta-analysis was used to combine results across genotyping initiatives within consortia and, assuming that the OR and HR estimates approximate the same underlying relative risk, across consortia.

Results from the combined meta-analysis are summarised in Supplementary Figure 1. There was minimal inflation of test statistics (lambda1000=1.004; Supplementary Figure 2). We identified 10 variants at nine novel loci that were independently associated with risk of ER-negative breast cancer at $P<5x10^{-8}$ (Table 1; Supplementary Table 3; Supplementary Figures 3-10). Two independent signals were observed within 12kb at 11q22.3, for rs74911261 (MAF=0.02) and rs11374964 (MAF=0.42); OR estimates and statistical significance were largely unchanged when

each variant was adjusted for the other (Supplementary Table 4). The association with 8p23.3-rs66823261 was not observed for *BRCA1* mutation carriers (P=0.32, P-heterogeneity=0.030).

For each of these 10 novel signals, we identified candidate causal SNPs analytically (see Online Methods) and combined multiple sources of *in silico* functional annotation from public databases to identify likely functional variants and target genes. Results are summarised in Supplementary Table 5 (including UCSC Genome Browser links; see also Supplementary Note 1), Figure 1 and Supplementary Figures 3-10 (data sources in Supplementary Table 6). Many candidate causal SNPs lie in predicted regulatory regions and are associated with expression of nearby genes in blood or other tissues. At 2p23, the predicted target genes include *ADCY3* and *NCOA1* (Supplementary Figure 3). At 6q23.1 (Supplementary Figure 4), the most plausible target gene is *L3MBTL3*[34]. A predicted target at 8q24.13 is *FBXO32*, which is expressed in ER-negative HMECs but not ER-positive MCF7 breast cancer cells (Supplementary Figure 6) and has a known role in cancer cachexia[35]. At 11q22.3 (Figure 1), a predicted target gene of common risk-associated variants is *NPAT*[36]. The rarer SNPs underlying the other 11q22.3 signal are predicted to target *ATM*, a known breast cancer susceptibility gene[37]. Three rare coding variants (MAF≤0.03) in *ATM, NPAT* and *KDELC2*, are also among the candidate causal SNPs at this locus. At 16p13, predicted target genes include *ADCY9* and *CREBBP* (Supplementary Figure 7). At 19q12 (Supplementary Figure 10), a potential target gene encodes cyclin E1 which is involved in cell cycle control and phosphorylation of NPAT[38].

Expression QTL associations were assessed between each candidate causal variant and genes within 1Mb using 79 ER-negative breast tumours from TCGA and 135 normal breast tissue samples from METABRIC[39-41]. The strongest associations identified were 6q23.1-rs6569648-*L3MBTL3* ($P=4.3\times10^{-6}$) and 18q12.1-rs12965632-*CDH2* ($P=1.0\times10^{-4}$), both in METABRIC (Supplementary Table 5). SNP rs6569648 was the top *cis*-eQTL (of all imputed variants within 1 Mb) for *L3MBTL3* while the p-value for the rs12965632-*CDH2* eQTL was within two orders of magnitude of the top *cis*-eQTLs for this gene (Supplementary Figures 11-12).

For 10 of the 11 variants previously identified through GWASs of ER-negative disease or overall disease in *BRCA1* mutation carriers[2,8,11,17,18,29,30], or reported as more strongly associated with ER-negative breast cancer[28], associations with ER-negative disease were replicated (P<0.05) using OncoArray data from BCAC, which does not overlap with any of the discovery studies (Table 2). Effect sizes were generally similar to those originally reported. Using all available CIMBA data, six of these 11 variants were associated with breast cancer risk (P<0.05) for *BRCA1* mutation carriers (Table 2). No evidence of association was observed for 20q11-rs2284378[11] in either BCAC or CIMBA (P≥0.46).

Based on estimated ORs using BCAC data for all cases with known ER status (16,988 ER-negative; 65,275 ER-positive), all 10 new and 10 previously reported and replicated ER-negative disease susceptibility SNPs were more strongly associated with risk of ER-negative than ER-positive subtype (P-heterogeneity<0.05, except for novel hit 19p13.2-rs322144; Supplementary Table 7). Two variants (1q32.1-rs4245739 and 19p13.11-rs67397200) were not associated with ER-positive disease. For four variants (11q22.3- rs11374964, 11q22.3-rs74911261, 1q32.1-

rs6678914 and 2p23.2-rs4577244), the risk-associated allele for ER-negative disease was associated with reduced risk of ER-positive disease (P<0.05).

For these 20 ER-negative breast cancer susceptibility SNPs, we also assessed associations by triple-negative (TN) status (negative for ER, progesterone receptor and HER2; Table 3), tumour grade (Table 4) and age at diagnosis (Supplementary Table 8) using BCAC data only. Five, including the novel susceptibility variants 11q22.3-rs11374964 and 11q22.3-rs74911261, were more strongly associated with risk of both TN and higher-grade disease (P<0.05), although after adjustment for TN status, heterogeneity by grade was observed only for 11q22.3-rs74911261 and 1q32.1-rs4245739 (P<0.05). For 2p23.3-rs4577244, heterogeneity was observed for grade only, while 6q25.2-rs2747652 was more strongly associated with risk of other (non-TN) ER-negative breast cancer subtypes (P<0.05). At younger ages, associations appeared to be stronger for two variants (5p15.33-rs10069690 and 19p13.11-rs67397200), and weaker for one (6q25.2-rs2747652) (P<0.05).

Elsewhere we report 65 novel susceptibility loci for overall breast cancer[42]. Three of these overlap within 500kb with the novel ER-negative disease-associated loci reported here (variants 2p23.3-rs200648189, 6q23.1-rs6569648 and 8q24.13-rs17350191). We assessed associations with risk of ER-negative disease, and with risk of overall breast cancer for *BRCA1* mutation carriers, for SNPs at the remaining 62 loci, as well as for the 96 previously reported breast cancer susceptibility variants that were not ER-negative specific. Of these 158 SNPs, 105 were associated (P<0.05) with risk of ER-negative breast cancer, and 24 with risk for *BRCA1* mutation carriers (Supplementary Tables 9-10). Results for *BRCA2* mutation carriers are presented in Supplementary Table 11.

Pathway analysis based on mapping each SNP to the nearest gene was performed using summary association statistics from the meta-analysis of BCAC and CIMBA data combined (see Online Methods). This identified several pathways implicated in ER-negative disease (enrichment score [ES]>0.4086; Supplementary Figure 13; Supplementary Tables 12-13), including a subset that was not enriched in susceptibility to ER-positive disease (ES<0; Supplementary Table 14). One of the latter subsets was the adenylate cyclase (AC) activating pathway (ES=0.62; Supplementary Figure 14). Two of the predicted target genes for the 10 novel ER-negative breast cancer susceptibility variants, based on the eQTL analysis (Supplementary Table 5), *ADCY3* (P[TCGA]=6.7×10^{-3}] and *ADCY9* (P[METABRIC]=1.3×10^{-4}), are part of this pathway, and their association signals were critical to the elevated ES observed (Supplementary Figure 13). ADCY9 is stimulated by β2 adrenergic receptor (β2AR) signalling[43] in ER-negative breast cancer[44], which in turn drives AC-cAMP signalling, including for example mitogenic signalling through β-arrestin-Src-ERK[45].

To further explore the functional properties of the genome that contribute to ER-negative breast cancer heritability, we conducted a partitioned heritability analysis using linkage disequilibrium (LD) score regression[46]. Considering 52 “baseline” genomic features, we observed the greatest enrichment for super-enhancers (2.5-fold, $p=2\times10^{-7}$) and the H3K4me3 histone mark (2.4-fold, p=0.0005), with 33% depletion (p=0.0002) observed for repressed regions (Supplementary Table 15). No differences in enrichment for these features were observed between susceptibility to ER-negative and ER-positive breast cancer, but baseline genomic features are not

specific to cell type[46]. The estimated correlation between ER-negative and ER-positive breast cancer based on ~1M common genetic variants[47] was 0.60 (standard error [SE], 0.03) indicating that, although these two breast cancer subtypes have a shared genetic component, a substantial proportion is distinct. The estimated correlation between ER-negative disease in the general population and overall breast cancer for *BRCA1* mutation carriers was 0.72 (SE, 0.11).

In summary, in this study of women of European origin, we have identified 10 novel susceptibility variants for ER-negative breast cancer and replicated associations with ER-negative disease for 10 SNPs identified by previous GWASs. Most of these were not associated, or more weakly associated, with ER-positive disease, consistent with the findings from pathway and partitioned heritability analyses showing that ER-negative breast cancer has a partly distinct genetic aetiology. We also confirmed associations with ER-negative disease for a further 105 susceptibility SNPs. Together, these 125 variants explain ~14% of an assumed 2-fold increased risk of developing ER-negative disease for the first degree female relatives of women affected with this subtype (the newly identified SNPs explain ~1.5%); Supplementary Table 16) and ~40% of the estimated familial risk that is attributable to all variants imputable from the Oncoarray (see Online Methods). We have also identified nine novel breast cancer susceptibility variants for *BRCA1* mutation carriers and confirmed associations for a further 30 previously reported SNPs; these 39 variants explain ~8% of the variance in polygenic risk for carriers of these mutations (Supplementary Table 17). However, the lower number of *BRCA1* risk-associated variants may merely be a consequence of the smaller sample size, since the genetic correlation with ER-negative breast cancer is high. These findings will inform improved risk prediction, both for the general population and for *BRCA1* mutation carriers[29,48,49]. Further investigation is required for other populations of non-European origin. Fine-mapping and functional studies should lead to a better understanding of the biological basis of ER-negative breast cancer, and perhaps inform the design of more effective preventive interventions, early detection and treatments for this disease.

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Competing Financial Interests

The authors confirm that they have no competing financial interests

Table 1: Ten novel loci associated with risk of estrogen receptor (ER)-negative breast cancer using meta-analysis of BCAC and CIMBA data

Location	SNP	Chr	Position	Nearest gene	Alleles[#]	BCAC ER-negative[†]			CIMBA *BRCA1* mutation carriers[‡]			Meta-analysis	Heterogeneity
						MAF	OR (95%CI)	P-value	MAF	HR (95%CI)	P-value	P-value	P-value[¥]
2p23.3	rs200648189	2	24739694	*NCOA1*	CT/C	0.19	0.94 (0.91-0.97)	4.7×10^{-4}	0.20	0.88 (0.84-0.92)	3.3×10^{-7}	9.7×10^{-9}	2.0×10^{-2}
6q23.1	rs6569648	6	130349119	*L3MBTL3*	T/C	0.23	0.93 (0.90-0.95)	4.3×10^{-8}	0.22	0.94 (0.90-0.98)	5.4×10^{-3}	8.3×10^{-10}	0.64
8p23.3	rs66823261	8	170692	*RPL23AP53*	T/C	0.23	1.09 (1.06-1.12)	5.6×10^{-9}	0.22	1.02 (0.98-1.07)	0.32	3.3×10^{-8}	3.0×10^{-2}
8q24.13	rs17350191	8	124757661	*ANXA13*	C/T	0.34	1.07 (1.04-1.09)	2.0×10^{-8}	0.34	1.08 (1.04-1.12)	1.9×10^{-4}	1.7×10^{-11}	0.81
11q22.3	rs11374964	11	108345515	*KDELC2*	G/GA	0.42	0.94 (0.92-0.96)	3.6×10^{-8}	0.43	0.91 (0.88-0.95)	1.3×10^{-6}	4.1×10^{-13}	0.26
11q22.3	rs74911261	11	108357137	*KDELC2*	G/A	0.02	0.82 (0.75-0.89)	2.3×10^{-6}	0.02	0.74 (0.65-0.84)	2.0×10^{-6}	5.4×10^{-11}	0.17
16p13.3	rs11076805	16	4106788	*ADCY9*	C/A	0.25	0.92 (0.90-0.95)	2.2×10^{-8}	0.25	0.96 (0.92-1.00)	0.073	1.4×10^{-8}	0.14
18q12.1	rs36194942	18	25401204	*CDH2*	A/AT	0.30	0.94 (0.91-0.96)	2.5×10^{-7}	0.31	0.95 (0.91-0.99)	1.4×10^{-2}	1.4×10^{-8}	0.50
19p13.2	rs322144	19	11423703	*TSPAN16*	C/G	0.47	0.95 (0.93-0.97)	2.4×10^{-5}	0.46	0.92 (0.89-0.96)	3.7×10^{-5}	7.4×10^{-9}	0.23
19q12	rs113701136	19	30277729	*CCNE1*	C/T	0.32	1.07 (1.04-1.09)	1.7×10^{-7}	0.32	1.05 (1.01-1.09)	1.2×10^{-2}	6.8×10^{-9}	0.57

[#]More common allele listed first, minor allele second; [†]Combined data from 21,468 ER-negative cases and 100,594 controls of European ancestry from the Breast Cancer Association Consortium (BCAC); [‡]Combined data from 18,908 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), 9,414 of whom had developed breast cancer; [¥]Test for heterogeneity in effect size for ER-negative disease and overall disease for *BRCA1* mutation carriers

Chr, chromosome; MAF, minor allele frequency; OR, odds ratio per copy of the minor allele; CI, confidence interval; HR, hazard ratio per copy of the minor allele

Table 2: Previously reported estrogen receptor (ER)-negative hits: replication using independent data from BCAC and combined results using all BCAC and CIMBA data

Location	SNP	Chr	Position	Ref	Nearest gene	Alleles[#]	INDEPENDENT REPLICATION			ALL AVAILABLE DATA COMBINED			
							BCAC ER-negative (OncoArray)*			BCAC ER-negative[†]		CIMBA *BRCA1*[‡]	
							MAF	OR (95%CI)	P-value	OR (95%CI)	P-value	HR (95%CI)	P-value
1q32.1	rs6678914	1	202187176	[18]	*LGR6*	G/A	0.41	0.94 (0.91-0.97)	1.1×10^{-4}	0.92 (0.90-0.94)	2.6×10^{-12}	0.98 (0.95-1.02)	0.31
1q32.1	rs4245739	1	204518842	[18]	*MDM4*	A/C	0.26	1.12 (1.09-1.17)	9.2×10^{-11}	1.14 (1.11-1.16)	3.1×10^{-23}	1.09 (1.04-1.13)	7.3×10^{-5}
2p24.1	rs12710696	2	19320803	[18]	*MIR4757*	C/T	0.37	1.04 (1.00-1.07)	2.5×10^{-2}	1.06 (1.04-1.09)	6.5×10^{-8}	1.01 (0.98-1.05)	0.49
2p23.2	rs4577244[‡]	2	29120733	[29]	*WDR43*	C/T	0.34	0.93 (0.89-0.96)	9.6×10^{-5}	0.92 (0.90-0.95)	1.5×10^{-9}	0.92 (0.88-0.96)	1.3×10^{-4}
5p15.33	rs10069690	5	1279790	[8,17]	*TERT*	C/T	0.26	1.19 (1.14-1.23)	3.8×10^{-21}	1.18 (1.15-1.21)	1.5×10^{-35}	1.18 (1.14-1.23)	3.7×10^{-16}
6q25.1	rs3757322[‡]	6	151942194	[28]	*ESR1*	T/G	0.32	1.14 (1.10-1.18)	5.5×10^{-14}	1.15 (1.12-1.18)	2.8×10^{-31}	1.14 (1.10-1.19)	2.9×10^{-12}
6q25.2	rs2747652[‡]	6	152437016	[28]	*ESR1*	C/T	0.48	0.92 (0.89-0.95)	1.1×10^{-7}	0.91 (0.89-0.93)	1.9×10^{-18}	1.00 (0.97-1.04)	0.96
13q22.1	rs6562760[‡]	13	73957681	[29]	*KLF5*	G/A	0.24	0.92 (0.88-0.95)	5.0×10^{-6}	0.92 (0.90-0.95)	8.7×10^{-10}	0.89 (0.86-0.93)	3.5×10^{-7}
16q12.2	rs11075995	16	53855291	[18]	*FTO*	T/A	0.30	1.07 (1.03-1.11)	3.3×10^{-4}	1.09 (1.06-1.12)	1.0×10^{-10}	1.01 (0.97-1.06)	0.49
19p13.11	rs67397200	19	17401404	[2,30]	*ANKLE1*	C/G	0.32	1.17 (1.13-1.21)	7.0×10^{-20}	1.17 (1.14-1.19)	2.7×10^{-37}	1.18 (1.14-1.23)	2.7×10^{-17}
20q11.21	rs2284378	20	32588095	[11]	*RALY*	C/T	0.32	0.99 (0.95-1.02)	0.46	1.03 (1.01-1.06)	1.7×10^{-2}	1.00 (0.97-1.04)	0.81

[#]More common allele listed first, minor allele second; *Includes Breast Cancer Association Consortium (BCAC) OncoArray data from 9,655 ER-negative cases and 45,494 controls cases and controls not included in previously published studies; [†]Combined data from 21,468 ER-negative cases and 100,594 controls of European ancestry from BCAC, which includes overlapping samples with previous publications for all SNPs; [‡]Combined data from 18,908 *BRCA1* mutation carriers from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), 9,414 of whom had developed breast cancer - includes overlapping samples with previous publications for SNPs rs4577244, rs3757322, rs2747652 and rs6562760

Chr, chromosome; Ref, publication(s) in reference list in which the association was identified; MAF, minor allele frequency; OR, odds ratio per copy of the minor allele; CI, confidence interval; HR, hazard ratio per copy of the minor allele

Table 3: Associations for 10 novel and 10 previously reported (and replicated) ER-negative breast cancer susceptibility loci, by triple-negative status (BCAC data only: ER-negative cases‡, all controls))

Location	SNP	Triple-negative		Other ER-negative		Heterogeneity
		OR (95%CI)	P-value	OR (95%CI)	P-value	P-value*
Loci identified by the present study						
2p23.3	rs200648189	0.95 (0.90-1.00)	4.8×10^{-2}	0.96 (0.91-1.03)	0.24	0.36
6q23.1	rs6569648	0.93 (0.89-0.97)	1.4×10^{-3}	0.93 (0.88-0.98)	5.6×10^{-3}	0.91
8p23.3	rs66823261	1.11 (1.05-1.16)	3.3×10^{-5}	1.12 (1.07-1.19)	2.4×10^{-5}	0.91
8q24.13	rs17350191	1.07 (1.03-1.11)	7.9×10^{-4}	1.07 (1.02-1.12)	4.0×10^{-3}	0.67
11q22.3	rs11374964	0.88 (0.85-0.91)	1.9×10^{-11}	0.99 (0.95-1.04)	0.75	1.5×10^{-5}
11q22.3	rs74911261	0.76 (0.66-0.87)	1.1×10^{-4}	0.98 (0.84-1.13)	0.76	3.0×10^{-2}
16p13.3	rs11076805	0.91 (0.87-0.96)	1.5×10^{-4}	0.95 (0.90-1.00)	4.5×10^{-2}	0.20
18q12.1	rs36194942	0.93 (0.89-0.96)	2.4×10^{-4}	0.92 (0.88-0.97)	9.9×10^{-4}	0.94
19p13.2	rs322144	0.94 (0.91-0.98)	5.9×10^{-3}	0.94 (0.90-0.98)	9.7×10^{-3}	0.68
19q12	rs113701136	1.10 (1.06-1.15)	9.1×10^{-7}	1.07 (1.02-1.12)	4.4×10^{-3}	0.12
Previously reported loci (associations replicated by the present study)						
1q32.1	rs6678914	0.94 (0.91-0.98)	2.1×10^{-3}	0.91 (0.87-0.95)	2.0×10^{-5}	0.45
1q32.1	rs4245739	1.18 (1.13-1.23)	4.3×10^{-15}	1.04 (1.00-1.10)	7.5×10^{-2}	6.5×10^{-4}
2p24.1	rs12710696	1.07 (1.03-1.11)	1.1×10^{-3}	1.04 (1.00-1.09)	6.1×10^{-2}	0.52
2p23.2	rs4577244	0.90 (0.86-0.94)	5.3×10^{-6}	0.94 (0.89-0.99)	1.9×10^{-2}	0.15
5p15.33	rs10069690	1.28 (1.23-1.33)	2.4×10^{-33}	1.07 (1.02-1.12)	5.4×10^{-3}	5.6×10^{-8}
6q25.1	rs3757322	1.15(1.10-1.19)	4.3×10^{-12}	1.14(1.10-1.20)	4.8×10^{-9}	0.35
6q25.2	rs2747652	0.93(0.89-0.96)	5.7×10^{-5}	0.87(0.83-0.91)	2.9×10^{-10}	9.6×10^{-3}
13q22.1	rs6562760	0.94 (0.90-0.98)	2.8×10^{-3}	0.92 (0.87-0.96)	8.8×10^{-4}	0.46
16q12.2	rs11075995	1.06 (1.02-1.11)	6.5×10^{-3}	1.08 (1.03-1.13)	3.1×10^{-3}	0.81
19p13.11	rs67397200	1.27 (1.22-1.32)	2.0×10^{-32}	1.05 (1.01-1.10)	2.7×10^{-2}	4.7×10^{-10}

‡Combined Breast Cancer Association Consortium (BCAC) data from 6,877 triple-negative and 4,467 other ER-negative cases and 83,700 controls; *ER-negative case-only analysis, by triple-negative status; OR, odds ratio per copy of the minor allele; CI, confidence interval

Table 4: Associations for 10 novel and 10 previously reported (and replicated) ER-negative breast cancer susceptibility loci, by grade (BCAC data only: ER-negative cases‡, all controls)

Location	SNP	Grade 1		Grade 2		Grade 3		Heterogeneity P-value*
		OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	
Loci identified by the present study								
2p23.3	rs200648189	1.11 (0.92-1.33)	0.28	0.95 (0.88-1.03)	0.23	0.96 (0.91-1.00)	$6.8x10^{-2}$	0.70
6q23.1	rs6569648	0.93 (0.79-1.09)	0.37	0.93 (0.87-0.99)	$1.6x10^{-2}$	0.94 (0.91-0.98)	$3.8x10^{-3}$	0.34
8p23.3	rs66823261	1.13 (0.96-1.34)	0.14	1.12 (1.04-1.19)	$1.2x10^{-3}$	1.10 (1.05-1.15)	$1.3x10^{-5}$	0.11
8q24.13	rs17350191	1.16 (1.01-1.34)	$3.0x10^{-2}$	1.05 (0.99-1.11)	0.10	1.09 (1.05-1.12)	$4.1x10^{-6}$	0.94
11q22.3	rs11374964	0.91 (0.79-1.04)	0.16	0.99 (0.94-1.05)	0.85	0.93 (0.90-0.96)	$1.3x10^{-5}$	$3.0x10^{-2}$
11q22.3	rs74911261	1.22 (0.81-1.84)	0.35	0.89 (0.73-1.07)	0.21	0.74 (0.65-0.85)	$7.4x10^{-6}$	$6.7x10^{-4}$
16p13.3	rs11076805	0.90 (0.76-1.06)	0.21	0.93 (0.87-0.99)	$3.2x10^{-2}$	0.92 (0.88-0.95)	$4.5x10^{-5}$	0.71
18q12.1	rs36194942	0.97 (0.84-1.13)	0.73	0.93 (0.88-0.99)	$2.2x10^{-2}$	0.96 (0.92-0.99)	$2.3x10^{-2}$	0.98
19p13.2	rs322144	0.94 (0.81-1.08)	0.38	0.95 (0.90-1.01)	0.11	0.96 (0.93-1.00)	$6.4x10^{-2}$	0.48
19q12	rs113701136	1.02 (0.89-1.18)	0.77	1.06 (1.01-1.13)	$3.0x10^{-2}$	1.10 (1.06-1.14)	$2.5x10^{-7}$	0.12
Previously reported loci (associations replicated by the present study)								
1q32.1	rs6678914	0.95 (0.83-1.09)	0.46	0.90 (0.85-0.95)	$9.3x10^{-5}$	0.92 (0.89-0.95)	$1.2x10^{-6}$	0.75
1q32.1	rs4245739	1.02 (0.88-1.19)	0.75	1.05 (0.99-1.12)	$8.7x10^{-2}$	1.18 (1.14-1.22)	$2.5x10^{-18}$	$4.3x10^{-5}$
2p24.1	rs12710696	1.08 (0.94-1.23)	0.28	1.10 (1.04-1.16)	$9.6x10^{-4}$	1.04 (1.01-1.08)	$1.6x10^{-2}$	0.28
2p23.2	rs4577244	1.02 (0.88-1.20)	0.77	0.95 (0.89-1.01)	$9.4x10^{-2}$	0.90 (0.86-0.93)	$1.2x10^{-7}$	$4.0x10^{-2}$
5p15.33	rs10069690	0.96 (0.83-1.12)	0.64	1.07 (1.01-1.14)	$2.2x10^{-2}$	1.21 (1.17-1.26)	$1.5x10^{-24}$	$7.3x10^{-4}$
6q25.1	rs3757322	1.16 (1.01-1.34)	0.04	1.13 (1.07-1.20)	$7.5x10^{-6}$	1.18 (1.14-1.22)	$4.5x10^{-20}$	0.16
6q25.2	rs2747652	0.86 (0.75-0.98)	0.02	0.92 (0.87-0.97)	$1.9x10^{-3}$	0.90 (0.87-0.93)	$1.6x10^{-9}$	0.61
13q22.1	rs6562760	0.98 (0.84-1.15)	0.82	0.92 (0.87-0.98)	$1.4x10^{-2}$	0.91 (0.88-0.95)	$1.2x10^{-5}$	0.52
16q12.2	rs11075995	1.16 (1.00-1.35)	$4.7x10^{-2}$	1.09 (1.02-1.15)	$7.5x10^{-3}$	1.08 (1.04-1.13)	$5.2x10^{28}$	0.42
19p13.11	rs67397200	1.01 (0.87-1.16)	0.91	1.08 (1.02-1.14)	$9.8x10^{-3}$	1.22 (1.18-1.26)	$5.3x10^{-37}$	$1.3x10^{-3}$

‡Combined Breast Cancer Association Consortium (BCAC) data from 492 grade 1, 3,243 grade 2 and 8,568 grade 3 cases and 82,347 controls; * ER-negative case-only analysis of BCAC data, by grade (trend test, 1df); OR, odds ratio per copy of the minor allele; CI, confidence interval

Figure legends

Figure 1. Genomic region around the two independent ER negative risk associated variants, 11_108345515_G_A (rs11374964) and 11_108357137_G_A (rs74911261). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants for two independent signals (shown as red or blue tick marks) in relation to RefSeq annotated genes. Missense variants are labelled with asterisks. Breast cell enhancers overlapping candidate SNPs predicted to target nearby genes by IM-PET (He et al., PNAS 2014) are depicted as black bars. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq, histone modification ChIP-seq and DNase hypersensitive site-seq) that overlap candidate variants are shown as red or blue segments, depending on the signal which is intersected. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C (Rao et al., Cell 2014) chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF > 1%) SNPs as red ticks. Supplementary Table 5 provides full details of functional annotation for each risk locus including a link to the UCSC Genome Browser, which allows these features to be examined in more detail.

Supplementary Figure 1. Manhattan plot of associations with breast cancer risk for all imputed and genotyped SNPs using combined data from ER-negative cases and controls and *BRCA1* mutation carriers, before (A) and after (B) excluding known breast cancer susceptibility loci.

Supplementary Figure 2. Quantile-quantile plot of associations with breast cancer risk for all imputed and genotyped SNPs using combined data from ER-negative cases and controls and *BRCA1* mutation carriers.

Supplementary Figure 3. Genomic region around the ER negative risk associated variant 2_24739694_CT_T (rs200648189). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Breast cell enhancers overlapping candidate SNPs predicted to target nearby genes by methods including IM-PET[50] and Hnisz[51] are depicted as black bars. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq, histone modification ChIP-seq and DNase hypersensitive site-seq) that overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) chromatin interactions are represented by black arcs. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 4. Genomic region around the ER negative risk associated variant 6_130349119_T_C (rs6569648). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq and histone modification ChIP-seq) which overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed)

as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 5. Genomic region around the ER negative risk associated variant 8_170692_T_C (rs66823261). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features derived from publicly available transcription factor ChIP-seq which overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position . All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 6. Genomic region around the ER negative risk associated variant 8_124757661_C_T (rs17350191). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq, histone modification ChIP-seq and DNase hypersensitive site-seq) that overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 7. Genomic region around the ER negative risk associated variant 16_4106788_C_A (rs11076805). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Breast cell enhancers overlapping candidate SNPs predicted to target nearby genes

by PreSTIGE[53] are depicted as black bars. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq and histone modification ChIP-seq) which overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 8. Genomic region around the ER negative risk associated variant 18_25401204_A_AT (rs36194942). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Epigenomic features (derived from publicly available transcription factor ChIP-seq, histone modification ChIP-seq and DNase hypersensitive site-seq) that overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 9. Genomic region around the ER negative risk associated variant 19_11423703_C_G (rs322144). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq and DNase hypersensitive site-seq) that overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7

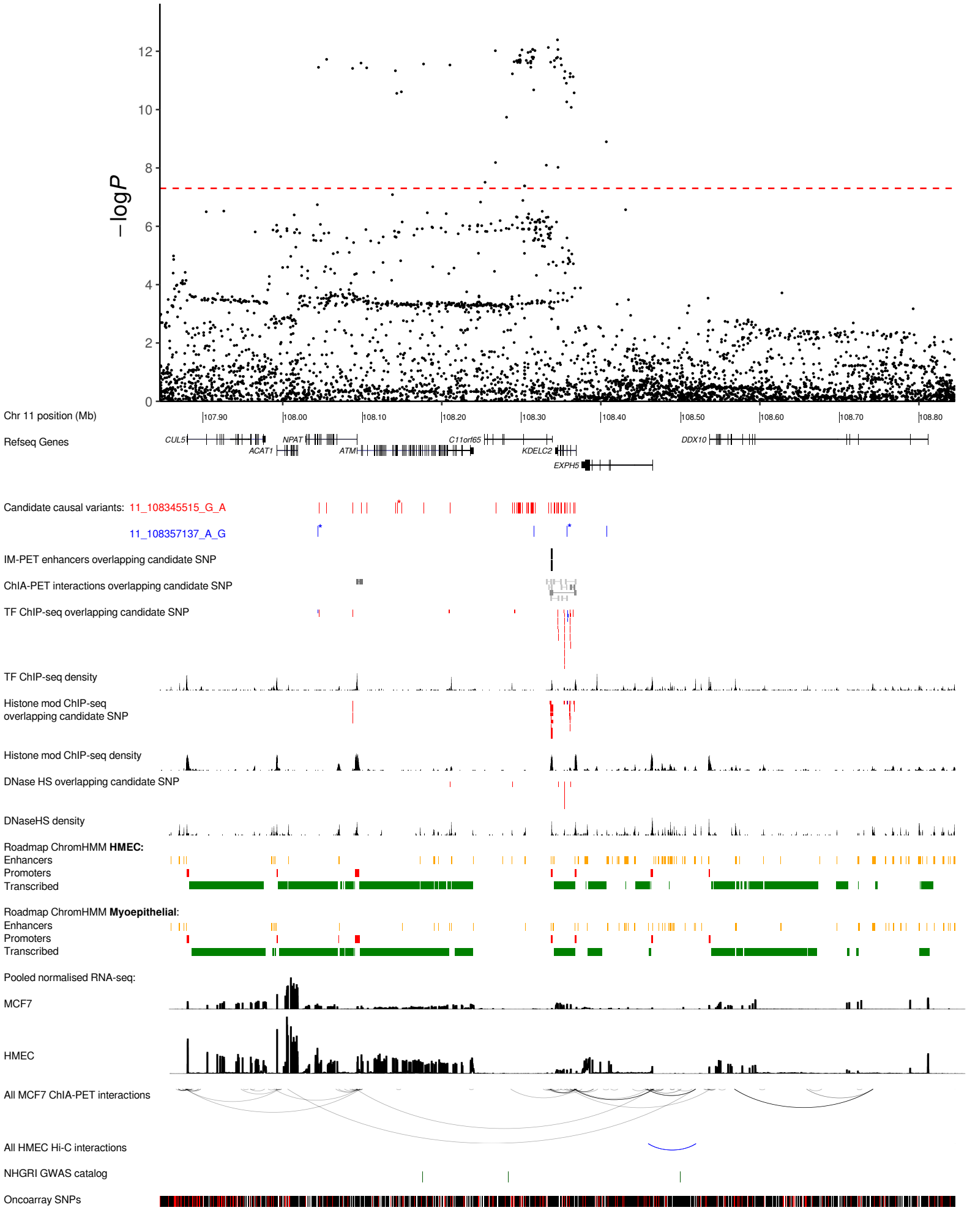
and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 10. Genomic region around the ER negative risk associated variant 19_30277729_C_T (rs113701136). One Mb region showing statistical significance of all genotyped and imputed SNPs (regional Manhattan plot) and positions of candidate causal variants in relation to RefSeq annotated genes. Chromatin interactions from ENCODE ChIA-PET experiments in MCF7 cells overlapping candidate variants are depicted as boxes connected by thin lines and shaded to reflect the confidence score of the interaction. Epigenomic features (derived from publicly available transcription factor ChIP-seq, histone modification ChIP-seq and DNase hypersensitive site-seq) that overlap candidate variants are shown as red segments. Density tracks show the summed occurrence of transcription factor ChIP-seq, histone modification ChIP-seq, and DNase hypersensitive site peaks at each genomic position. Roadmap Epigenomics Project chromatin state models for HMEC and myoepithelial cells grouped into enhancer, promoter or transcribed annotations are shown as yellow, red or green segments, respectively. Transcript levels in MCF7 and HMEC cells are represented by histograms depicting the mean of combined and normalised RNA-seq expression level at each genomic position. All MCF7 ChIA-PET (ENCODE) and HMEC Hi-C[52] chromatin interactions are represented by black and blue arcs, respectively. Published GWAS signals from the NHGRI catalog are shown as green ticks. The last track shows tested Oncoarray SNPs (genotyped or imputed) as black ticks and uninterrogated, common (dbSNP 138 EUR MAF>1%) SNPs as red ticks.

Supplementary Figure 11. Regional eQTL association plot for all variants within 1 Mb of gene *L3MTBL3* and expression of gene *L3MTBL3*. Red dots indicate candidate causal risk variants from the meta-analysis of BCAC ER-negative case-control and CIMBA *BRCA1* mutation carrier data.

Supplementary Figure 12. Regional eQTL association plot for all variants within 1 Mb of gene *CDH2* and expression of gene *CDH2*. Red dots indicate candidate causal risk variants from the meta-analysis of BCAC ER-negative case-control and CIMBA *BRCA1* mutation carrier data.

Supplementary Figure 13. Enrichment map for pathways enriched in susceptibility to ER-negative breast cancer. (A) Enriched pathways (enrichment score [ES]>0.4086) are grouped into themes and annotated with genes that appeared to drive the enrichment signal (see Online Methods). (B) Zoom-in on the adenylate cyclase theme. Shaded circles represent pathways (darker red indicates higher ES and larger size denotes a greater number of genes in the pathway) and green lines connect those that are most similar in terms of gene set overlap (>70%), with thicker lines denoting greater similarity.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EXPH5
DDX10
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IM-PET enhancers overlapping candidate SNP
ChIA-PET interactions overlapping candidate SNP
TF ChIP-seq overlapping candidate SNP
TF ChIP-seq density
Histone mod ChIP-seq overlapping candidate SNP
Histone mod ChIP-seq density
DNase HS overlapping candidate SNP
DNaseHS density
Roadmap ChromHMM HMEC:
Enhancers
Promoters
Transcribed
Roadmap ChromHMM Myoepithelial:
Enhancers
Promoters
Transcribed
Pooled normalised RNA-seq:
MCF7
HMEC
All MCF7 ChIA-PET interactions
All HMEC Hi-C interactions
NHGRI GWAS catalog
Oncoarray SNPs