Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses

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Abstract

Breast cancer susceptibility variants frequently show heterogeneity in associations by tumor subtype. To identify novel loci, we performed a genome-wide association study (GWAS) including 133,384 breast cancer cases and 113,789 controls, plus 18,908 *BRCA1* mutation carriers (9,414 with breast cancer) of European ancestry, using both standard and novel methodologies that account for underlying tumor heterogeneity by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status and tumor grade. We identified 32 novel susceptibility loci ($P < 5.0 \times 10^{-8}$), 15 of which showed evidence for associations with at least one tumor feature (false discovery rate < 0.05). Five loci showed associations ($P < 0.05$) in opposite directions between luminal- and non-luminal subtypes. *In-silico* analyses showed these five loci contained cell-specific enhancers that differed between normal luminal and basal mammary cells. The genetic correlations between five intrinsic-like subtypes ranged from 0.35 to 0.80. The proportion of genome-wide chip heritability explained by all known susceptibility loci was 37.6% for triple-negative and 54.2% for luminal A-like disease. These findings provide an improved understanding of genetic predisposition to breast cancer subtypes and will inform the development of subtype-specific polygenic risk scores.

GWAS have identified over 170 independent breast cancer susceptibility loci, many of which show differential associations by tumor subtypes, particularly ER-positive versus ER-negative or triple negative (TN) disease¹⁻³. However, prior GWAS have not simultaneously investigated multiple, correlated tumor markers to identify additional source(s) of etiologic heterogeneity. We performed a breast cancer GWAS using both standard analyses and a novel two-stage polytomous regression method that efficiently characterizes etiologic heterogeneity while accounting for tumor marker correlations and missing data⁴.

The study populations and genotyping are described elsewhere^{1,2,5,6} and in the **Online Methods**. Briefly, we analyzed data from 118,474 cases and 96,201 controls of European ancestry participating in 82 studies from the Breast Cancer Association Consortium (BCAC) and 9,414 affected and 9,494 unaffected *BRCA1* mutation carriers from 60 studies from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) with genotyping data from one of two Illumina genome-wide custom arrays. In analyses of overall breast cancer, we also included summary level data from 11 other breast cancer GWAS (14,910 cases and 17,588 controls) without subtype information. Our study expands upon previous BCAC GWAS¹ with additional data on 10,407 cases and 7,815 controls, an approximate increase of 10% and 9%, respectively. (**Supplementary Tables 1-4**).

The statistical methods are further described in the **Online Methods** and in **Supplementary Figure 1**. To identify single nucleotide polymorphisms (SNPs) for overall breast cancer (invasive, *in situ* or unknown invasiveness) in BCAC, we used standard logistic regression to estimate odds ratios (OR) and 95% confidence-intervals

(CI) adjusting for country and principal components (PCs). iCOGS and OncoArray data were evaluated separately and results combined with those from the 11 other GWAS using fixed-effects meta-analysis.

To identify invasive breast cancer susceptibility SNPs displaying evidence of heterogeneity, we used a novel score-test based on a two-stage polytomous model⁴ that allows flexible, yet parsimonious, modelling of associations in the presence of underlying heterogeneity by ER, PR, HER2 and/or grade (**Online Methods, Supplementary Note**). The model handles missing tumor characteristic data by implementing an efficient Expectation-Maximization algorithm^{4,7}. These analyses were restricted to BCAC controls and invasive cases (**Online Methods**). We fit an additional two-stage model to estimate case-control ORs and 95% CI between the SNPs and intrinsic-like subtypes defined by combinations of ER, PR, HER2 and grade (**Online Methods**): (1) luminal A-like, (2) luminal B/HER2-negative-like, (3) luminal B-like, (4) HER2-enriched-like and (5) TN or basal-like. We analyzed iCOGS and OncoArray data separately, adjusting for PCs and age, and meta-analyzed the results using a fixed-effects model. We evaluated the effect of country using a leave-one-out sensitivity analysis (**Online Methods**).

We used data from the *BRCA1* mutation carriers who are prone to develop TN disease⁸, to estimate per-allele hazard ratios (HRs) within a retrospective cohort analysis framework. We assumed the estimated ORs for BCAC TN cases and the HRs estimated from CIMBA *BRCA1* carriers approximated the same underlying relative risk⁸, and used a fixed-effect meta-analysis to combine these risk estimates (**Online Methods**). We used the two-stage polytomous model to test for heterogeneity in

associations for all newly identified SNPs across subtypes, globally and by tumor-specific markers (**Online Methods**).

Overall, we identified 32 novel independent susceptibility loci marked by SNPs with $P < 5.0 \times 10^{-8}$ (**Figure 1, Supplementary Table 5-7, Supplementary Figure 2-6**): 22 SNPs using standard logistic regression, eight SNPs using the two-stage polytomous model and three SNPs in the CIMBA/BCAC-TN meta-analysis (rs78378222 was also detected by the two-stage polytomous model in BCAC). Fourteen additional significant ($P < 5.0 \times 10^{-8}$) SNPs were excluded, 13 because they lacked evidence of association independent of previously reported susceptibility SNPs in conditional analyses ($P \geq 1.0 \times 10^{-6}$; **Supplementary Table 8-10**), and one (chr22:40042814) for showing a high-degree of sensitivity to leave-one-out country analysis (**Supplementary Figure 7**). **Supplemental figures 8-9** show the associations between all 32 SNPs and the intrinsic-like subtypes.

Fifteen of the 32 SNPs showed evidence of heterogeneity ($FDR < 0.05$) according to the global heterogeneity test (**Figure 2, Supplementary Table 11**). Nine of these were identified in analyses accounting for tumor marker heterogeneity. ER (7 SNPs) and grade (7 SNPs) most often contributed to observed heterogeneity (marker-specific $P < 0.05$), followed by HER2 (4 SNPs) and PR (2 SNPs). rs17215231, identified in the CIMBA/BCAC-TN meta-analysis, was the only SNP found exclusively associated with TN disease ($OR = 0.85$, $95\%CI = 0.81-0.89$; $P = 8.6 \times 10^{-13}$). rs2464195, also identified in the CIMBA/BCAC-TN meta-analysis, was associated with both TN ($OR = 0.93$, $95\%CI = 0.91-0.96$; $P = 2.5 \times 10^{-8}$) and luminal B-like subtypes ($OR = 0.96$, $95\%CI = 0.92-0.99$; $P = 0.02$; **Supplementary Table 7, Supplementary Figure 9**). This SNP is in LD ($r^2 = 0.62$) with

rs7953249, which is differentially associated with risk of subtypes of ovarian cancer⁹.

Five of the heterogeneous SNPs showed associations with luminal and non-luminal subtypes in opposite directions (**Figure 3**). For example, four SNPs were associated in opposite directions with luminal A-like and TN subtypes (respectively, for rs78378222 OR=1.13, 95%CI=1.05-1.20 vs OR=0.67, 95%CI=0.57-0.80; for rs206435 OR=1.03, 95%CI=1.01-1.05 vs OR=0.95, 95%CI=0.92-0.98; for rs141526427 OR=0.96, 95%CI=0.94-0.98 vs OR=1.04, 95%CI=1.01-1.08; and for rs6065254 OR=0.96, 95%CI=0.94-0.97 vs OR=1.04, 95%CI=1.01-1.07). The specific tumor-marker heterogeneity test showed rs78378222 associated with ER ($P_{ER}=7.0 \times 10^{-6}$) and HER2 ($P_{HER2}=2.07 \times 10^{-4}$), rs206435 associated with ER ($P_{ER}=2.8 \times 10^{-3}$) and grade ($P_{grade}=2.8 \times 10^{-4}$) and rs141526427 ($P_{ER}=1.3 \times 10^{-3}$) and rs6065254 ($P_{ER}=4.3 \times 10^{-3}$) associated with ER. rs7924772 showed opposite associations between HER2-negative and HER2-positive subtypes (e.g., OR=1.04, 95%CI=1.03-1.06 for luminal A-like disease and OR=0.95, 95%CI=0.92-0.99 for luminal B-like disease) and, consistent with these findings, was exclusively associated with HER2 ($P_{HER2}=1.4 \times 10^{-6}$; **Figure 3**). Notably, rs78378222 located in the 3' UTR of *TP53* also showed opposite associations with high-grade serous cancers (OR=0.75, $P=3.7 \times 10^{-4}$) and low-grade serous cancers (OR=1.58, $P=1.5 \times 10^{-4}$; <http://ocac.ccge.medschl.cam.ac.uk>). Moreover, prior analyses did not find rs78378222 associated with risk of breast cancer, likely due to its opposite effects between subtypes¹⁰.

We defined a set of candidate causal variants (CCVs; **Online Methods**) for each novel locus and investigated the CCVs in relation to previously-annotated enhancers in primary breast cells¹¹. Based on combinations of H3K4me1 and H3K27ac histone

modification ChIP-seq signals, putative enhancers in basal cells (BC), luminal progenitor cells (LP) and mature luminal cells (LM) were characterized as “OFF,” “PRIMED”, and “ACTIVE” (**Online Methods**). We defined “ANYSWITCH” enhancers as those exhibiting different characterizations between cell types. Among the five loci showing evidence of having associations in opposite directions between some subtypes, at least one CCV per locus overlapped an “ANYSWITCH” enhancer (**Figure 4**). For example, rs78378222 overlapped an ACTIVE enhancer in BC, PRIMED in LP and OFF in LM. In comparison, 63% of the loci with consistent direction of associations across subtypes overlapped with an “ANYSWITCH” enhancer (**Supplementary Table 12-13**). These results support the hypothesis that some variants may modulate enhancer activity in a cell-type specific manner and thus differentially influence the risk of developing different tumor subtypes.

We used INQUIST to intersect each of the CCVs with functional annotation data from public databases to identify potential target genes¹ (**Online Methods, Supplementary Table 14**). We predicted 179 unique target genes for 26 of the 32 independent signals. Twenty-three target genes in 14 regions were predicted with high confidence (designated “Level 1”), of which 22 target genes in 13 regions were predicted to be distally regulated. These targets include four genes predicted as INQUISIT targets in previous studies^{12,13} *POLR3C*, *RNF115*, *SOX4* and *TBX3*, a known somatic breast cancer driver gene¹⁴, and genes implicated by transcriptome-wide association studies (*LINC00886*¹⁵ and *YBEY*¹⁶).

We used LD-regression to investigate the genetic architecture of molecular subtypes by evaluating the genetic correlations^{17,18} between subtypes and to compare

enrichment of genomic features¹⁹ between luminal A-like and TN subtypes (**Online Methods**). All intrinsic-like subtypes were moderately- to highly-correlated, with luminal B-like and HER2-enriched-like ($r=0.35$, standard error (SE) =0.10) having the lowest genetic correlation. The correlations between luminal A-like and TN was $r=0.46$ (SE=0.05), and between TN and *BRCA 1* carriers was $r=0.84$ (SE=0.15) (**Figure 4; Supplementary Table 15**). To compare genomic enrichment, we first evaluated 53 annotations and found TN tumors were most enriched for “super-enhancers, extend500bp” (3.04-fold, $P= 3.3 \times 10^{-6}$), and “digital genomic footprint, extend500bp” (from DNase hypersensitive sites) (2.2-fold, $P=4.0 \times 10^{-4}$) (**Supplementary Table 16, Supplementary Figure 10**). However, none of the 53 annotations significantly differed between luminal A-like and TN tumors. We also investigated cell-specific enrichment of four histone markers - H3K4me1, H3K3me3, H3K9ac and H3K27ac (**Online Methods**) - and found enrichment in both luminal-A and TN subtypes for gastrointestinal cell types and suppression of central nervous system cell types (**Supplementary Figure 11**).

The proportion of genome-wide chip heritability explained by the 32 SNPs identified in these analyses, plus 178 previously identified susceptibility SNPs^{1,2,20}, was 54.2% for luminal A-like disease, 37.6% for TN disease and 26.9% for *BRCA1* carriers (**Table1**). Moreover, these 210 susceptibility SNPs explained approximately 18.3% of the two-fold familial relative risk for invasive breast cancer, while all reliably imputable SNPs on the OncoArray could explained 37.1% (**Online Methods**). Collectively, these analyses demonstrate the benefit of combining standard GWAS methods with methods accounting for underlying tumor heterogeneity. Moreover, these methods and results may help clarify mechanisms predisposing to specific molecular subtypes, and provide

precise risk estimates for molecular subtypes to inform the development of subtype-specific polygenic risk scores²¹.

Online Methods

Study populations

The overall breast cancer analyses included women of European ancestry from 82 BCAC studies from over 20 countries, with genotyping data derived from two Illumina genome-wide custom arrays, the iCOGS and OncoArray (**Supplementary Table 1**). Most of the studies were case-control studies in the general population, or hospital setting, or nested within population-based cohorts, but a subset of studies oversampled cases with a family history of the disease. We included controls and cases of invasive breast cancer, carcinoma *in-situ*, and cases of unknown invasiveness. Information on clinicopathologic characteristics were collected by the individual studies and combined in a central database after quality control checks. We used BCAC database version ‘freeze’ 10 for these analyses. Among a subset of participants (n=16,766) that were genotyped on both the iCOGS and OncoArray arrays, we kept only the OncoArray data. One study (LMBC) contributing to the iCOGS dataset was excluded due to inflation of the test statistics that was not corrected by adjustment for the first ten PCs. We also excluded OncoArray data from Norway (the Norwegian Breast Cancer Study) because there were no controls available from Norway with OncoArray data. All participating studies were approved by their appropriate ethics or institutional review board and all participants provided informed consent. The total sample size for this analysis, including iCOGS, OncoArray and other GWAS data, comprised 133,384 cases and 113,789 controls.

In the GWAS analyses accounting for underlying heterogeneity according to ER, PR, HER2 and grade, we included genotyping data from 81 BCAC studies. These analyses were restricted to controls and cases of invasive breast cancer; we excluded cases of carcinoma *in-situ* and cases with missing information on invasiveness, as these cases would potentially bias the implicit “imputation” of tumor marker in the underlying EM algorithm (**Supplemental Table 2**). We also excluded all studies from a specific country if there were no controls for that country, or if the tumor marker data were missing on two or more of the tumor marker subtypes (see footnote of **Supplemental Table 2** for further explanation of excluded studies). We did not include the summary results from the 14,910 cases and 17,588 controls from the 11 other GWAS in subtype analyses because these studies did not provide data on tumor characteristics. We also excluded invasive cases (n=293) and controls (n=4,285) with missing data on age at diagnosis or age at enrollment, information required by the EM algorithm to impute missing tumor characteristics. In total, the final sample for the two-stage polytomous logistic regression comprised 106,278 invasive cases and 91,477 controls.

Participants included from CIMBA were women of European ancestry, aged 18 years or older with a pathogenic *BRCA1* variant. Most participants were sampled through cancer genetics clinics. In some instances, multiple members of the same family were enrolled. OncoArray genotype data was available from 58 studies from 24 countries. Following quality control and removal of participants that overlapped with the BCAC OncoArray study, data were available on 15,566 *BRCA1* mutation carriers, of whom 7,784 were affected with breast cancer (**Supplementary Table 3**). We also

obtained iCOGS genotype data on 3,342 *BRCA1* mutation carriers (1,630 with breast cancer) from 54 studies through CIMBA. All *BRCA1* mutation carriers provided written informed consent and participated under ethically approved protocols.

Genotyping, quality control, and imputation

Details on genotype calling, quality control and imputation for the OncoArray, iCOGS, and GWAS are described elsewhere^{1,2,5,6}. Genotyped or imputed SNPs marking each of the loci were determined using the iCOGS and the OncoArray genotyping arrays and imputation to the 1000 Genomes Project (Phase 3) reference panel. We included SNPs, from each component GWAS with an imputation quality score of >0.3. We restricted analysis to SNPs with a minor allele frequency >0.005 in the overall breast cancer analysis and >0.01 in the subtype analysis.

Known breast cancer susceptibility variants

Prior studies identified susceptibility SNPs from genome-wide analyses at a significance level $P < 5.0 \times 10^{-8}$ for all breast cancer types, ER-negative or ER-positive breast cancer, in *BRCA1* or *BRCA2* mutation carriers, or in meta-analyses of these^{1,2}. We defined known breast cancer susceptibility variants as those variants that were identified or replicated in prior BCAC analyses^{1,2}. We also excluded from consideration variants within 500kb of a previously published locus, since these regions have been subject to separate conditional analyses¹³.

Standard analysis of BCAC data

Logistic regression analyses were conducted separately for the iCOGS and OncoArray datasets, adjusting for country and the array-specific first 10 PCs for ancestry informative SNPs. The methods for estimating PCs have been described elsewhere^{1,2}. For the remaining GWAS, adjustment for inflation was done by adjusting for up to three PCs and using genomic control adjustment, as previously described¹. We evaluated the associations between approximately 10.8 million SNPs with imputation quality scores ($r^2 \geq 0.3$ and MAF > 0.005). We excluded SNPs located within ± 500 KB of, or in LD ($r^2 \geq 0.1$) with known susceptibility SNPs²⁰. The association effect size estimates from these, and the previously derived estimates from the 11 other GWAS, were then combined using a fixed effects meta-analysis. Since individual level genotyping data were not available for some previous GWAS, we conservatively approximated the potential overlap between the GWAS and iCOGS and OncoArray datasets, based on the populations contributing to each GWAS (iCOGS/GWAS: 626 controls and 923 cases; OncoArray/GWAS: 20 controls and 990 cases). We then used these adjusted data to estimate the correlation in the effect size estimates, and incorporated these into the meta-analysis using the method of Lin and Sullivan²².

Subtypes analysis of BCAC data

We described the two-stage polytomous logistic regression in more detail elsewhere^{4,23} (**Supplementary Note**). In brief, this method allows for efficient testing of a SNP-disease association in the presence of tumor subtype heterogeneity defined by multiple tumor characteristics, while accounting for multiple testing and missing data on tumor characteristics. In the first stage, the model uses a polytomous logistic regression

to model case-control ORs between the SNPs and all possible subtypes that could be of interest, defined by the combination of the tumor markers. For example, in a model fit to evaluate heterogeneity according to ER, PR and HER2 positive/negative status, and grade of differentiation (low, intermediate and high grade), the first stage incorporates case-control ORs for 24 subtypes defined by the cross-classification of these factors. The second stage restructures the first-stage subtype-specific case-control ORs parameters into second-stage parameters through a decomposition procedure resulting in a second-stage baseline parameter that represents a case-control OR of a baseline cancer subtype, and case-case ORs parameters for each individual tumor characteristic. The second-stage case-case parameters can be used to perform heterogeneity tests with respect to each specific tumor marker while adjusting for the other tumor markers in the model. The two-stage model efficiently handles missing data by implementing an Expectation-Maximization algorithm^{4,7} that essentially performs iterative “imputation” of the missing tumor characteristics conditional on available tumor characteristics and baseline covariates based on an underlying two-stage polytomous model.

To identify novel susceptibility loci, we used both a fixed-effect two-stage polytomous model and a mixed-effect two-stage polytomous model. The score-test we developed based on the mixed-effect model allows coefficients associated with individual tumor characteristics to enter as either fixed- or random-effect terms. Our previous analyses have shown that incorporation of random effect terms can improve power of the score-test by essentially reducing the effective degrees-of-freedom associated with fixed effects related to exploratory markers (*i.e.*, markers for which there

is little prior evidence to suggest that they are a source of heterogeneity)²⁴. On the other hand, incorporation of fixed-effect terms can preserve distinct associations of known important tumor characteristics, such as ER. In the mixed-effect two-stage polytomous model, we therefore kept ER as a fixed effect, but modeled PR, HER2 and grade as random effects. We evaluated SNPs with MAF >0.01 (~10.0 million) and $r^2 \geq 0.3$, and excluded SNPs within ± 500 kb of, or in LD ($r^2 \geq 0.1$) with known susceptibility SNPs, including those identified in the standard analysis for overall breast cancer. We reported SNPs that passed the p-value threshold of $P < 5.0 \times 10^{-8}$ in either the fixed- or mixed-effects models.

We assessed the influence of country on signals identified by the two-stage models by performing a ‘leave one out’ sensitivity analyses in which we reevaluated novel signals after excluding data from each individual country. Data from the OncoArray and iCOGS arrays were analyzed separately and then meta-analyzed using fixed-effects meta-analysis.

Statistical analysis of CIMBA data

We tested for associations between SNPs and breast cancer risk for *BRCA1* mutation carriers using a score test statistic based on the retrospective likelihood of observing the SNP genotypes conditional on breast cancer phenotypes (breast cancer status and censoring time)²⁵. Analyses were performed separately for iCOGS and OncoArray data. To allow for non-independence among related individuals, a kinship-adjusted test was used that accounted for familial correlations²⁶. We stratified analyses by country of residence and, for countries where the strata were sufficiently large

(United States and Canada), by Ashkenazi Jewish ancestry. The results from the iCOGS and OncoArray data were then pooled using fixed-effects meta-analysis.

Meta-analysis of BCAC and CIMBA

We performed a fixed-effects meta-analysis of the results from BCAC TN cases and CIMBA *BRCA1* mutation carriers, using an inverse-variance fixed-effects approach implemented in METAL²⁷. The estimates of association used were the logarithm of the per-allele hazard ratio estimate for association with breast cancer risk for *BRCA1* mutation carriers from CIMBA and the logarithm of the per-allele odds ratio estimate for association with risk of TN breast cancer based on BCAC data.

Conditional analyses

We performed two sets of conditional analyses. First, we investigated for evidence of multiple independent signals in identified loci by performing forward selection logistic regression, in which we adjusted the lead SNP and analyzed association for all remaining SNPs within ± 500 kb of the lead SNPs, irrespective of LD. Second, we confirmed the independence of 20 SNPs that were located within ± 2 MB of a known susceptibility region by conditioning the identified signals on the nearby known signal. Since these 20 SNPs are already genome-wide significant in the original GWAS scan and the conditional analyses restricted to local regions, we therefore used a significance threshold of $P < 1 \times 10^{-6}$ to control for type-one error²⁸.

Heterogeneity analysis of new association signals

We evaluated all novel signals for evidence of heterogeneity using the two-stage polytomous model. We first performed a global test for heterogeneity under the mixed-effect model test to identify SNPs showing evidence of heterogeneity with respect to any of the underlying tumor markers, ER, PR, HER2 and/or grade. We accounted for multiple testing of the global heterogeneity test using a FDR <0.05 under the Benjamini-Hochberg procedure²⁹. Among the SNPs with observed heterogeneity, we then further used a fixed-effect two-stage model to evaluate influence of specific tumor characteristic(s) driving observed heterogeneity, adjusted for the other markers in the model. We also fit a separate fixed-effect two-stage models to estimate case-control ORs and 95% confidence intervals (CI) for five surrogate intrinsic-like subtypes defined by combinations of ER, PR, HER2 and grade³⁰: (1) luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2); (2) luminal B/HER2-negative-like (ER+ and/or PR+, HER2-, grade 3); (3) luminal B-like (ER+ and/or PR+, HER2+); (4) HER2-enriched-like (ER- and PR-, HER2+), and (5) TN (ER-, PR-, HER2-).

Candidate causal variants

We defined credible sets of candidate causal variants (CCVs) as variants located within $\pm 500\text{kb}$ of the lead SNPs in each novel region and with P values within 100-fold of magnitude of the lead SNPs. This is approximately equivalent to selecting variants whose posterior probability of causality is within two orders of magnitude of the most significant SNP^{31,32}. This approach was applied for detecting a set of potentially causal variants for all 32 identified SNPs. For the novel SNPs located within $\pm 2\text{Mb}$ of the

known signals, we used the conditional P values to adjust for the known signals' associations.

eQTL Analysis

Data from breast cancer tumors and adjacent normal breast tissue were accessed from The Cancer Genome Atlas (TCGA)³³. Germline SNP genotypes (Affymetrix 6.0 arrays) were processed and imputed to the 1000 Genomes reference panel (October 2014) and European ancestry ascertained as previously described¹. Tumor tissue copy number was estimated from the Affymetrix 6.0 and called using the GISTIC2 algorithm³⁴. Complete genotype, RNA-seq and copy number data were available for 679 genetically European patients (78 with adjacent normal tissue). Further, RNA-seq for normal breast tissue and imputed germline genotype data were available from 80 females from the GTEx Consortium³⁵. Genes with a median expression level of 0 RPKM across samples were removed, and RPKM values of each gene were log2 transformed. Expression values of samples were quantile normalized. Genetic variants were evaluated for association with the expression of genes located within ± 2 Mb of the lead variant at each risk region using linear regression models, adjusting for ESR1 expression. Tumor tissue was also adjusted for copy number variation, as previously described³⁶. eQTL analyses were performed using the MatrixEQTL program in R³⁷.

INQUISIT target gene analysis

Logic underlying INQUISIT predictions: Details of the INQUISIT pipeline have been previously described¹. Briefly, genes were evaluated as potential targets of candidate causal variants through effects on: (1) distal gene regulation, (2) proximal regulation, or (3) a gene's coding sequence. We intersected CCV positions with multiple sources of genomic information, chromatin interaction analysis by paired-end tag sequencing (ChIA-PET)³⁸ in MCF7 cells, and genome-wide chromosome conformation capture (Hi-C) in HMECs³⁹. We used breast cell line computational enhancer–promoter correlations (PreSTIGE⁴⁰, IM-PET⁴¹, FANTOM5⁴²) breast cell super-enhancer⁴³, breast tissue-specific expression variants (eQTL) from multiple independent studies (TCGA (normal breast and breast tumor) and GTEx breast, **See eQTL Methods**), transcription factor and histone modification chromatin immunoprecipitation followed by sequencing (ChIP-seq) from the ENCODE and Roadmap Epigenomics Projects together with the genomic features found to be significantly enriched for all known breast cancer CCVs¹³, gene expression RNA-seq from several breast cancer lines and normal samples (ENCODE) and topologically associated domain (TAD) boundaries from T47D cells (ENCODE⁴⁴). To assess the impact of intragenic variants, we evaluated their potential to alter primary protein coding sequence and splicing using Ensembl Variant Effect Predictor⁴⁵ using MaxEntScan and dbSNV modules for splicing alterations based on “ada” and “rf” scores. Nonsense and missense changes were assessed with the REVEL ensemble algorithm, with CCVs displaying REVEL scores > 0.5 deemed deleterious.

Scoring hierarchy: Each target gene prediction category (distal, promoter or coding) was scored according to different criteria. Genes predicted to be distally-regulated targets of CCVs were awarded two points based on physical links (for

example ChIA-PET), and one point for computational prediction methods, or eQTL associations. All CCVs were considered as potentially involved in distal regulation and all CCVs (including coding SNPs) were scored in this category. Intersection of a putative distal enhancer with genomic features found to be significantly enriched²⁰ were further upweighted with an additional point. In the case of multiple, independent interactions, an additional point was awarded. CCVs in gene proximal regulatory regions were intersected with histone ChIP-Seq peaks characteristic of promoters and assigned to the overlapping transcription start sites (defined as -1.0 kb - +0.1 kb). Further points were awarded to such genes if there was evidence for an eQTL association, while a lack of expression resulted in down-weighting as potential targets. Potential coding changes including missense, nonsense and predicted splicing alterations resulted in addition of one point to the encoded gene for each type of change, while lack of expression reduced the score. We added an additional point for predicted target genes that were also breast cancer drivers (278 genes^{1,20}). For each category, scores potentially ranged from 0-8 (distal); 0-4 (promoter) or 0-3 (coding). We converted these scores into 'confidence levels': Level 1 (highest confidence) when distal score >4, promoter score ≥ 3 or coding score >1; Level 2 when distal score ≤ 4 and ≥ 1 , promoter score=1 or=2, coding score=1; and Level 3 when distal score <1 and >0, promoter score <1 and >0, and coding <1 and >0. For genes with multiple scores (for example, predicted as targets from multiple independent risk signals or predicted to be impacted in several categories), we recorded the highest score.

Enhancer states analysis in breast sub-populations

We obtained enhancer maps for three enriched primary breast sub-populations (basal, luminal progenitor, and mature luminal) from Pellacani et al.¹¹. Enhancer annotations were defined as ACTIVE, PRIMED, or OFF based on a combination of H3K27ac and H3K4me1 histone modification ChIP-seq signals using FPKM thresholds as previously described¹¹. Briefly, genomic regions containing high H3K4me1 signal observed in any cell type were used to define the superset of breast regulatory elements. Sub-population cell type-specific H3K27ac signal (which is characteristic of active elements) within these elements was used as a measure of overall regulatory activity, where "ACTIVE" sites were characterized by H3K4me1-high, H3K27ac-high; "PRIMED" by H3K4me1-high, H3K27ac-low; and "OFF" by H3K4me1-low, H3K27ac-low. This enabled annotation of each enhancer element as either "OFF", "PRIMED" or "ACTIVE" in all cell types. We then defined enhancers which exhibit differing states between at least one cell type as "ANYSWITCH" enhancers.

Genetic correlation analyses

We used LD score regression¹⁷⁻¹⁹ to estimate the genetic correlation between five intrinsic-like breast cancer subtypes. The analysis used the summary statistics based on the meta-analysis of the OncoArray, and iCOGS, and CIMBA meta-analysis. The genetic correlation¹⁷ analysis was restricted to the ~1 million SNPs included in HapMap 3 with MAF > 1% and imputation quality score R²>0.3 in the OncoArray data. Since two-stage polytomous models integrated an imputation algorithm for missing tumor characteristic data, we modified the LD score regression to generate the effective sample size for each SNP (**Supplementary Note**).

Global genomic enrichment analyses

We performed stratified LD score regression analyses¹⁷⁻¹⁹ as previously described¹ for two major intrinsic-like subtypes, luminal A-like and TN, using the summary statistics from the meta-analyses of OncoArray, iCOGs, and CIMBA. The analysis included all SNPs in the 1000 Genome Project Phase 1v3 release with MAF>1% and imputation quality score R²>0.3 in the OncoArray data. We restricted analysis to all SNPs present on the HapMap version 3 dataset. We first fit a model that included 24 non-cell-type-specific, publicly available annotations as well as 24 additional annotations that included a 500-bp window around each of the 24 main annotations. We also included 100-bp windows around ChIP-seq peaks and one annotation containing all SNPs, leading to a total of 53 overlapping annotations. In addition to the baseline model using 24 main annotations, we also performed cell-type-specific analyses using annotations of the four histone marks (H3K4me1, H3K4me3, H3K9ac and H3K27ac). Each cell-type-specific annotation corresponds to a histone mark in a single cell type (for example, H3K27ac in adipose nuclei tissues)¹⁹. There was a total of 220 such annotations. We further subdivided these 220 cell-type-specific annotations into 10 categories by aggregating the cell-type-specific annotations within each group (for example, SNPs related with any of the four histone modifications in any hematopoietic and immune cells were considered as one category). To estimate the enrichment of each marker, we ran 220 LD score regressions after adding each different histone mark to the baseline model. We used a Wald test to evaluate the differences in the functional enrichment between the luminal A-like and TN subtypes, using the regression

coefficients and standard error based on the models above. After Bonferroni correction none of the differences were significant. Notably, the Wald test assumes that the enrichment estimates of luminal A-like and TN subtypes were independent, but this assumption was violated by the sharing of controls between the subtypes. Under this scenario, our Wald test statistics were less conservative than had we adjusted for the correlation between estimates. However, given the lack of significant differences observed between luminal A-like and TN subtypes we had no concern about a type one error.

Genetic variance explained by identified susceptibility SNPs and all genome-wide imputable variants

Genetic variance corresponds to heritability on the frailty-scale, which assumes a polygenetic log-additive model as the underlying model. Under the log-additive model, the frailty-scale heritability explained by the identified variants can be estimated by:

$$\sum_{i=1}^n 2p_i(1 - p_i)(\hat{\beta}_i^2 - \tau_i^2),$$

where n is the total number of identified SNPs, p_i is the MAF for i th variant, $\hat{\beta}_i$ is the log odds ratio estimate for the i th variant, and τ_i is the standard error of $\hat{\beta}_i$. To obtain the frailty scale heritability for invasive breast cancer explained by all of the GWAS variants, we used LD score regression to estimate heritability (σ_{GWAS}^2) using the full set of summary statistics from either standard logistic regression for overall invasive breast cancer, the two-stage polytomous regression for the intrinsic-like subtypes, or the CIMBA *BRCA1* analysis for *BRCA1* carriers. σ_{GWAS}^2 is characterized by population

variance of the underlying true polygenetic risk scores as $\sigma_{GWAS}^2 = Var(\sum_{m=1}^M \beta_m G_m)$, where G_m is the standardized genotype for the m th SNP, β_m is the true log odds ratio for the m th SNP and M are the total number of causal SNPs among the GWAS variants. Thus, the proportion of heritability explained by identified variants relative to all imputable SNPs is:

$$\sum_{i=1}^n 2p_i(1 - p_i)(\hat{\beta}_i^2 - \tau_i^2) / \sigma_{GWAS}^2.$$

To estimate the proportion of the familial risk of invasive breast cancer that is explained by susceptibility variants, we defined the familial relative risk, λ , as the familial relative risk assuming a polygenic log-additive model that explains all the familial aggregation of the disease⁴⁶. Under the frailty scale, we define the broad sense heritability⁴⁷ as σ^2 . The relationship between λ and σ^2 was shown to be $\sigma^2 = 2 * \log(\lambda)$ ⁴⁶. We assumed $\lambda = 2$ as the overall familial relative risk of invasive breast cancer, thus $\sigma^2 = 2\log(2)$ and the proportion of the familial relative risk explained by identified susceptibility SNPs is $\sum_{i=1}^n p_i(1 - p_i)(\hat{\beta}_i^2 - \tau_i^2) / \log(2)$, and the proportion of the familial relative risk explained by GWAS variants is $\sigma_{GWAS}^2 / [2 * \log(2)]$. Analyses of heritability and the proportion of explained familial risk were restricted to 106,278 invasive cases and 91,477 controls (**Supplementary Table 2**).

Figure 1. Manhattan plots showing 32 independent susceptibility loci crossing genome-wide significant threshold for associations with breast cancer risk. **a)** Twenty-two loci (**Supplementary Table 6**) were identified from standard logistic regression analysis using 133,384 breast cancer cases and 113,789 controls from BCAC; **b)** eight loci (**Supplementary Table 7**) identified from two-stage polytomous regression using 106,278 invasive cases and 91,477 controls from BCAC; **c)** three loci (**Supplementary Table 8**) were identified from meta-analysis of triple negative in BCAC and 18,908 female *BRCA1*(unaffected *BRCA1* mutation carriers = 9,494). SNP rs78378222 was also detected in two-stage polytomous regression model.

Figure 2. Heatmap and clustering of p-values from marker specific heterogeneity test for 32 breast cancer susceptibility loci. P-values are for associations between the most significant SNPs marking each loci and estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) or grade, adjusting for top ten principal components and age. Fifteen SNPs in red color were significant according to the global heterogeneity tests (FDR <0.05) that evaluates if a SNP's risk estimates vary by at least one of the four tumor characteristics.

Figure 3. Susceptibility SNPs with associations in opposite direction across subtypes. The case-control odds ratios (OR) and 95% confidence intervals (95% CI)¹ (left panel) are for associations of each of the five SNPs and risk for breast cancer intrinsic-like subtypes² estimated from the first-stage of the two-stage polytomous regression fixed-effects model. The case-case ORs 95%CI (right panel) are estimated from the second stage parameters of a fixed effect two-stage polytomous models testing for heterogeneity between the five SNPs and estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and grade, where ER, PR, HER2, and grade are mutually adjusted for each other.

1 Per-minor allele odds ratio and 95% confidence limits
 2 luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2); luminal B/HER2-negative-like (ER+ and/or PR+, HER2-, grade 3); luminal B-like (ER+ and/or PR+, HER2+); (4) HER2-enriched-like (ER- and PR-, HER2+), and triple-negative (ER-, PR-, HER2-)

Figure 4. Heatmap of candidate causal variants (CCVs) overlapping results with enhancer states in primary breast subpopulations for five SNPs **(a)** rs78378222 **(b)** rs141526427 **(c)** rs6065254 **(d)** rs7924772 **(e)** rs206435 with associations in opposite direction across subtypes. Three different breast subpopulations were considered: basal cells (BC), luminal progenitor (LP) and luminal cells mature (LM). Based on a combination of H3K4me1 and H3K27ac histone modification ChIP-seq signals, putative enhancers in BC, LP, and LM were characterized as “OFF”, “PRIMED” and “ACTIVE” (**Online Methods**). The CCVs overlapping with enhancers were colored as red, otherwise were white.

Figure 5. Genetic correlation between the five intrinsic-like breast cancer subtypes and *BRCA1* mutation carriers estimated through LD score regression. See **Supplementary Table 14** for further details. Both the color and size of the circles reflect the strength of the genetic correlations.

Table 1. Genetic variance of invasive breast cancer explained by identified susceptibility SNPs and all reliably genome-wide imputable variants¹

Phenotype	Genetic variance for 210 identified susceptibility SNPs ²	Genetic variance for 32 newly identified SNPs ²	Genetic variance for all GWAS variants ³	Proportion of genetic variance explained by identified susceptibility loci ⁴
Invasive breast cancer⁵	0.253	0.016	0.515	45.51%
Luminal A-like	0.336	0.022	0.620	54.22%
Luminal B/HER2-negative-like	0.233	0.018	0.597	38.95%
Luminal B-like	0.270	0.020	0.740	36.46%
HER2-enriched-like	0.200	0.011	0.689	29.05%
Triple negative	0.185	0.025	0.492	37.63%
CIMBA <i>BRCA1</i> carriers	0.083	0.016	0.309	26.86%

¹ Genetic variance corresponds to heritability on the frailty-scale, which assumes the polygenetic log-additive model as the underlying model.

² Susceptibility SNPs included 178 SNPs identified or replicated in Nature 551, 92-94 (2017) and Nat Genet 49, 1767-1778 (2017) and 32 newly identified SNPs in this paper.

³ Genetic variance of all reliably genome-wide imputable variants was estimated through LD-score regression described in Nat Genet 47, 291-5 (2015). and Nat Genet 47, 1236-41 (2015). Under the frailty-scale, the genetic variance for all GWAS variants is characterized by population variance of the underlying true polygenic risk score as $\sigma_{GWAS}^2 = Var(\sum_{m=1}^M \beta_m G_m)$, where G_m is the standardized genotype for the m th SNP, β_m is the true log odds ratio for the m th SNP and M are the total number of causal SNPs among the GWAS variants. (**Online Methods**).

⁴ Proportion of genetic variance explained by 210 identified GWAS significant SNPs over the genetic variance explained by all GWAS variants.

⁵ Invasive breast cancer summary level statistics were generated from 106,278 invasive cases and 91,477 controls, which were the same samples used in subtypes analyses (**Supplementary Table 2**).

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